CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20622/ S89

Trade Name: **COPAXONE**

Generic Name: Glatiramer Acetate

Sponsor: **TEVA Pharmaceuticals**

Approval Date: 01/28/2014

Indications: COPAXONE is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

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APPLICATION NUMBER:

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020622/S-089

SUPPLEMENT APPROVAL

Teva Pharmaceuticals USA
Attention: Dennis Ahern
Senior Director, Regulatory Affairs
41 Moores Road, PO Box 4011
Frazer, PA 19355

Dear Mr. Ahern:

Please refer to your Supplemental New Drug Application (sNDA) dated March 29, 2013, received March 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Copaxone (glatiramer acetate injection) for subcutaneous use.

We acknowledge receipt of your amendments dated:

April 23, 2013	July 30, 2013	November 7, 2013
May 10, 2013	August 7, 2013	November 15, 2013
June 25, 2013	August 12, 2013	December 13, 2013
June 26, 2013	August 15, 2013	December 18, 2013
July 17, 2013	September 11, 2013	
July 26, 2013	October 10, 2013	

This "Prior Approval" supplemental new drug application provides for a new dosing strength of 40 mg per mL administered three times per week.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending "Changes Being

Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations for all changes, supplement number(s), and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on December 13, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 020622/S-089**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

2114-1 A randomized, controlled, parallel group, superiority study in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of glatiramer acetate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Final Protocol Submission:	09/2017
Study Completion:	08/2020
Final Report Submission:	12/2021

2114-2 A juvenile animal toxicology study in rats to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development.

Final Protocol Submission:	02/2015
Study Completion:	11/2016
Final Report Submission:	01/2017

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit the draft protocols at least 3 months prior to the final protocol submission date to allow for review and agreement on the protocol design.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research

Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-126

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
01/28/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COPAXONE® safely and effectively. See full prescribing information for COPAXONE.

COPAXONE (glatiramer acetate injection) for subcutaneous use
Initial U.S. Approval: 1996

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Recommend Dose (2.1)	01/2014
Dosage and Administration, Instructions for Use (2.2)	01/2014
Warnings and Precautions, Immediate Post-Injection Reaction (5.1)	01/2014
Warnings and Precautions, Chest Pain (5.2)	01/2014
Warnings and Precautions, Lipoatrophy and Skin Necrosis (5.3)	01/2014

----------INDICATIONS AND USAGE----------

COPAXONE is indicated for the treatment of patients with relapsing-forms of multiple sclerosis (1).

----------DOSAGE AND ADMINISTRATION----------

- For subcutaneous injection only; doses are not interchangeable (2.1)
- COPAXONE 20 mg/mL per day (2.1)
- COPAXONE 40 mg/mL three times per week (2.1)
- Before use, allow the solution to warm to room temperature (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 20 mg/mL in a single-dose prefilled syringe with a white plunger (3)
- Injection: 40 mg/mL in a single-dose, prefilled syringe with a blue plunger (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to glatiramer acetate or mannitol (4)

----------WARNINGS AND PRECAUTIONS----------

- Immediate Post-Injection Reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting (5.1)
- Chest pain, usually transient (5.2)
- Lipoatrophy and skin necrosis may occur. Instruct patients in proper injection technique and to rotate injection sites (5.3)
- COPAXONE can modify immune response (5.4)

----------ADVERSE REACTIONS----------

- In controlled studies of COPAXONE 20 mg/mL, most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)
- In a controlled study of COPAXONE 40 mg/mL, most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA at 1-800-221-4026 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: It is not known if COPAXONE is excreted in human milk (8.3)
- Pediatric Use: The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION
COPAXONE (glatiramer acetate injection)

1 INDICATIONS AND USAGE

COPAXONE is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

COPAXONE is for subcutaneous use only. Do not administer intravenously. The dosing schedule depends on the product strength that is selected. The recommended doses are:

- COPAXONE 20 mg per mL: administer once per day

or

- COPAXONE 40 mg per mL: administer three times per week and at least 48 hours apart

COPAXONE 20 mg per mL and COPAXONE 40 mg per mL are not interchangeable.

2.2 Instructions for Use

Remove one blister-packaged prefilled syringe from the refrigerated carton. Let the prefilled syringe stand at room temperature for 20 minutes to allow the solution to warm to room temperature. Visually inspect the syringe for particulate matter and discoloration prior to administration. The solution in the syringe should appear clear, colorless to slightly yellow. If particulate matter or discoloration is observed, discard the syringe.

Areas for subcutaneous self-injection include arms, abdomen, hips, and thighs. The prefilled syringe is for single use only. Discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg per mL in a single-dose, prefilled syringe with a white plunger. For subcutaneous use only.
- Injection: 40 mg per mL in a single-dose, prefilled syringe with a blue plunger. For subcutaneous use only.

4 CONTRAINDICATIONS

COPAXONE is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

5 WARNINGS AND PRECAUTIONS

5.1 Immediate Post-Injection Reaction

Approximately 16% of patients exposed to COPAXONE 20 mg per mL in the 5 placebo-controlled trials compared to 4% of those on placebo, and approximately 2% of patients exposed to COPAXONE 40 mg per mL in a placebo-controlled trial compared to none on placebo, experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. Typically, the symptoms were transient and self-limited and did not require treatment; however, there have been reports of patients with similar symptoms who received emergency medical care. Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

5.2 Chest Pain

Approximately 13% of COPAXONE 20 mg per mL patients in the 5 placebo-controlled studies compared to 6% of placebo patients, and approximately 2% of patients exposed to COPAXONE 40 mg per mL in a placebo-controlled trial compared to 1% of placebo patients, experienced at least one episode of transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection was not always known. The pain was usually transient, often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

5.3 Lipoatrophy and Skin Necrosis

At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis may occur. Lipoatrophy occurred in approximately 2% of patients exposed to COPAXONE 20 mg per mL in the 5 placebo-controlled trials compared to none on placebo, and 0.5% of patients exposed to COPAXONE 40 mg per mL in a single placebo-controlled trial and none on placebo. Skin necrosis has only been observed in the post-marketing setting. Lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites with each injection.

5.4 Potential Effects on Immune Response

Because COPAXONE can modify immune response, it may interfere with immune functions. For example, treatment with COPAXONE may interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that COPAXONE does this, but there has not been a systematic evaluation of this risk. Because COPAXONE is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

Although COPAXONE is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with COPAXONE may result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in most patients receiving glatiramer acetate. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RRMS patients given COPAXONE 20 mg per mL, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Incidence in Controlled Clinical Trials

<u>COPAXONE 20 mg per mL per day</u>

Among 563 patients treated with COPAXONE in blinded placebo-controlled trials, approximately 5% of the subjects discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity.

The most common adverse reactions were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE 20 mg per mL in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with COPAXONE than in patients treated with placebo. Adverse reactions were usually mild in intensity**.**

Table 1: Adverse reactions in controlled clinical trials with an incidence ≥2% of patients and more frequent with COPAXONE (20 mg per mL daily) than with placebo

		COPAXONE 20 mg/mL (n=563)	**Placebo (n=564)**
Blood And Lymphatic System Disorders	Lymphadenopathy	7%	3%
Cardiac Disorders	Palpitations	9%	4%
	Tachycardia	5%	2%
Eye Disorders	Eye Disorder	3%	1%
	Diplopia	3%	2%
Gastrointestinal Disorders	Nausea	15%	11%
	Vomiting	7%	4%
	Dysphagia	2%	1%
General Disorders And Administration Site Conditions	Injection Site Erythema	43%	10%
	Injection Site Pain	40%	20%
	Injection Site Pruritus	27%	4%
	Injection Site Mass	26%	6%
	Asthenia	22%	21%
	Pain	20%	17%
	Injection Site Edema	19%	4%
	Chest Pain	13%	6%
	Injection Site Inflammation	9%	1%
	Edema	8%	2%
	Injection Site Reaction	8%	1%
	Pyrexia	6%	5%
	Injection Site Hypersensitivity	4%	0%
	Local Reaction	3%	1%
	Chills	3%	1%
	Face Edema	3%	1%
	Edema Peripheral	3%	2%
	Injection Site Fibrosis	2%	1%
	Injection Site Atrophy*	2%	0%
Immune System Disorders	Hypersensitivity	3%	2%
Infections And Infestations	Infection	30%	28%
	Influenza	14%	13%
	Rhinitis	7%	5%
	Bronchitis	6%	5%
	Gastroenteritis	6%	4%
	Vaginal Candidiasis	4%	2%
Metabolism And Nutrition Disorders	Weight Increased	3%	1%

		COPAXONE 20 mg/mL (n=563)	Placebo (n=564)
Musculoskeletal And Connective Tissue Disorders	Back Pain	12%	10%
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Neoplasm of Skin	2%	1%
Nervous System Disorders	Tremor	4%	2%
	Migraine	4%	2%
	Syncope	3%	2%
	Speech Disorder	2%	1%
Psychiatric Disorders	Anxiety	13%	10%
	Nervousness	2%	1%
Renal And Urinary Disorders	Micturition Urgency	5%	4%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	14%	4%
	Cough	6%	5%
	Laryngospasm	2%	1%
Skin And Subcutaneous Tissue Disorders	Rash	19%	11%
	Hyperhidrosis	7%	5%
	Pruritus	5%	4%
	Urticaria	3%	1%
	Skin Disorder	3%	1%
Vascular Disorders	Vasodilatation	20%	5%

*Injection site atrophy comprises terms relating to localized lipoatrophy at injection site

Adverse reactions which occurred only in 4 to 5 more subjects in the COPAXONE group than in the placebo group (less than 1% difference), but for which a relationship to COPAXONE could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE. Clinically-significant laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia (16 $x10^9$/L), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials of COPAXONE 20 mg per mL were analyzed to evaluate differences based on sex. No clinically-significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with COPAXONE were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age subgroups.

Other Adverse Reactions

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled premarketing studies (n= 979), the role of COPAXONE in their causation cannot be reliably determined. Furthermore, variability associated

with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used COPAXONE and reported a reaction divided by the total number of patients exposed to COPAXONE. All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse reactions are defined as those occurring in at least 1/100 patients and *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients.

Body as a Whole:

Frequent: Abscess

Infrequent: Injection site hematoma, moon face, cellulitis, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:

Frequent: Hypertension.

Infrequent: Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic:

Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing’s syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

Infrequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle

disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation and hay fever.

Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

Frequent: Visual field defect.

Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency, and vaginal hemorrhage.

Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

<u>COPAXONE 40 mg per mL three times per week</u>

Among 943 patients treated with COPAXONE 40 mg per mL three times per week in a blinded, placebo-controlled trial, approximately 3% of the subjects discontinued treatment because of an adverse reaction. The most common adverse reactions were injection site reactions, which were also the most common cause of discontinuation.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE 40 mg per mL in the blinded, placebo-controlled trial. These signs and symptoms were numerically more common in patients treated

with COPAXONE 40 mg per mL than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 2: Adverse reactions in a controlled clinical trial with an incidence ≥2% of patients and more frequent with COPAXONE (40 mg per mL three times per week) than with placebo

		COPAXONE 40 mg/mL (n=943)	Placebo (n=461)
General Disorders And Administration Site Conditions	Injection Site Erythema	22%	2%
	Injection Site Pain	10%	2%
	Injection Site Mass	6%	0%
	Injection Site Pruritus	6%	0%
	Injection Site Edema	6%	0%
	Pyrexia	3%	2%
	Influenza-like Illness	3%	2%
	Injection Site Inflammation	2%	0%
	Chills	2%	0%
	Chest Pain	2%	1%
Infections And Infestations	Nasopharyngitis	11%	9%
	Respiratory Tract Infection Viral	3%	2%
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	3%	0%
Vascular Disorders	Vasodilatation	3%	0%
Gastrointestinal Disorders	Nausea	2%	1%
Skin And Subcutaneous Tissue Disorders	Erythema	2%	0%
	Rash	2%	1%

No new adverse reactions appeared in subjects treated with COPAXONE 40 mg per mL three times per week as compared to subjects treated with COPAXONE 20 mg per mL per day in clinical trials and during postmarketing experience. Data on adverse reactions occurring in the controlled clinical trial of COPAXONE 40 mg per mL were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-eight percent of patients in this clinical trial were Caucasian and the majority were between the ages of 18 and 50. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age groups.

6.2 Postmarketing Experience

The following adverse events occurring under treatment with COPAXONE 20 mg per mL since market introduction and not mentioned above have been identified during postapproval use of COPAXONE. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung

Special Senses: glaucoma; blindness

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

7 DRUG INTERACTIONS

Interactions between COPAXONE and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE has not been formally evaluated in combination with interferon beta.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal

reproduction studies are not always predictive of human response, COPAXONE should be used during pregnancy only if clearly needed.

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/m^2 basis). In rats receiving subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

8.2 Labor and Delivery

The effects of COPAXONE on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

It is not known if glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age.

8.5 Geriatric Use

COPAXONE has not been studied in elderly patients.

8.6 Use in Patients with Impaired Renal Function

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

11 DESCRIPTION

Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

(Glu, Ala, Lys, Tyr)$_x$•xCH$_3$COOH
($C_5H_9NO_4$•$C_3H_7NO_2$•$C_6H_{14}N_2O_2$•$C_9H_{11}NO_3$)$_x$•xC$_2$H$_4$O$_2$
CAS - 147245-92-9

COPAXONE is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of COPAXONE solution contains 20 mg or 40 mg of glatiramer acetate and the following inactive ingredient: 40 mg of mannitol. The pH of the solutions is approximately 5.5 to 7.0. The biological activity of glatiramer acetate is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS are not fully understood. However, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally-occurring immune responses. There is no evidence that glatiramer acetate does this, but this has not been systematically evaluated *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m^2 basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in neoplasms was observed.

Glatiramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m^2 basis) no adverse effects were observed on reproductive or developmental parameters.

14 CLINICAL STUDIES

Evidence supporting the effectiveness of COPAXONE derives from five placebo-controlled trials, four of which used a COPAXONE dose of 20 mg per mL per day and one of which used a COPAXONE dose of 40 mg per mL three times per week.

COPAXONE 20 mg per mL per day

Study 1 was performed at a single center. Fifty patients were enrolled and randomized to receive daily doses of either COPAXONE, 20 mg per mL subcutaneously, or placebo (COPAXONE: n=25; placebo: n=25). Patients were diagnosed with RRMS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurological signs for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: the frequency of attacks during the trial, and the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 3 presents the values of the three outcomes described above, as well as several protocol-specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

Table 3: Study 1 Efficacy Results

	COPAXONE 20 mg/mL (n=25)	**Placebo (n=25)**	**P-Value**
% Relapse-Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Prestudy	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

Study 2 was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (COPAXONE: n=125; placebo: n=126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. Table 4 presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

Table 4: Study 2 Efficacy Results

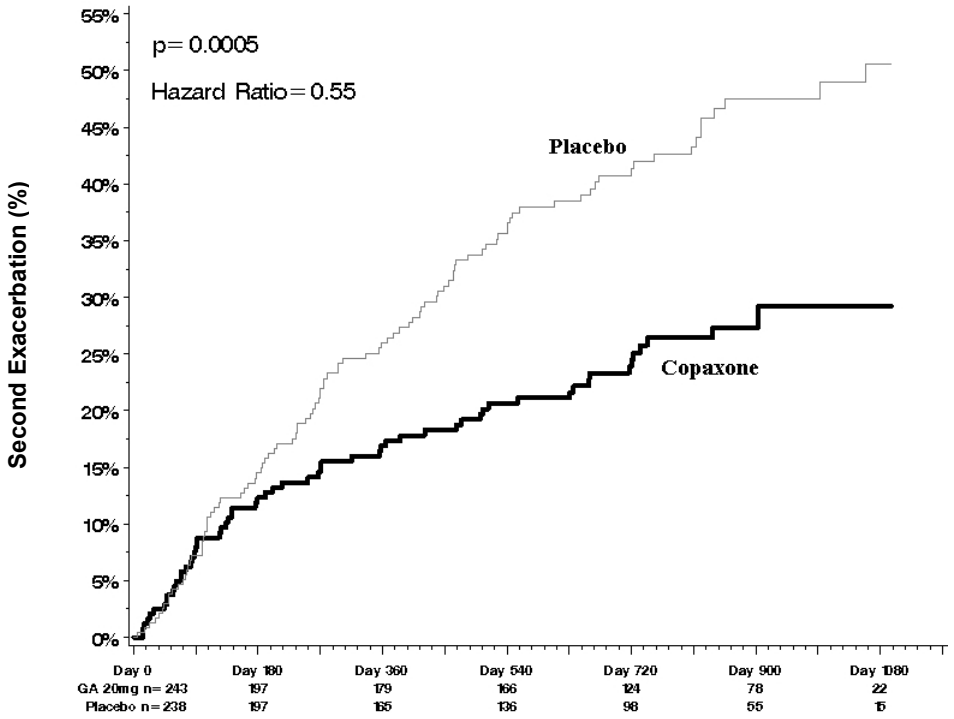
	COPAXONE 20 mg/mL (n=125)	**Placebo (n=126)**	**P-Value**
Mean No. of Relapses	1.19/2 years	1.68 /2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

In both studies, COPAXONE exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that COPAXONE is considered effective.

In Study 3, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either COPAXONE 20 mg per mL (n=243) or placebo (n=238). The primary outcome measure was time to development of a second exacerbation. Patients were followed for up to three years or until they reached the primary endpoint. Secondary outcomes were brain MRI measures, including number of new T2 lesions and T2 lesion volume.

Time to development of a second exacerbation was significantly delayed in patients treated with COPAXONE compared to placebo (Hazard Ratio = 0.55; 95% confidence interval 0.40 to 0.77; Figure 1). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the COPAXONE group.

Figure 1: Time to Second Exacerbation



Patients treated with COPAXONE demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; $p < 0.0001$). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (ratio of 0.89; confidence interval 0.84 to 0.94; $p = 0.0001$).

Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 5 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 5: Study 4 MRI Results

	COPAXONE 20 mg/mL (n=119)	**Placebo (n=120)**	**P-Value**
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

Figure 2 displays the results of the primary outcome on a monthly basis.

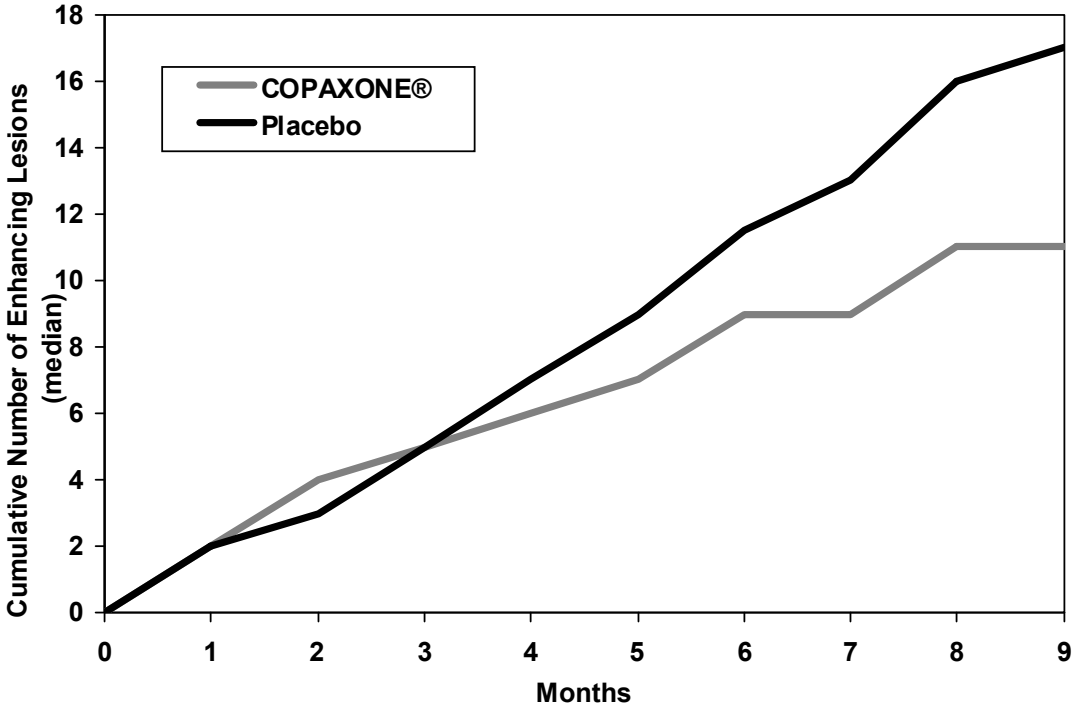


Figure 2: Median Cumulative Number of Gd-Enhancing Lesions

COPAXONE 40 mg per mL three times per week

Study 5 was a double-blind, placebo-controlled, multinational study with a total of 1404 patients with RRMS randomized in a 2:1 ratio to receive either COPAXONE 40 mg per mL (n=943) or placebo (n=461) three times a week for 12 months. Patients had a median of 2 relapses in the 2 years prior to screening and had not received any interferon-beta for at least 2 months prior to screening. Baseline EDSS scores ranged from 0 to 5.5 with a median of 2.5. Neurological evaluations were performed at baseline, every three months, and at unscheduled visits for suspected relapse or early termination. MRI was performed at baseline, months 6 and 12, or early termination. A total of 91% of those assigned to COPAXONE and 93% of those assigned to placebo completed treatment at 12 months.

The primary outcome measure was the total number of confirmed relapses (persistence of neurological symptoms for at least 24 hours confirmed on examination with objective signs). The effect of COPAXONE on several magnetic resonance imaging (MRI) variables, including number of new or enlarging T2 lesions and number of enhancing lesions on T1-weighted images, was also measured at months 6 and 12.

Table 6 presents the results for the intent-to-treat population.

Table 6: Study 5 Efficacy and MRI Results

	COPAXONE 40 mg/mL (n=943)	Placebo (n=461)	P-Value
Clinical Endpoints			
Number of confirmed relapses during the 12-month placebo-controlled phase			
Adjusted Mean Estimates Relative risk reduction	0.331 34%	0.505	<0.0001
MRI Endpoints			
Cumulative number of new or enlarging T2 lesions at Months 6 and12			
Adjusted Mean Estimates Relative risk reduction	3.650 35%	5.592	<0.0001
Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12			
Adjusted Mean Estimates Relative risk reduction	0.905 45%	1.639	<0.0001

16 HOW SUPPLIED/STORAGE AND HANDLING

COPAXONE (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger, in individual blister packages supplied in 30-count cartons (NDC 68546-317-30).
- 40 mg per mL in a single-dose, prefilled syringe with a blue plunger, in individual blister packages supplied in 12-count cartons (NDC 68546-325-12).

Store COPAXONE refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store COPAXONE at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze COPAXONE. If a COPAXONE syringe freezes, it should be discarded.

17 PATIENT COUNSELING INFORMATION

[See Patient Information Leaflet (Patient Information and Instructions for Use)]

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking COPAXONE they should inform their physician.

Immediate Post-Injection Reaction

Advise patients that COPAXONE may cause various symptoms after injection, including flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms are generally transient and self-limited and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

Chest Pain

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation. Inform patients that the pain should be transient. Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patients should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

Lipoatrophy and Skin Necrosis at Injection Site

Advise patients that localized lipoatrophy, and rarely, skin necrosis may occur at injection sites. Instruct patients to follow proper injection technique and to rotate injection areas and sites with each injection to minimize these risks.

Instructions for Use

Instruct patients to read the COPAXONE Patient Information leaflet carefully. COPAXONE 20 mg per mL and COPAXONE 40 mg per mL are not interchangeable. COPAXONE 20 mg per mL is administered daily and COPAXONE 40 mg per mL is administered three times per week. Caution patients to use aseptic technique. The first injection should be performed under the supervision of a health care professional. Instruct patients to rotate injection areas and sites with each injection. Caution patients against the reuse of needles or syringes. Instruct patients in safe disposal procedures.

Storage Conditions

Advise patients that the recommended storage condition for COPAXONE is refrigeration at 36°F to 46°F (2°C to 8°C). If needed, the patient may store COPAXONE at room temperature, 59°F to 86°F (15°C to 30°C), for up to one month, but refrigeration is preferred. COPAXONE should not be exposed to higher temperatures or intense light. Do not freeze COPAXONE.

[TEVA NEUROSCIENCE LOGO]

Marketed by: TEVA Neuroscience, Inc., Overland Park, KS 66211
Distributed by: TEVA Pharmaceuticals USA, Inc., North Wales, PA 19454
Product of Israel

Patient Information

COPAXONE (co-PAX-own)
(glatiramer acetate injection)
for subcutaneous use

Read this Patient Information before you start using COPAXONE and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is COPAXONE?

COPAXONE is prescription medicine used for the treatment of people with relapsing forms of multiple sclerosis (MS).

It is not known if COPAXONE is safe and effective in children under 18 years of age.

Who should not use COPAXONE?

- Do not use COPAXONE if you are allergic to glatiramer acetate, mannitol or any of the ingredients in COPAXONE. See the end of this leaflet for a complete list of the ingredients in COPAXONE.

What should I tell my doctor before using COPAXONE?

Before you use COPAXONE, tell your doctor if you:

- are pregnant or plan to become pregnant. It is not known if COPAXONE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if COPAXONE passes into your breast milk. Talk to your doctor about the best way to feed your baby while using COPAXONE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

COPAXONE may affect the way other medicines work, and other medicines may affect how COPAXONE works.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I use COPAXONE?

- For detailed instructions, see the **Instructions for Use** at the end of this leaflet for complete information on how to use COPAXONE**.**
- Your doctor will tell you how much COPAXONE to use and when to use it.
- COPAXONE is given by injection under your skin (subcutaneously).

- Use COPAXONE exactly as your doctor tells you to use it.
- Since every body type is different, talk with your doctor about the injection areas that are best for you.
- You should receive your first dose of COPAXONE with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will teach you how to give your COPAXONE injections.

What are the possible side effects of COPAXONE?

COPAXONE may cause serious side effects, including:

- **Post-Injection Reactions.** Serious side effects may happen right after you inject COPAXONE at any time during your course of treatment. Call your doctor right away if you have any of these post-injection reaction symptoms including:
    - redness to your cheeks or other parts of the body (flushing)
    - chest pain
    - fast heart beat
    - anxiety
    - breathing problems or tightness in your throat
    - swelling, rash, hives, or itching

  If you have symptoms of a post-injection reaction, do not give yourself more injections until a doctor tells you to.
- **Chest Pain.** You can have chest pain as part of a post-injection reaction or by itself. This type of chest pain usually lasts a few minutes and can begin around 1 month after you start using COPAXONE. Call your doctor right away if you have chest pain while using COPAXONE.
- **Damage to your skin.** Damage to the fatty tissue just under your skin's surface (lipoatrophy) and, rarely, death of your skin tissue (necrosis) can happen when you use COPAXONE. Damage to the fatty tissue under your skin can cause a "dent" at the injection site that may not go away. You can reduce your chance of developing these problems by:
    - following your doctor's instructions for how to use COPAXONE
    - choosing a different injection area each time you use COPAXONE. **See Step 4 in the Instructions for Use, "Choose your injection area".**

The most common side effects of COPAXONE include:

- skin problems at your injection site including:
    - o redness
    - o pain

  - swelling
  - itching
  - lumps
- rash
- shortness of breath
- flushing (vasodilation)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of COPAXONE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COPAXONE?

- Store COPAXONE in the refrigerator between 36°F to 46°F (2°C to 8°C).
- When you are not able to refrigerate COPAXONE, you may store it for up to 1 month at room temperature between 59°F to 86°F (15°C to 30°C).
- Protect COPAXONE from light or high temperature.
- Do not freeze COPAXONE syringes. If a syringe freezes, throw it away in a sharps disposal container. **See Step 13 in the Instructions for Use, "Dispose of needles and syringes".**

Keep COPAXONE and all medicines out of the reach of children.

General information about the safe and effective use of COPAXONE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use COPAXONE for a condition for which it was not prescribed. Do not give COPAXONE to other people, even if they have the same symptoms as you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about COPAXONE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE that is written for health professionals.

For more information, go to www.copaxone.com or call 1-800-887-8100.

What are the ingredients in COPAXONE?

Active ingredient: glatiramer acetate

Inactive ingredients: mannitol

Instructions for Use

COPAXONE (co-PAX-own)
(glatiramer acetate injection)
for subcutaneous use

For subcutaneous injection only.

Do not inject COPAXONE in your veins (intravenously).

Do not re-use your COPAXONE prefilled syringes.

Do not share your COPAXONE prefilled syringes with another person. You may give another person an infection or get an infection from them.

You should receive your first dose of COPAXONE with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will show you how to give your own injections.

COPAXONE comes in either a 20 mg Prefilled Syringe with needle attached or a 40 mg Prefilled Syringe with needle attached. How often a dose is given depends on the product strength that is prescribed. Your doctor will prescribe the correct dose for you.

Instructions for Using Your COPAXONE 20 mg Prefilled Syringe dose:

- **COPAXONE 20 mg** is injected 1 time each day, in the fatty layer under your skin (subcutaneously).
- Each COPAXONE 20 mg prefilled syringe is for single use (1 time use) only.
- The COPAXONE 20 mg dose is packaged in boxes of 30 prefilled syringes with needles attached. COPAXONE 20 mg prefilled syringes have **white** plungers.

Instructions for Using Your COPAXONE 40 mg Prefilled Syringe:

- **COPAXONE 40 mg** is injected 3 times each week in the fatty layer under your skin (subcutaneously).
- COPAXONE 40 mg should be given on the same 3 days each week, if possible for example, Monday, Wednesday, and Friday. Give your COPAXONE injections at least 48 hours (2 days) apart.
- Each COPAXONE 40 mg prefilled syringe is for single use (1 time use) only.
- The COPAXONE 40 mg dose is packaged in boxes of 12 prefilled syringes with needles attached. COPAXONE 40 mg prefilled syringes have **blue** plungers.

How do I inject COPAXONE?

Step 1: Gather the supplies you will need to inject COPAXONE. **See Figure A.**

- 1 blister pack with a COPAXONE Prefilled Syringe with needle attached
- Alcohol wipe (not supplied)
- Dry cotton ball (not supplied)
- A place to record your injections, like a notebook (not supplied)
- Sharps disposal container (not supplied). **See Step 13 below, "Dispose of needles and syringes".**

Figure A

Step 2: Remove only 1 blister pack from the COPAXONE prefilled syringe carton. **See Figure B.**

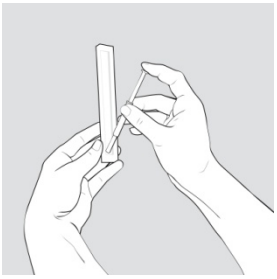


Figure B

- Place the supplies you will need on a clean, flat surface in a well-lit area.
- After you remove 1 blister pack from the carton, keep all unused syringes in the carton and store them in the refrigerator.
- Let the blister pack, with the syringe inside, warm to room temperature for about 20 minutes.

- Wash your hands. Be careful not to touch your face or hair after washing your hands.

Step 3: Look closely at your COPAXONE prefilled syringe.

- There may be small air bubbles in the syringe. **Do not** try to push the air bubble from the syringe before giving your injection so you do not lose any medicine.
- Check the liquid medicine in the syringe before you give your injection. The liquid in the syringe should look clear, and colorless, and may look slightly yellow. If the liquid is cloudy or contains any particles, do not use the syringe and throw it away in a sharps disposal container. **See Step 13 below, "Dispose of needles and syringes."**

Step 4: Choose your injection area. **See Figure C.**

See the injection areas you should use on your body. Talk with your doctor about the injection areas that are best for you.

- The possible injection areas on your body include **(See Figure C)**:
    - your stomach area (abdomen) around the belly button
    - the back of your upper arms
    - upper hips (below your waist)
    - your thighs (above your knees)

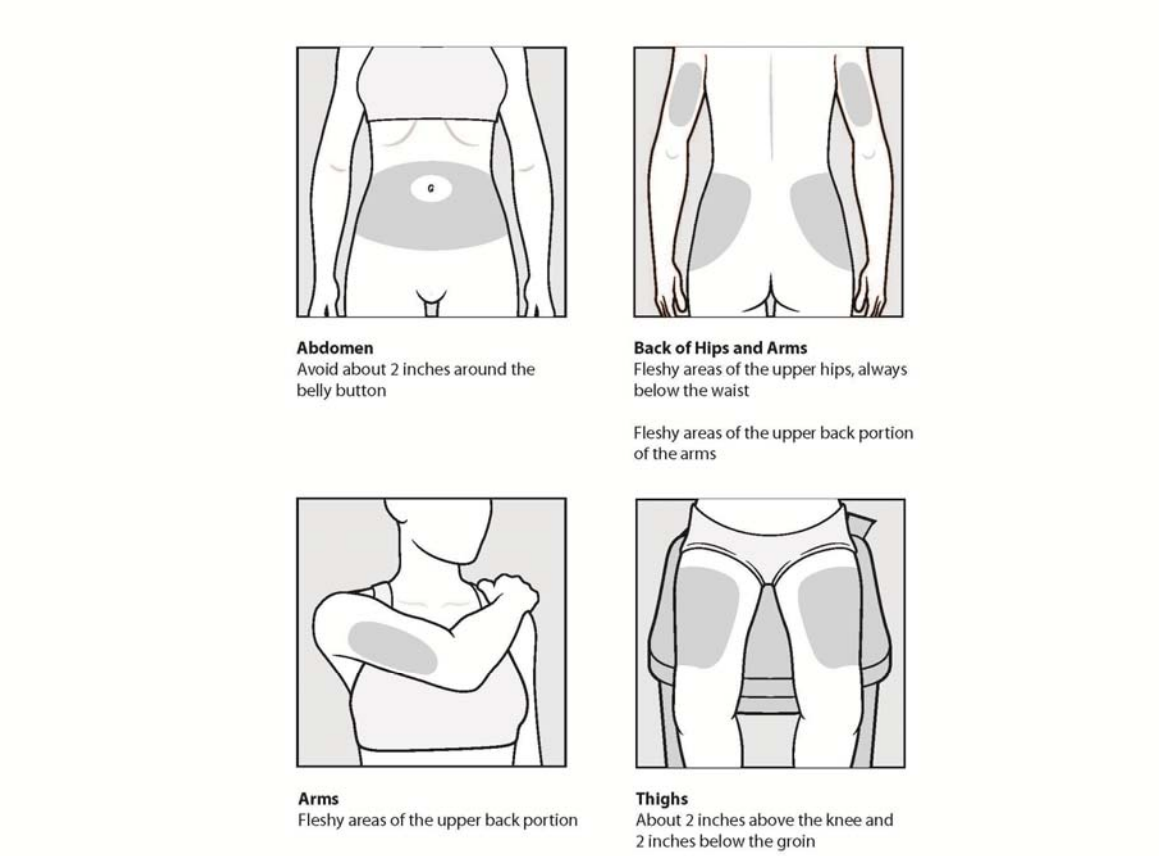


Figure C

- For each COPAXONE dose, choose a different injection area from 1 of the areas shown above. **See Figure C.**
- **Do not stick the needle in the same place (site) more than 1 time each week**. Each injection area contains multiple injection sites for you to choose from. Avoid injecting in the same site over and over again.
- Keep a record of the sites where you give your injection each day so you will remember where you already injected**.**

Step 5: Prepare to give your injection.

- There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.
- Do not inject in sites where the skin has scarring or "dents". Using scarred or dented skin for your injections may make your skin worse.

Step 6: Clean your injection site.

- Clean the injection site using the alcohol wipe and allow your skin to air dry. **See Figure D.**

Figure D

Step 7: Pick up the syringe with 1 hand and hold it like a pencil. Remove the needle cover with your other hand and set it aside. **See Figure E.**

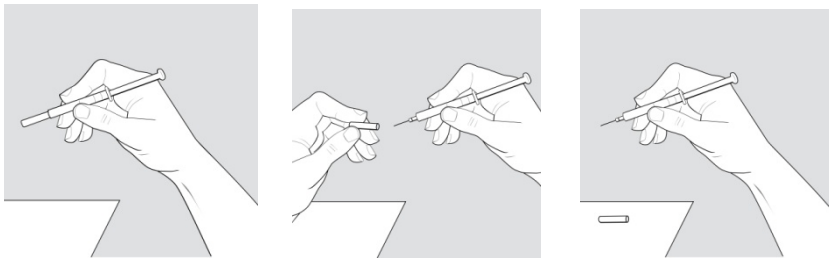


Figure E

Step 8: Pinch about a 2 inch fold of skin between your thumb and index finger. **See Figure F.**

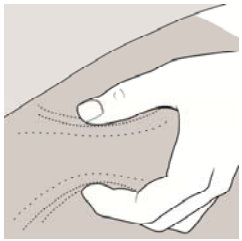


Figure F

Step 9: Giving your injection.

- Rest the heel of your hand holding the syringe against your skin at the injection site. Insert the needle at a 90 degree angle straight into your skin. **See Figure G.**

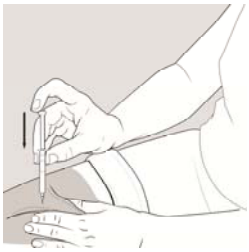


Figure G

- When the needle is all the way into your skin, release the fold of skin. **See Figure H.**

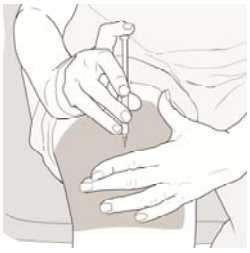


Figure H

Step 10: Give your COPAXONE injection.

To inject the medicine, hold the syringe steady and slowly push down the plunger. **See Figure I.**

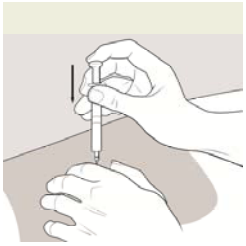


Figure I

Step 11: Remove the needle.

After you have injected all of the medicine, pull the needle straight out. **See Figure J.**

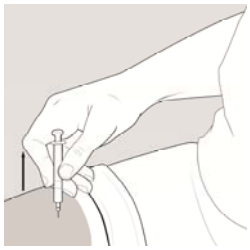


Figure J

Step 12: Use a clean, dry cotton ball to gently press on the injection site for a few seconds. Do not rub the injection site or re-use the needle or syringe. **See Figure K.**

Figure K

Step 13: Dispose of your needles and syringes.

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal .
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Figure L

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

[TEVA NEUROSCIENCE LOGO]

Marketed by: TEVA Neuroscience, Inc., Overland Park, KS 66211

Distributed by: TEVA Pharmaceuticals USA, Inc., North Wales, PA 19454

Product of Israel

Revised: January 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # Supplement #	20622/S-089
Applicant Name	Teva Pharmaceuticals
Date of Submission	3/29/13
PDUFA Goal Date	1/29/14
Proprietary Name / Established (USAN) Name	Copaxone/glatiramer acetate injection
Dosage Forms / Strength	40 mg per ml subcutaneous injection
Proposed Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jody Green, MD; Gerard Boehm, MD
Statistical Review	Sharon Yan, PhD
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	Kavita Vyas, PhD
Microbiology Review	Jessica Cole, PhD
Clinical Pharmacology Review	Xinning Yang, PhD
OPDP	Melinda McLawhorn, PharmD, BCPS
OSI	N/A
CDTL Review	John Marler, MD
OSE/DMEPA	Jacqueline Sheppard, PharmD
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	Twanda Scales, RN, MSN/Ed.
PMHS	Donna Snyder, MD
SEALD	Elizabeth Donohoe, MD
Other	N/A

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development

1. Introduction

Copaxone (glatiramer acetate; GA) is an approved drug product for reducing the frequency of relapses in patients with relapsing-remitting multiple sclerosis (RRMS).

Teva Pharmaceuticals (Teva) has submitted an efficacy supplement for a new dosage strength and regimen (40 mg per ml given three times per week) of GA. This new regimen is supported by the results of one primary randomized, double-blind, placebo-controlled trial in patients with RRMS known as GALA (study MS-GA-301). The GA9006 trial and the GA9016 trial (the latter known as FORTE) contribute additional safety data.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

GA was initially approved in 1996. It is currently indicated for the reduction of the frequency of relapses in patients with RRMS. The current marketed and labeled dose is a 20 mg subcutaneous injection administered daily.

(b) (4)

A pre-NDA meeting held on October 31, 2012, led to agreement with the sponsor that data from a single study, GALA, could be submitted as primary support for this efficacy supplement.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months at 5±3ºC (unchanged from approved 20 mg per ml product). There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

As discussed by Dr. Marler and Dr. Yang, immunogenicity data from a supportive study (GA9006) using a different dosing regimen than that used in the GALA study appears generally consistent with that described in currently approved labeling, but is not definitive. While not needed to support this application, immunogenicity results from the GALA study will be submitted and reviewed in the future. As agreed to at the pre-NDA meeting, no other pharmacokinetic or pharmacodynamic data were submitted with this application. After discussion with Dr. Yang concerning the submitted immunogenicity data, I concur with him that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As discussed by Dr. Marler, Dr. Green, and Dr. Yan, data supporting efficacy comes from the GALA trial. This was a randomized, double-blind, placebo-controlled, parallel-group trial of GA 40 mg three times per week in patients with RRMS, 461 on placebo and 943 on GA. The primary efficacy endpoint was the total number of confirmed relapses during the 12-month double-blind placebo-controlled treatment period. Secondary MRI measures (cumulative number of new/enlarging T2 lesions at Months 6 and 12 and cumulative mean number of Gd-enhancing lesions on T1-weighted images at Months 6 and 12) and various exploratory endpoints were also assessed. A detailed discussion of these findings is presented by the clinical reviewers and is summarized below.

	ARR	risk reduction compared to placebo	p-value
placebo	0.505		
GA	0.331	34%	< 0.0001

	T2 lesions	risk reduction compared to placebo	p-value
placebo	5.59		
GA	3.65	35%	<0.0001

	Gd T1 lesions	risk reduction compared to placebo	p-value
placebo	1.64		
GA	0.91	45%	<0.0001

Various sensitivity analyses of these outcomes were consistent and supportive.

Measurements of clinical disability “progression” and brain volume on MRI did not differ significantly between treatment groups.

This pattern of clinical and MRI results is consistent with that described in currently approved GA labeling for the 20 mg daily dose.

8. Safety

The safety profile of the currently approved formulation of GA is well established and described in labeling. Dr. Green, Dr. Boehm, and Dr. Marler present a thorough discussion of safety analyses related to the current submission. After careful consideration, there are no safety issues that appear unique to this formulation. In fact, injection site reactions and immediate post-injection reactions, the two major adverse events associated with the use of approved GA, actually occurred less often with the new regimen. Dr. Green theorizes that this may be due to the slightly reduced overall dose of the new regimen compared with the currently approved regimen. Overall, there are no new safety findings of significant concern.

9. Advisory Committee Meeting

N/A

10. Pediatrics

As this application proposes a new regimen, PREA is triggered. (b) (4) consistent with the Division's general approach to approved MS drugs, we will waive the requirement for pediatric studies in 0 to 9 year old pediatric patients and defer a required pediatric study in 10 to 17 year old pediatric patients as a postmarketing requirement.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The applicant has provided substantial evidence of effectiveness from the GALA trial, as supported by the known benefits and effects of approved Copaxone in a dose of 20 mg daily, for Copaxone in a dose of 40 mg three times per week as a treatment for relapsing forms of multiple sclerosis. There are no safety concerns that preclude approval. Given the consistency of clinical results between the new formulation and the currently approved formulation, the risk benefit assessment for the two formulations is similar.

Both a juvenile animal toxicology study and a study in pediatric MS patients aged 10 to 17 years are needed and will be conducted as postmarketing requirements.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of Copaxone 40 mg three times per week for the treatment of relapsing forms of multiple sclerosis.

For these reasons, I will issue an approval letter for this supplemental NDA, to include the agreed-upon product labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
01/28/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

OFFICER/EMPLOYEE LIST

NDA 020622/S-089
Copaxone (glatiramer acetate injection) for subcutaneous use
40 mg/ml three times a week

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Boehm, Gerard
Bradley, Nicole
Chan, Irene
Cole, Jessica
Donohoe, Elizabeth
Duer, Robin
Dunn, Billy
Green, Jody
Griffiths, LaShawn
Heimann, Martha
Holquist, Carol
McLawhorn, Melinda
Men, Angela
Riley, Bryan
Sachs, Hari
Scales, Twanda
Snyder, Donna
Yang, Xinning
Yasuda, Sally

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 19, 2014
From	John Marler, MD
Subject	Cross-Discipline Team Leader Review
NDA **Supplement** **Source Document**	NDA 020622 Efficacy Supplement 89 Number 1167
Applicant	Teva Pharmaceuticals
Date of Submission	March 29, 2013
PDUFA Goal Date	January 29, 2014
Proprietary Name / Established (USAN) names	Copaxone
Dosage forms / Strength	40 mg/mL, one milliliter in pre-filled syringe
Proposed Indication(s)	Relapsing Multiple Sclerosis
Recommended:	Approval

1. Introduction

The sponsor submits a supplement to an approved new drug application (NDA) to support the marketing of a new dosing strength of glatiramer acetate (Copaxone 40 mg/mL) for the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. Glatiramer acetate (GA) is approved for treating MS using GA with a dosing strength of 20 mg/mL.

The sponsor proposes to market the new dosing strength of GA for subcutaneous administration three times per week (TIW or thrice weekly) using prefilled syringes containing one milliliter of solution.

FDA first approved GA in 1996. FDA last approved revised prescribing information for the drug on March 8, 2013.

The review team for this NDA supplement included the following primary reviewers:

Chemistry – Kavita Vyas, PhD
Product Quality Microbiology – Jessica Cole, PhD
Clinical Pharmacology – Xinning Yang, PhD
Statistics – Sharon Yan, PhD
Clinical (Safety – Breast Cancer) – Gerard Boehm, MD
Clinical – Jody Green, MD
Pediatric and Maternal Health Staff (Pediatric) – Donna Synder, MD
Division of Medication Error Prevention and Analysis – Jacqueline Sheppard, PharmD
Division of Medical Policy Programs (Patient Labeling) – Twanda Scales, RN, MSN/Ed.
Office of Prescription Drug Promotion – Melinda McLawhorn, PharmD, BCPS
Study Endpoints and Labeling Development – Elizabeth Donohoe, MD

Summaries of the key conclusions of these reviewers are presented below with comments and further recommendations arising from this review.

2. Background

At a pre-NDA meeting on October 31, 2012, FDA agreed that, based on the preliminary topline results, the applicant could submit data from a single trial, the GALA trial, as substantial evidence of safety and effectiveness. Additional supporting evidence would be provided by the results of two other randomized controlled trials testing the GA 40 mg/mL dosage strength: the FORTE and GA9006 trials.

This sponsor proposes the same indication and patient population, but a different dosing strength and treatment regimen. The approved: dosage is GA 20 mg/mL, one mL daily, delivered subcutaneously via prefilled syringe. The proposed: dosage is GA 40 mg/mL, one mL three times per week, also via pre-filled syringe.

Glatiramer acetate is the acetate salt of a mixture of synthetic polypeptides composed of four amino acids, L-alanine, L-glutamic acid, L-lysine, and L-tyrosine with molecular weight from 4,700 to 13,000 daltons. GA suppresses or modifies experimental allergic encephalomyelitis in several species of mammals, possibly through cross-reactivity with myelin basic protein.

3. CMC/Device

No CMC issues are pending. Kavita Vyas, PhD and Jessica Cole, PhD reviewed the submission and found it acceptable.

The CMC primary reviewer is Kavita A. Vyas, Ph.D. No changes are proposed in the drug substance, excipients, or the container closure system for the pre-filled syringe. The manufacturing process for the 40mg/mL dosage strength is similar to

that for the approved strength product [redacted], [redacted]. [redacted] (v) change the container label, carton, and prescriber information labeling to include the proposed strength and dosing regimen.

The clinical trials to support the proposed strength were performed using drug substance produced using the approved process [redacted], and primary registration stability studies were conducted using drug substance produced using the proposed process [redacted] The evidence submitted shows consistency in quality (based on comparability of the release specifications) for batches produced by the approved and proposed processes.

[redacted]

The applicant revised the drug product release and stability specifications for the 40 mg/mL strength to match those approved for the 20 mg/mL strength in an amendment dated 12/18/13 to the supplement that is the subject of this review.

In summary, Dr. Vyas and her branch chief, Dr. Patel report that **no CMC issues are pending**, that the Office of Compliance rates the manufacturing site "Acceptable," that the microbiology reviewer recommends approval, and that the DMEPA reviewer, Jacqueline Sheppard, concludes that carton and container labels are acceptable. CMC review recommends approval.

4. Nonclinical Pharmacology/Toxicology

At the pre-NDA meeting, FDA agreed that the applicant did not need to submit any new non-clinical pharmacology or toxicology data. Instead, the application cross references the nonclinical data for the approved drug product for NDA 20622.

5. Clinical Pharmacology/Biopharmaceutics

As agreed at the pre-NDA meeting, the applicant submitted no additional pharmacokinetic or pharmacodynamic data in this efficacy supplement. The clinical pharmacology team focused their review on immunogenicity of the new 40mg per kg dosage strength.

The sponsor submitted immunogenetic data from a different trial, GA-0006, than the pivotal GALA trial that is the basis for the effectiveness claim. GA-0006 compared glatiramer acetate at a dose of one milliliter of GA 40 mg/mL injected once daily for 9-months to a one mL GA 20mg/mL daily dose in 46 and 44 RRMS patients, respectively. The pharmacology reviewer, Xinning Yang, Ph.D., notes the following problems with the immunology data from the GA-0006 trial: the once daily dosing regimen for 40 mg/mL GA in GA-0006 is different from the thrice weekly dose used in the GALA trial and described in the proposed label, the treatment period in GA-0006 differed from the 12-month period of the GALA trial, and the sponsor optimized but did not validate the anti-GA IgE antibodies used in analysis of the GA-0006 trial samples.

With these limitations in place, the applicant reports detecting anti-GA IgG antibodies in most patients in GA-0006. The GA 40mg/mL dosage strength yielded a higher peak antibody level, but the time course was similar. Peaks for both dosage strengths occurred near 3 months. The following table from the submission is copied from Dr. Yang's review:

Table 1 Number and percentage of the IgG responders in each treatment group at each tested time point of the treatment in trial GA-0006

GA-9006 Time Points	Treatment		
	GA 20mg	GA 40mg	Total
Screening	1 (2.3%)	0 (0.0%)	1 (1.2%)
Baseline	2 (4.5%)	1 (2.2%)	3 (3.3%)
Month 1	38 (86.4%)	44 (95.7%)	82 (91.1%)
Month 3	42 (97.7%)	41 (95.3%)	83 (96.5%)
Month 6	34 (91.9%)	39 (97.5%)	73 (94.8%)
Month 9	31 (83.8%)	29 (74.4%)	60 (78.9%)

The applicant reports detection of GA IgE antibodies in fewer GA 40mg/mL than 20 mg/mL subjects, and overall, the GA 40mg/mL group IgE antibody levels are lower than those for the 20mg group. In both groups the peak IgE levels occurred between one and six months.

Dr. Xinning Yang concludes that the results for IgG antibodies are generally in line with the description of immune response to 20 mg/mL GA in the current approved labeling. The pharmacology team recommends approval. They suggest that the applicant develop a validated assay for antibodies to GA and use the assay in the future to analyze the samples from the GALA study.

6. Clinical Microbiology

Not relevant for glatiramer acetate.

7. Clinical/Statistical- Efficacy

The primary clinical reviewer, Dr. Jody Green, recommends approval for the GA 40 mg/mL dosage strength. Dr. Sharon Yan, the statistical reviewer, agrees.

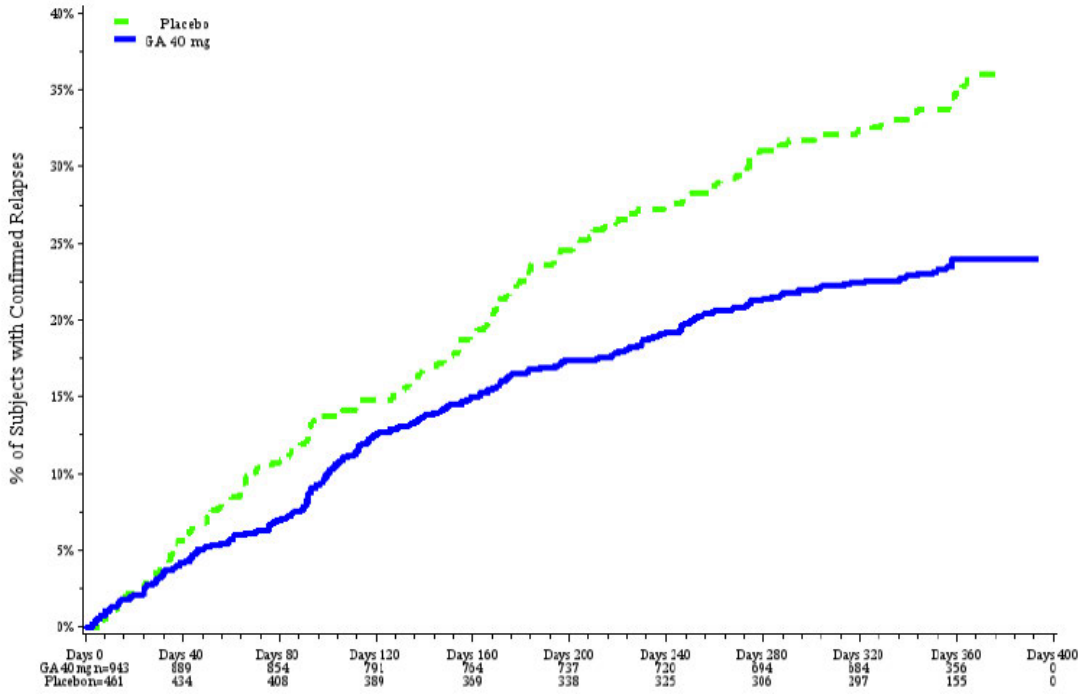
The pivotal GALA trial is a 1404-patient, double-blind, multi-national, randomized (2:1) trial that compares one mL of GA 40mg/mL given subcutaneously thrice weekly via prefilled syringes for one year to placebo. The GALA trial shows benefit for GA 40mg/mL on the primary and several secondary outcomes.

GALA includes relapsing MS patients, ages 18 to 55, with at least one documented T1 Gd-enhancing lesion in an MRI performed within 12 months prior to screening, with EDSS score of 0.0 to 5, and more than two MS attacks occurring in the prior 24 months and more than one MS attack in the prior 12 months. Analyses of baseline demographics and markers of disease severity do not show significant differences between the two treatment groups. The patients selected for the trial are typical of the population of MS patients in most relapsing MS trials. As in many other MS trials, US patients comprise a minority (6%) of GALA trial subjects.

Overall, the GALA trial protocol compliance is relatively good for MS trials with 93% and 91% completion rates for placebo and GA 40mg/mL. Mean treatment compliance rates are 99.3% and 98.5% for placebo and GA, respectively.

The primary outcome measure is the total number of confirmed relapses over twelve months. The sponsor reports this as an average number of relapses per patient estimated using the negative binomial regression. The primary analysis, as confirmed by Dr. Yan includes all 1404 randomized patients. The primary outcomes are 0.505 and 0.331confirmed relapses per patient per year for the placebo and GA groups, respectively. The risk ratio is 0.656. The p-value is less than 0.0001. See Figure 1, below.

Figure 1 Time to First Confirmed Relapse in GALA Trial



These values are compared to Study 2 results described in the current approved label for daily GA 20 mg/mL dosage strength in Table 2, below. Dr. Yan agrees that the results for the GALA trial are in line with those reported in the approved label for the GA 20mg/mL dosage strength.

Dr. Yan's estimates of the proportions of patients with no confirmed relapses for 12 months are 65.5% and 77.0% in the placebo and GA groups prospectively. Consistent with the reduced relapse rate there is a statistically significant reduction of the time to first confirmed relapse and a reduction the proportion of patients that had no relapses in 12 months. These two outcomes are not pre-specified primary or secondary outcomes.

Table 2 Clinical Outcomes for the GALA Trial and Trial 2 in the Approved Copaxone Label

	GALA Trial (40 mg/mL thrice weekly)		Trial 2 (20mg/mL daily)	
Outcome	**Placebo**	**GA**	**Placebo**	**GA**
ARR	.482	.322	.84	.59
ARR Risk Ratio		.656		.70
Proportion Relapse-Free (PRF)	65.5%	77.0%	34%	27%
PRF Benefit Ratio*		1.18*		1.26*
*calculated by CDTL reviewer				

The secondary endpoints are MRI measurements on scans performed at baseline, then 6 and 12 months after baseline. They are analyzed in a pre-specified order to address issues of multiplicity:

1. The cumulative number of new/enlarging T2 lesions at Months 6 and 12.
2. The cumulative number of T1 enhancing lesions at Months 6 and 12.
3. Percentage brain volume change from baseline to Month 12.

GALA results show statistically significant treatment effects on the number of T2 and T1-enhancing lesion counts. There is no significant effect on brain volume. The MRI Gd-enhancing lesion count data from Trial 4 on the approved label is presented in Table 3, below, for comparison with the GALA results. Note that the relative risk is similar for the three MRI outcomes.

Table 3 MRI Data from Gala Compared with MRI Data in Approved Label

Trial (Drug Dosage strength)	GALA Trial (40 mg/mL)		Trial 4 (20mg/mL)	
Outcome	**Placebo**	**GA**	**Placebo**	**GA**
Mean Cumulative NOE* T2 Lesions at Months 6 and 12	5.592	3.650		
Risk Ratio		.653		
Mean Cumulative Enhancing T1 Lesions at Months 6 and 12	1.939	0.905		
Risk Ratio		.552		.
Median Cumulative Gd-Enhancing T1 Lesions over 9 month			17	11
Risk Ratio*				0.65*
*computed by CDTL reviewer **new or enlarging				

The applicant performed analyses for a number of exploratory MRI outcomes. P-values uncorrected for multiplicity and less than 0.05 are reported for the following MRI measurements in the GALA trial:

Cumulative number of new/enlarging T1 hypointense at 6 and 12 months.
Volume of hypointense T1 lesions at 12 months
Cumulative number of new T2 lesions at 6 and 12 months.
Cumulative number of enlarging T2 lesions at 6 and 12 months
Volume of T2 lesions at 12 months

Estimates of brain volume are not significantly different for treatment groups.

Disability outcomes in GALA are Expanded Disability Status Score (EDSS) progression and Ambulation Index (AI).[1] These are exploratory outcomes that are not statistically significantly different. Confirmed progression of EDSS was defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, and by a 0.5 point increase from baseline on EDSS score if baseline EDSS was higher than 5.0, confirmed 3 months later. Progression could not be confirmed during a relapse.

[1] See definition of Hauser Ambulation Index in Appendix Table 10. This index takes values from 0 (normal walking) to 9 (bedridden).

There are no statistically significant differences between treatment groups for EDSS or AI disability outcomes in GALA. See Table 4, immediately below. This is consistent with the lack of any disability claims in the current approved label. Note that the mean change point estimate shows a slight, but not statistically significant, benefit for placebo treatment.

Table 4 Disability Exploratory Outcomes in GALA Trial

Disability Related Endpoints	Placebo N=461	GA 40 mg/mL TIW N = 943
Number with progression (%) Proportion from the logistic model Odds Ratio P-value	17 (3.7%) 3.0%	42 (4.5%) 3.5% 1.182 0.5726
EDSS Mean (Median) Change Estimate mean from ANCOVA P-value	0.1 (0.0)) 0.193	0.0 (0.0) 0.161 0.2449
Ambulation Index Mean (Median) Change Estimate mean from ANCOVA P-value	0.1 (0.0) 0.171	0.0 (0.0) 0.157 0.6339

Dr. Yan performed an analysis of primary GALA outcomes by region. The relapse risk ratio is 0.785 for the US compared to 0.647 for all other regions combined.

In conclusion, the GALA trial provides adequate well-controlled evidence of the effectiveness of glatiramer acetate 40mg/mL thrice weekly for reducing the rate of relapses in patients with relapsing multiple sclerosis. The differences correlate with pre-specified MRI outcome measures. There is no evidence of an affect on disability progression.

8. Safety

Dr. Green reviewed this submission and found no serious issues related to safety that might prevent approval. Because of six cases of breast cancer in the three trials submitted with the application, Dr. Gerald Boehm from the Division of Neurology Products Safety Team performed an in-depth review of the risk of breast cancer with GA.

As noted above, GA 20 mg/mL is approved since 1996 for use at a higher weekly dose than the GA 40 mg/mL dosage strength that is the subject of this submission for use three times per week (140 mg/week versus 120 mg/week). The drug has been prescribed for many thousands of patients in the 15 years since its approval. Safety issues are generally well defined. The primary safety concern is whether the higher concentration of GA 40 mg/mL causes an increase in some adverse events, particularly those related to immune responses.

Exposure

Estimates of safety for the GA 40 mg/mL dosage strength given TIW are based on two populations, Pool 1 and Pool 2.

Pool 1 is 2649 subjects in three double-blind trials. This pool includes all the subjects in the double-blind portion of the **GALA trial** described above in the efficacy section of this review. In addition it includes all the subjects in two other double blind trials. **Trial GA9006** compared GA 20 mg/mL daily to GA 40 mg/mL in 90 subjects with a primary MRI outcome. The results show a 38% reduction in T1-Gd-enhancing lesions in the GA 40 mg/mL treatment group. **Trial GA9016 (FORTE)**, like trial GA9006, compared GA 20 mg/mL daily to GA 40 mg/mL. FORTE is an 1155-patient, randomized (1:1), controlled, double blind trial that shows no significant difference in the mean number of relapses.

Pool 2 consists of 2258 subjects in open-label extension studies for the GALA FORTE trials.

The patients in Pool 2 are also in Pool 1. Hence the total exposures to GA of either dosage strength is 2649 minus the 461 placebo patients, or 2188. Of these, 1558 received some exposure to GA 40 mg/mL. See Table 5, below. In total 846 subjects were exposed to GA 40 mg/mL, either 3 or 7 times per week for at least one year.

Table 5 Exposure to GA in Pool 1 and Pool 2 for Safety Review

Pool	Dose	Patients Exposed	Years of Exposure	
			One Year or Less	More than 1 year
Pool 1	20 mg daily	630	575	0
	40 mg daily	615	540	0
	40 mg thrice weekly	943	875	0
	Placebo	461	438	0
	Total	2649	2428	0
Pool 2	40 mg thrice weekly	1253	282	572
	40 mg daily	1005	395	274
	Total	2258	677	846

The safety population is adequate, especially in light of the fact that the currently widely marketed dose is actually higher than the dose evaluated in this review, the fact that there is extensive and long-term experience with the drug substance, and relatively low loss to follow-up during the double-blind trials.

Deaths

In Pool 1, randomized trials, two deaths are reported: one, an sudden cardiovascular death in the placebo group, and the other, the result of a motorcycle accident, in the GA 40mg/mL daily group. Neither of these had a clear relation to GA. One death occurred in Pool 2 in a 40-year-old male who took GA 40 mg/mL thrice weekly for 489 days prior to his death. The cause of this death is undetermined. The most likely explanation is acute heart failure because of his history of obesity, smoking, and MI at age 26. Dr. Green concludes that myocardial infarction does not belong in the prescribing information and that none of the deaths are likely to have been caused by GA.

Serious adverse events

The point estimate of the rate of serious adverse events is slightly lower with GA than placebo for all the dosages in Pool 1 (See Table 6, below). In Pool 2 there are fewer adverse events with thrice weekly GA 40mg/mL than either GA 40mg/mL qd or GA 20mg/mL given daily.

Overall, 4.3% of Pool 1 subjects had SAEs.

Table 6 Serious Adverse Events in Pool 1: Placebo-Controlled Trials

Serious Adverse Events						
Treatment group / Category	Placebo	GA Total	GA 20 daily	GA 40mg daily	GA 40 mg TIW	Total
Number of subjects	461	2188	630	615	943	2649
SAEs all severity	43	165	44	49	72	208
Individuals with SAEs	21	94	26	26	42	115
% Subjects with SAE	4.6%	4.3%	4.1%	4.2%	4.5%	4.3%
Mean SAEs per subject	2.0	1.8	1.7	1.9	1.7	1.8

In Pool 1, 1.2% and 1.0% of individuals taking GA 40mg TIW have SAEs in the infection and nervous system disorders SOC (System Organ Class) categories, respectively. The corresponding percentage of placebo-treated subjects in Pool 1 with SAEs in these categories is 0.6% and 0.6%. The incidence of malignancies in the placebo group is higher than for all other treatment groups in Pool 1. However, there are three cases of breast cancer in GA-treated subjects from the FORTE (GA-9016) trial that are discussed in more detail below.

Table 7, below, from Table 27 in Dr. Green's review lists SAEs by MedDRA System Organ Class (SOC).

Table 7 Table of All Serious Adverse Events in Pool 1 by SOC From Dr. Green's Review. The table is sorted by decreasing order of percent of GA 40 mg/mL TIW subjects. The two most common SAE events and malignancies are highlighted in blue.

Primary System Organ Class r number of SAE n number of subjects % of subjects	GA 20 mg/day N = 630			GA 40 mg/day N = 615			Placebo TIW N = 461			GA 40 mg TIW N = 943		
	r	n	(%)	r	n	(%)	r	n	(%)	r	n	(%)
Any class	44	26	4.1%	49	26	4.2	43	21	4.6	72	42	4.5
Infections and infestations	4	4	0.6	3	2	0.3	4	3	0.7	15	11	1.2
Nervous system disorders	4	4	0.6	7	7	1.1	5	3	0.7	11	9	1.0
Gastrointestinal disorders	4	3	0.5	5	3	0.5	1	1	0.2	4	4	0.4
Hepatobiliary disorders	2	2	0.3	1	1	0.2	1	1	0.2	4	4	0.4
Skin and subcutaneous tissue disorders	0	0	0	2	2	0.3	1	1	0.2	6	4	0.4
Musculoskeletal and connective tissue disorders	3	3	0.5	1	1	0.2	0	0	0	5	3	0.3
Neoplasms benign, malignant and unspecified	5	4	0.6	1	1	0.2	2	2	0.4	1	1	0.1
Psychiatric disorders	1	1	0.2	3	2	0.3	0	0	0	3	2	0.2
Ear and labyrinth disorders	2	2	0.3	0			0			2	2	0.2
General disorders and administration site conditions	2	2	0.3	4	4	0.7	1	1	0.2	2	2	0.2
Surgical and medical procedures	5	4	0.6	1	1	0.2	4	4	0.9	2	2	0.2
Immune System disorder	1	1	0.2	3	3	0.5	0	0	0	2	2	0.2
Eye Disorders	0	0	0	0			0	0	0	1	1	0.1
Metabolism and nutritional disorders	0	0	0	1	1	0.2	0	0	0	2	1	0.1
Cardiac disorders	1	1	0.2	5	4	0.7	3	3	0.7	5	2	0.2
Vascular disorders	2	2	0.3	0	0	0	0	0	0	1	1	0.1
Renal and urinary disorders	1	1	0.2	0	0	0	7	2	0.4	1	1	0.1
Pregnancy, puerperium and perinatal conditions	0	0	0	1	1	0.2	2	2	0.4	1	1	0.1
Reproductive system and breast disorders	1	1	0.2	0	0	0	2	2	0.4	1	1	0.1
Injury, poisoning and procedural complications	5	2	0.3	3	2	0.3	7	3	0.7	2	1	0.1
Respiratory, thoracic and mediastinal disorders	1	1	0.2	5	5	0.8	2	1	0.2	0	0	0
Investigations	0	0	0	3	1	0.2	1	1	0.2	1	1	0.1

SAEs are less frequent in Pool 2, the open-label extension trials. There were 51 patients with SAEs, or 2.3% compared to 4.3%. Again, infections and nervous system

disorders are most common at 0.2% and 0.4%, respectively. There is no placebo group for comparison.

The serious infections in both pools had diverse causes and no particular infectious agent predominated. Dr. Green looked into a possible case of tuberculosis but determined that it is not likely related to GA treatment. There is a slight excess in the rate of infections with GA. 1.2% of subjects on GA 40mg/mL compared to 0.7% of subjects on placebo in the GALA trial had SAEs caused by infections. These SAEs are consistent with the information on the approved label.

The rate of serious nervous system disorder adverse events is 1.0% in GA 40mg/mL thrice weekly compared to 0.7% in placebo subjects in the GALA trial. The most common serious neurological event is MS relapse: 0.5% in the GA tiw group and 0.2% in the placebo group. The rate of serious neurological events appears to be no greater than that already in the approved label for the 20mg/mL preparation.

Dr. Green reviews the most of the remaining serious adverse events on pages 71 to 104 of her review. Other than immediate post-infusion reactions (IPIRs), no SAEs are clearly related to GA. She reviews some serious adverse events as adverse events of special interest.

Adverse Events of Special Interest

By agreement with the applicant some pre-specified adverse events were selected for detail evaluationl. These events include breast cancer, embolic and thrombotic events, hepatitis and liver injury, lipoatrophy, hypersensitivity reactions, and thrombocytopenia.

There are 6 cases of possible *breast cancer* reported in the three trials submitted with this application: three in controlled trials and three in extension trials. Breast cancer is not named as a risk in the current approved label for GA 20mg/mL. However, Dr. Green, using Empirica Signal, noted several postmarketing reports of breast cancer and because three cases are reported in the GA 9016 trial, she requested a safety team evaluation of a link between GA and breast cancer.

Dr. Gerald Boehm reviewed the breast cancer cases that occurred during the three trials. He notes that there are three cases of breast cancer detected during the double-blind portion of the GA 9016 trial (there is no placebo group). Two of the three cases are in the 20mg/mL qd group; one in the 40 mg/mL qd group. There are three cases of breast cancer reported in Pool 2, the open-label extension trials. Two of the cases are in the GA 40mg/mL qd treatment group and two cases are in the GA 40mg/mL tiw group.

The small samples of Pools 1 and 2 prevent accurate estimates of breast cancer incidence rates. The trials did not screen for evidence of cancer before randomization.

Three of the six index cases had only 6 month exposures to GA, which suggests that the cancer may have been pre-existing. Because of difficulties comparing the GA trial populations with standard reference populations, Dr. Boehm found it most relevant to compare breast cancer rates in other MS trials. Using this reference database, he concludes that "the data provide some comfort in that for similar exposure and observation periods, the observed risk with Copaxone is comparable to the risk with other recently reviewed MS treatments." He recommends no regulatory action.

Embolic and thrombotic events have special interest because of their presence in post-marketing reports. There is no mention of these events in the current approved label for 20 mg/mL. There are 10 subjects in Pool 1 and 5 in Pool 2 with possible embolic or thrombotic events. See Dr. Green reviewed each of the cases and often found other possible causes such as cardiovascular risk factors or ambiguous symptoms without confirmatory objective evidence. Her conclusion is that there is no evidence of a relationship between GA and the occurrence of thrombotic and embolic events.

Table 8 Embolic and Thrombotic Events in Pool 1

Embolic and thrombotic events						
Treatment group / Category	Placebo	GA Total	GA 20 daily	GA 40mg daily	GA 40 mg TIW	Total
Number of subjects	461	2188	630	615	943	2649
Individuals with Embolic or Thrombotic Events	1	10	4	3	3	115
Percent with Events	0.2%	0.5%	0.6%	0.5%	0.3%	0.4%

Dr. Green finds no evidence that GA causes significant *hepatitis or liver injury*. There is one case that may have met some of the Hy's law criteria for predicting drug-induced liver injury (DILI) [3-fold or greater elevations above the upper limits of normal (ULN) for ALT or AST: AST=347 and ALT=577]. Serum total bilirubin (TBL) is 25 μmol/L and at 1.1xULN does not meet the 2 x ULN criterion. Alkaline phosphatase is not reported. Other drug exposures are steroids including estrogen birth control pills. A gastroenterologist diagnosed drug-induced liver dysfunction. The patient stopped taking GA and liver function tests returned to normal. Dr. Green does not find the attribution to GA entirely convincing because of concomitant medications associated with DILI. "Liver damage," "hepatitis," and "hepatomegaly," and "liver function abnormality" are listed in the approved label for the 20 mg/mL dosage strength.

The higher concentration of GA 40 mg/mL may increase *hypersensitivity reactions* even though the total dose per week is lower. Dr. Green reviews each of the 12 serious hypersensitivity reactions in Pool 1 patients. She finds no reason to conclude that the higher concentration produced more hypersensitivity reactions. There are 4 reported cases of anaphylaxis Dr. Green considers likely related to treatment with GA. Two of the four cases are in the GA 40 mg/mL tiw group. She concludes that the new 40mg/mL dosage strength is unlikely to produce more hypersensitivity or anaphylactic reactions than the approved product.

Hypersensitivity and Anaphylaxis Events						
Treatment group / Category	**Placebo**	**GA Total**	**GA 20 daily**	**GA 40mg daily**	**GA 40 mg TIW**	**Total**
Number of subjects	461	2188	630	615	943	2649
Individuals Hypersensitivity (includes anaphylaxis)	2 0.4%	21 1.0%	4 0.6%	10 1.6%	7 0.7%	23 .9%
Individuals with confirmed anaphylaxis	0 0.0%	4 0.2%	1 0.2%	1 0.2%	2 0.2%	4 0.2%

Injection site reactions overall are the most common adverse event in the GALA trial. *Lipoatrophy* is one of the most permanent of the skin reactions. None of the 26 cases reported is severe. Two subjects stopped taking the study treatment because of lipoatrophy. The mean time to from start of treatment to the report of atrophy is approximately 228 days.

Pool 1 Injection Site Reactions and Lipoatrophy						
Treatment group / Category	**Placebo**	**GA Total**	**GA 20 daily**	**GA 40mg daily**	**GA 40 mg TIW**	**Total**
Number of subjects	461	2188	630	615	943	2649
Individuals with Injection Site Reactions	23 5.0%	1056 48.3%	361 57.3%	363 59.0%	332 35.2%	1079 40.7%
Individuals with Injection Site Skin	0	26	7	14	5	26

Atrophy	0.0%	1.2%	1.1%	2..3%	0.5%	1.0%
Individuals discontinued study treatment early due to injection site reactions	0%		1.6%	4.2%	1%	
Individuals who discontinued study treatment for any reason	31 6.7%	246 11.2%	69 11%	93 15.1%	84 8.9%	277 10.5%

Immediate Post-Injection Reaction (IPIR) is a syndrome consisting of two or more of the following symptoms: flushing, chest pain, palpitations, anxiety, dyspnea, throat tightness, and urticaria. The current label describes IPIR in 16% of clinical trial subjects treated with GA and in 4% of those treated with placebo. Perhaps consistent with the low dose, only 1.5% of subjects in the GALA trial on GA 40 mg/mL TIW show IPIR compared to none in the placebo group. In her review, Dr. Green concludes that there are fewer IPIR events in the GALA trial than described in the approved label and that the lower incidence may relate to the dose.

Thrombocytopenia, another AE of special interest, occurs in two Pool 1 patients: One in the GA 20 mg/mL qd group and one in the GA 40 mg/mL TIW group. The low platelet count resolved spontaneously in both cases without treatment or stopping GA.

The current label warns that chest pain with no clinical sequelae is associated with GA 20 mg/mL. In the GALA trial, some form of *chest pain* occurred in 17 (1.7%) subjects in the GA 40 mg/mL TIW treatment group and 0.9% of subjects in the placebo group. This incidence is much lower than that observed in other Pool 1 subjects treated with GA 20 mg/mL qd (8.8%) and GA 40 mg/mL qd (8.0%). In the 5 trials on the approved label the incidence of chest pain is 13% for the GA groups and 6% for the placebo groups.

Dr. Green observes that the chest pain has short duration and no sequelae, consistent with the approved label. The reason for the lower incidence in the GALA trial is unknown.

Discontinuations due to adverse events

The discontinuations in Pool one is described below in Table 9. The discontinuations in Pool 2 are similar. For GA 40 mg/mL, the percentage of all subjects who discontinued treatment is 8.9%. Of these, approximately one third or 3.1% withdrew from treatment because of AEs, primarily injection site reactions.

Table 9 Discontinuation Due to Adverse Events in Pool 1 Patients

Pool 1 Discontinuations Due to Adverse events						
Treatment group / Category	Placebo	GA Total	GA 20 daily	GA 40mg daily	GA 40 mg TIW	Total
Number of subjects	461	2188	630	615	943	2649
Individuals Who Discontinued Study Treatment Because of AEs	6 1.2%	117 5.3%	31 4.9%	57 9.3%%	29 3.1%	123 4.6%
Individuals who discontinued study treatment for any reason	31 6.7%	246 11.2%	69 11%	93 15.1%	84 8.9%	277 10.5%

In her review, Dr. Green comments that the only AEs leading to discontinuation in more than 1% of the subjects in their treatment group are shown in Table 10, below.

Table 10 Discontinuations Due to AEs in Pool 1 by GA dosage/dosage strength

AE	GA 40 mg/mL qd	GA 20 mg/mL qd	GA 40 mg/mL tiw
Injection site erythema	1.8%	0.5%	0.3%
Injection site pain	1.0%	0.6%	0.4%
Dyspnea	1.1%	0.8%	0.1%

Narratives describing the course for each of the subjects who discontinued treatment suggest that the GA 40 mg/mL dosage strength may have fewer injection-related side effects than either the GA 20 mg/mL qd or GA 40 mg/mL TIW dose.

Common adverse events

Table 11, below, (Table 80 from Dr. Green's review) shows common adverse events during Year 1 of the GALA trial, the only placebo controlled trial that compares the GA 40 mg/mL dosage strength to placebo. The table lists all AEs that occurred with incidence 2% greater on GA 40 mg/mL TIW than the incidence on placebo.

The AEs in the GALA trial are similar to those already in the approved label for the GA 20 mg/mL approved product. All AEs are adequately characterized in the current approved label.

Table 11 Adverse Events During Placebo Phase of GALA Trial with Incidence on GA 40 mg/mL TIW ≥2% More Than On Placebo

SOC	Preferred Term	GA 40 mg/mL TIW (N=943)	Placebo (N=461)
General Disorders And Administration Site Conditions	Injection Site Erythema	22%	2%
	Injection Site Pain	10%	2%
	Injection Site Mass	6%	0%
	Injection Site Pruritus	6%	0%
	Injection Site Edema	6%	0%
	Pyrexia	3%	2%
	Influenza Like Illness	3%	2%
	Injection Site Inflammation	2%	0%
	Chills	2%	0%
	Chest Pain	2%	1%
Infections And Infestations	Nasopharyngitis	12%	9%
	Respiratory Tract Infection Viral	3%	2%
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	3%	0%
Vascular Disorders	Vasodilatation	3%	0%
Gastrointestinal Disorders	Nausea	2%	1%
Skin And Subcutaneous Tissue Disorders	Erythema	2%	0%
	Rash	2%	1%

Laboratory tests

Dr. Green reviewed the few cases of abnormal laboratory tests reported as SAEs and concluded that most can be related to the subjects' prior medical history and are unlikely related to GA. Others are associated with adverse events discussed for other SOCs, such as liver injury. The current label adequately describes adverse events identified as laboratory findings (SOC: Investigations).

Vital Signs

Hypertension is an SAE for two subjects on GA 40 mg/mL in the GALA trial. Both had histories of hypertension. A fever in one GALA subject is attributed to a hypersensitivity reaction presumably caused by injection of GA. Overall, any effect of GA 40 mg/mL on vital signs is not apparent.

Immunogenicity

The immunogenicity of GA is poorly understood, presumably because of the inherent complexity of the drug substance. As noted above in the section on clinical pharmacology the results of the immunogenicity testing do not indicate any significant potential problems.

Special safety concerns

There are no special safety concerns that relate to approvability. There are adverse events of special interest, but careful evaluation showed no need for concern.

Discussion of primary reviewer's comments and conclusions

All primary reviewers are aligned in their recommendations for approval.

9. Advisory Committee Meeting

N/A.

10. Pediatrics

The Division of Neurological Products requested assistance from the Pediatric and Maternal Health Staff (PMHS) to assist with paperwork required by the Pediatric Review Committee. Donna Snyder, MD, from PMHS attended team meetings, assisted with the preparation of paperwork for PeRC, and made recommendations.

Copaxone 40 mg/mL was discussed at a PeRC/PREA Subcommittee meeting on December 4, 2013. The Division presented a request for partial waiver for patients 0-9 years and deferral for patients 10 to 17 years of age because the product is ready for approval in adults before pediatric studies have been completed. PeRC agrees with the Division and recommends that the Division of Neurology Products determine whether a juvenile toxicology study is required, and, if not, accelerate the start of clinical studies. After the meeting, the DNP pharmacology/toxicology team determined that a non-clinical pediatric toxicology study is needed.

The following language is being considered:

> Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.
>
> We are waiving the pediatric study requirement from birth to nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

2114-1 A randomized, controlled, parallel group superiority study in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of glatiramer acetate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Final Protocol Submission:	09/2017
Study Completion:	08/2020
Final Report Submission:	12/2021

2114-2 A juvenile animal toxicology study in rats to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development.

Final Protocol Submission:	02/2015
Study Completion:	11/2016
Final Report Submission:	01/2017

11. Other Relevant Regulatory Issues

None.

12. Labeling

The sponsor submitted proposed labeling. See the separate labeling document for the labeling negotiated with the sponsor. Liu Liu, PharmD, reviewed the proposed trade name, Copaxone, and found it acceptable.

Jacqueline Sheppard, PharmD, evaluated the revised syringe label, blister pack labeling, and carton labeling for Copaxone. She concludes that the revised labels and labeling are acceptable.

Twanda Scales, RN, and Melinda McLawhorn, PharmD, reviewed patient labeling labeling and found the Patient Package Insert and the Instructions for Use acceptable with their recommendations which have been accepted by the sponsor.

Melinda MacLawhorn, PharmD, reviewed the prescribing information (PI) and provided comments which are incorporated in FDA-recommended revisions to the PI and accepted by the sponsor.

13. CDTL Recommendations/Risk Benefit Assessment

Agreeing with the entire review team, I recommend approval for the new 40 mg/mL dosing strength of Copaxone for administration three times per week.

There is strong evidence of effectiveness and safety from a single adequate and well-controlled clinical trial that confirms relative benefit of the GA 40 mg/mL dosage strength at a dose of 1 mL by prefilled syringe three times per week. The consistency of the results of the GALA trial with the original trials that supported approval of the 20 mg/mL dosage is reassuring.

Previous experience with use of GA 20 mg/mL to treat MS at a more frequent dose and cumulatively higher dose has demonstrated a relatively low risk during the fifteen or more years of post-marketing experience. The GALA trial of the new 40 mg/mL dosage strength confirms previous trials of GA 20 mg/mL that demonstrate a reduction in relapse rates. The applicant has not provided evidence to demonstrate that either GA 20 mg/mL daily or GA 40 mg/mL TIW reduce MS disability. These benefits of GA, although limited, more than balance the minor risks associated with the drug.

The applicant has submitted no evidence that allows an adequate comparison of the effectiveness or safety of the two dosages of the drug,

The results of the pre-specified primary and the two positive MRI secondary outcomes from the pivotal GALA trial should be added to the clinical section of the Prescribing Information in order to maintain consistency with the information from the four clinical trials in most recent approved label for the 20 mg/mL dosage strength.

A nonclinical toxicology study and clinical pediatric development program in patients 10-17 years of age will be required. No additional post-marketing requirements are needed.

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/s/

JOHN R MARLER
01/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA-089
Application Number(s)	020622
Priority or Standard	Standard
Submit Date(s)	March 29, 2013
Received Date(s)	March 29, 2013
PDUFA Goal Date	January 29, 2014
Division / Office	OND-I/DNP
Reviewer Name(s)	Jody E. Green, MD.
Review Completion Date	December 6, 2013
Established Name	Glatiramer Acetate
(Proposed) Trade Name	COPAXONE
Therapeutic Class	Immunomodulator
Applicant	Teva Pharmaceuticals
Formulation(s)	40 mg per 1mL
Dosing Regimen	Three times a week SQ
Indication(s)	Multiple Sclerosis
Intended Population(s)	Ages 18-65

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

Copaxone is currently approved as a daily injection of 20 mg/mL. This application presents new data on a new dosage of Copaxone 40 mg/mL three times a week. This reviewer recommends approval of Copaxone 40 mg/mL three times a week for treatment of the relapsing forms of multiple sclerosis. The clinical data supports the conclusion that Copaxone 40 mg/mL three times a week is both safe and effective. In addition, Copaxone 40 mg/mL administered three times a week by subcutaneous injection compares favorably from a safety perspective to the approved product, Copaxone 20 mg/mL/day. The overall risk to benefit ratio is acceptable.

1.1 Recommendation on Regulatory Action

The sponsor demonstrated in this application substantial evidence in an adequate and well-controlled trial that Copaxone 40 /mL three times a week is safe and effective and should be approved. In addition, the indication for the product can be modified. Previously the product had demonstrated efficacy for patients with relapsing remitting multiple sclerosis (RRMS) as well as for those with a first clinical episode and MRI features consistent with disease. This can be broadened to an indication of treatment of the relapsing forms of multiple sclerosis to conform to other immunomodulators with similar benefits.

1.2 Risk Benefit Assessment

The single pivotal trial, GALA, was a placebo-controlled, double-blind prospective multinational year-long trial followed by an open-label on-going extension phase. In the controlled trial 943 subjects on Copaxone 40 mg three times a week were compared to 416 subjects on placebo three times a week. A robust treatment effect was seen on the primary outcome, the annualized relapse rate ($p < 0.001$). Multiple sensitivity analyses of the primary endpoint such as the completer's population, the evaluable population, those with confirmed and unconfirmed relapses, and those with missing data were performed; all groups showed statistically significant benefits. Two of the three secondary endpoints provided supportive confirmatory evidence. The two confirmatory endpoints included the cumulative number of new or enlarging T2 lesions at months 6 and 12 and the cumulative number of enhancing lesions on T1-weighted images taken at months 6 and 12 (both $p<0.001$). The study was well controlled, withdrawal rates were low, and the subjects were well matched for baseline demographics and clinical characteristics. Although the primary endpoint and secondary endpoints demonstrated for Copaxone 40 mg three times a week cannot be compared directly to the marketed product in the trials submitted, Copaxone 20 mg/day, when compared across separate controlled trials, appears comparable to the marketed product.

The sponsor proposes marketing Copaxone 40 mg three times a week in addition to Copaxone 20 mg/day. The current study indicated that serious SAEs were no greater on the new product than the marketed product, nor than placebo. No new toxicities of Copaxone have been identified. The major toxicities of Copaxone previously identified are adverse events related to injection site reaction (ISR) and immediate post-injection reaction (IPIR), and these occurred less frequently on the new formulation than on the marketed product. Overall, Copaxone 40 mg three times a week appeared to have comparable effectiveness to the marketed product with less associated adverse events.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

As discussed with PeRC two postmarketing requirements are recommended:

- A juvenile animal toxicology study in rats to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development.

- A randomized controlled parallel group superiority trial in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of Copaxone compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

2 Introduction and Regulatory Background

Multiple Sclerosis (MS) is a chronic and potentially progressive inflammatory demyelinating illness of the central nervous system. It remains the most common causes of disability in young adults. Approximately 2.5 million people suffer from the disease worldwide and more than half are in the temperate climates of Europe. The prevalence and incidence of MS is not uniform in Europe and varies between different ethnic populations; MS is noted to be greatest at the northern latitudes. The prevalence of the disease has been noticed to increase over time from past estimates and is higher in females than males (average prevalence 1.6 to 3:1 ratio).[1]

For many patients the disease is characterized by recurrent “relapses” or neurological symptoms that occur with variable recovery between attacks. Attacks may affect the optic nerve, brain, or spinal cord. Approximately 85% of patients initially present with a

1 Kingwell E, Marrriott JJ, Pringsheim T, Makhani N, Morrow SA, Fisk JD, Evans C, Beland SG, Kulaga S, Dykeman J, Wolfson C, Koch MS, Marrie RA, Incidence and Prevalence of MS in Europe: a Systematic Review, BMC Neurolo 2013 Sep 26; (1):128.

relapsing form of MS and are treated with various immunomodulatory medications. Current choices of therapy include drugs which are oral or parenteral and which are used with different frequency. Copaxone is the only subcutaneous medication for this condition and it is currently used daily. After 15 to 20 years with this condition, many develop a progressive form of the illness known as secondary progressive multiple sclerosis with increasing disability such as difficulty with ambulation.

Relapsing MS is associated with the activation of specific T cells directed against myelin antigen as well as B cells that enter the CNS. Breakdown of the blood-brain barrier (BBB) causes an influx of inflammatory T cells into the CNS which is followed by an influx of B cells, antibodies and macrophage; early neuropathologic findings include axonal damage as a result of inflammation and demyelination. White and gray matter damage are seen which contribute to the burden of disease.

2.1 Product Information

Glatiramer Acetate (GA), the active ingredient of Copaxone, consists of the acetate salts of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine in fixed proportion arranged randomly in molecules with average molecular weight ranging from 5,000 to 9,000 Dalton. It resembles myelin basic protein (MBP), and is otherwise known as Copolymer-1 and COP-1. The marketed dose is Copaxone 20 mg/mL as a subcutaneous injection once daily. The solution for injection is in a pre-filled syringe which contains 20 mg GA and 40 mg mannitol in water for injections. The excipients used in the manufacturing of Copaxone 40 mg/mL are the same compendial excipients used for the marketed product, GA Injection 20 mg/1 mL as demonstrated in Table 1.

Copaxone was first approved in Israel in November, 1996 and subsequently approved in the US on December 20, 1996 as an orphan drug. Thereafter, the drug was approved in many of the European Union countries. Copaxone is currently viewed as a first-line immunomodulatory product for the treatment of relapsing remitting multiple sclerosis (RRMS) to decrease the frequency of relapses. It is the brand name for GA which is currently approved in a dosage of 20 mg/1 mL subcutaneously (SC) daily. Since Copaxone's approval, more than one million patient-years of exposure to the drug have taken place worldwide and the drug is currently registered in 54 countries.

Table 1 Drug-product composition

Raw Material	Quantity per Dosage Unit	Unit	Function	Reference to Standard
Active Ingredient				
Glatiramer Acetate (GA)	40.0[1]	mg	Active	In-house specification
Other Ingredients				
Mannitol	40.0	mg	(b) (4)	
Water for Injection(s)	q. s. to 1.0[2]	mL		

(b) (4)

Module 3.2.P.1 sponsor Table 1 Supplement 089

The current application is for new dose strength of Copaxone available in a 40 mg/mL pre-filled syringe intended for injection three times a week SC and is referred to as GA 40 mg TIW throughout this application. The new product is based on the formulation of the marketed 20 mg/mL injection which will be referred to as GA 20 mg/day throughout the application; the only difference in formulation is dose strength which results in a solution that is double the concentration of GA. The product is prefilled in a colorless glass barrel fitted with a (b) (4) needle and stoppered with a (b) (4) plunger (b) (4). The (b) (4) components are:

- (b) (4)

All of these components are described in the latest revision of the (b) (4) dated September 12, 2011 and were submitted in the past to the FDA Central Document Room. The sponsor has certified that the material will be manufactured in accordance with methods previously referenced in the above document. In addition a (b) (4) (b) (4) dated September 15, 2010. (b) (4) was authorized on August 7, 2012 for (b) (4) for the use with the product. The drug product was authorized with (b) (4) on December 28, 1996.

2.1.1 Copaxone Autoinjector

Copaxone is delivered using the currently approved autoinjector, a non-sterile, fully automatic FDA approved device, for prescription only, under number KO13362. It is produced by Owen Mumford and is approved in the US under 510(k) and can hold the 1 mL syringes filled with medication.

2.2 Tables of Currently Available Treatments for Proposed Indications

MS Drug	Indication	Effect on relapse rate	Effect on disability progression	Approved dose
Avonex (RMS)	Decreases relapses, slow physical disability	32% reduction	37% reduction	30 mcg IM qweek
Betaseron (RMS)	Decreases relapses	30% reduction	No claim	0.25 mg SC qod
Rebif (RMS)	Decreases relapses, delay physical disability	22 mcg 29% reduction 44 mcg 32 % reduction vs. placebo and Avonex*	27% reduction	22 mcg or 44 mcg tiw
GA (glatiramer acetate) (RMS)	Reduce relapses including patients with CIS	75% reduction in first trial (n=48) 29% reduction in second trial (n=251)	No claim	20 mg SC qday
Mitoxantrone (SPMS or worsening RRMS)	Reduce neurologic disability and/or relapses	60% reduction; Primary outcome: 86% reduction in new enhancing lesions	64% reduction	12 mg/m^2 IV q3 months
Tysabri (natalizumab) (RMS)	To delay physical disability and reduce relapses	61% reduction	33% reduction	300 mg IV q 4 weeks
Gilenya (fingolimod) (RMS)	Decrease ARR and reduce disability progression	54% reduction	30% reduction	0.5 mg PO q day
Teriflunomide	Treatment of RMS	32% reduction	26% reduction 14 mg	7 mg or 14 mg q day
Tecfidera	Treatment of RMS	44-53 % reduction	21-38% reduction	120 mg bid then 240 mg bid

2.3 Availability of Proposed Active Ingredient in the United States

Glatiramer acetate (GA) was approved for use in the US for the treatment of RRMS under the trade name Copaxone. It is marketed as a 20 mg/1mL subcutaneous injection. No other generic forms of GA are sold in the US at this time, although applications are pending.

2.4 Important Safety Issues with Consideration to Related Drugs

The Table below summaries the Boxed Warnings, Warnings, and/or Precautions in the Prescribing Information for the immunomodulatory medications used to treat the relapsing forms of MS including RRMS.

Table 2 Safety issues with disease-modifying medications approved for the use in relapsing forms of multiple sclerosis

Brand Name/ Generic Name	Presently identified safety issues
Avonex/ Interferon β-1a	**Warnings:** Depression and suicide Anaphylaxis (rare) and other allergic reactions Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation Albumin in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) **Precautions:** Seizures – an increased rate of seizures was seen in Avonex-treated subjects in 2 placebo-controlled trials in MS Cardiomyopathy and congestive heart failure – post-marketing cases were reported in patients without known predisposition to these events Autoimmune disorders – post-marketing cases of disorders including idiopathic thrombocytopenia, hyper-and hypothyroidism, and autoimmune hepatitis have been reported
Betaseron/ Interferon β-1b	**Warnings:** Depression and suicide Injection-site necrosis reported in 4% of patients in controlled clinical trials Anaphylaxis (rare) and other allergic reactions Albumin in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) **Precautions:** Flu-like symptoms, Abortifacient potential
Extavia/ Interferon β-1b	**Warnings and Precautions:** Depression and suicide Injection-site necrosis reported in 4% of patients in controlled clinical trials

Extavia/ Interferon β-1b	Injection-site reactions (injection site inflammation, pain, hypersensitivity, mass, or edema) in 78% of controlled clinical trial subjects Anaphylaxis (rare) and other allergic reactions Flu-like symptoms, Leukopenia, Hepatic enzyme elevation Laboratory tests – in addition to tests normally required for monitoring patients with MS, complete blood count and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests are recommended at regular intervals. Thyroid function tests are recommended every 6 months in patients with thyroid dysfunction. Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases, CJD
Mitoxantrone	**Boxed Warnings:** May only be given into a freely flowing intravenous infusion. Severe injury may occur if there is extravasation during administration or if it is given subcutaneously, intramuscularly, intra-arterially, or intrathecally. Bone marrow suppression, primarily nonlymphocytic leukopenia Cardiotoxicity – potentially fatal congestive heart failure may occur during or after termination of therapy Secondary acute myelogenous leukemia **Warnings:** Safety in patients with hepatic insufficiency has not been established May cause fetal harm when given to pregnant women
Rebif/ Interferon β-1a	**Warnings:** Depression and suicide Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation Anaphylaxis (rare) and other allergic reactions Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or CJD **Precautions:** Seizures – an increased rate of seizures has been seen with beta-interferons Leukopenia Worsening thyroid abnormalities Possible abortifacient effects
Tysabri/ Natalizumab	**Boxed Warning:** Increased risk of Progressive Multifocal Leukoencephalopathy (PML) Available only under a special restricted distribution program (REMS) called the TOUCH Prescribing Program **Warnings and Precautions:** Hypersensitivity reactions (incl. anaphylaxis) occurred at incidence of <1% Hypersensitivity reactions were more common in patients with antibodies to Tysabri. Immune system effects may increase the risk for infections. Hepatotoxicity – clinically significant liver injury has been reported in the postmarketing setting. Laboratory test abnormalities – Tysabri induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells.

Gilenya/ Fingolimod Gilenya/ Fingolimod	**Warnings and Precautions:** Bradyarrhythmia and atrioventricular blocks following the first dose. Dose-dependent reduction in peripheral lymphocyte count may increase risk of infections. Macular edema Respiratory Effects – dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) Elevation of liver enzymes Fetal harm - women of childbearing potential should use effective contraception during and for 2 months after stopping Gilenya treatment Increase in blood pressure Blood Pressure Effects – needs to be monitored Immune system effects upon discontinuation
Aubagio/ Teriflunomide	**Boxed Warning:** Severe liver injury including fatal liver failure reported with leflunomide and a similar risk expected. Concomitant use with other potentially hepatotoxic drugs may increase the risk of liver injury. Laboratory tests: should obtain transaminase and bilirubin levels within 6 months before initiation of therapy and then monthly for 6 months after starting. Stop Aubagio if drug induced liver injury is suspected and start the accelerated elimination procedure with cholestyramine or charcoal. **Contraindications:** The drug is contraindicated in those with severe hepatic impairment. The drug may cause major birth defects if used during pregnancy and is contraindicated in women not using reliable contraception or during pregnancy. Co-administration with leflunomide is contraindicated as well. **Warnings and Precautions:** Hepatotoxicity, Alt levels rose most frequently in the first year of therapy and half returned to normal without discontinuing the drug. Use in women of childbearing potential Procedure for accelerated elimination of teriflunomide is with either cholestyramine or activated charcoal powder Bone Marrow Effects/Immunosuppression Potential/Infections A CBC should be obtained before initiating therapy and monitoring should be done as needed. A tuberculin skin test should be done at screening. Patients with active or acute TB infection should not start the product and patients with severe immunodeficiency, bone marrow disease, or uncontrolled infections should not be treated. Live vaccinations not recommended. The risk of malignancy may be increased. Peripheral neuropathy occurs more frequently especially in those over age 60. Acute Renal Failure without symptoms has been observed, resolves spontaneously, Hyperkalemia has been observed. There are rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. There are cases of increased blood pressure, monitor. Interstitial lung disease may be expected. Co-administration with immunosuppressive or immunomodulating therapies has not been evaluated and if done need to monitor for hematologic toxicity.
Tecfidera/ BG-12	**Warnings and Precautions:** Lymphopenia. A CBC should be checked before initiating treatment, annually and as clinically indicated. Flushing may occur.

The following are excerpts from the approved GA 20 mg/day label dated 2009.

Table 3 Known Safety issues with GA described in the current label (2009)

Warnings and Precautions from Copaxone label	**Immediate Post-Injection Reaction** Approximately 16% of patients exposed to GA in the 5 placebo-controlled trials compared to 4% of those on placebo experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. The symptoms were generally transient and self-limited and did not require treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care. Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown. **Chest Pain** Approximately 13% of GA patients in the 5 placebo-controlled studies compared to 6% of placebo patients experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection of GA was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. **Lipoatrophy and Skin Necrosis** At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during the postmarketing experience. Lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites daily. **Potential Effects on Immune Response** Because GA can modify immune response, it may interfere with immune functions. For example, treatment with GA may interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that GA does this, but there has not been a systematic evaluation of this risk. Because GA is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken. Although GA is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with GA may result in untoward effects.

	Glatiramer acetate-reactive antibodies are formed in most patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RRMS patients given GA, 20 mg, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.
Use in Women of Childbearing Potential	There are no adequate and well-controlled studies in pregnant women. The effects of GA on labor and delivery are also unknown. It is not known if glatiramer acetate is excreted in human milk. Hence use of GA during pregnancy should be only if clearly needed and caution should be used when administered to a nursing woman.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

2.5.1 Regulatory history relevant to Copaxone 20 mg/mL and 40 mg/mL

The sponsor's original development plan included 11 clinical trials with 857 patients exposed to GA 20 mg/day. These included two randomized, double-blind, placebo-controlled trials for the treatment of RRMS, BR-1 and trial 01-9001 used to support efficacy. An additional trial, BR-2, for the treatment of chronic progressive multiple sclerosis did not demonstrate efficacy but was used to support safety.[2]

There were two subsequent trials, trial 3, the preCIS trial, where those with an isolated demyelinating lesion and MRI evidence for MS were shown to have a delay in time to next relapse and trial 4, which evaluated MRI endpoints. The later trials also are reported in the label. A further summary of past regulatory activity with regard to the product are provided in Appendix 2 to justify the change in indication recommended for this product.

GA9006 and GA9016 (FORTE) trials
The sponsor completed a pilot trial, GA9006, which suggested that GA 40 mg/day might be more efficacious than GA 20 mg/day. This was a pilot study with 44 subjects treated with GA 20 mg and 46 subjects treated with GA 40 mg for 36 weeks. The trial design was a superiority study with an active control where GA 40 mg/day was compared to GA 20 mg/day. The primary endpoint was the cumulative number of T1-Gd enhancing lesions at months 7, 8, and 9. There was a 38% reduction in cumulative T1-Gd

2 Original Agencies reviews for Copaxone NDA written by Janeth Rouzer Kammeyer,MD (Efficacy 1995) and John Dikran Ballan, MD (Safety 1996).

enhancing lesions using GA 40 mg/day. A post-hoc analysis showed a 50% reduction in risk of relapse on the 40 mg/day dose.

The sponsor then performed the FORTE trial which was planned as a pivotal trial. This was an actively controlled superiority trial of GA 40 mg/mL/day compared to GA 20 mg/mL/day. The primary endpoint was the rate of confirmed relapses during the 12 month double-blind (DB) phase. A total of 1155 subjects were randomized in a 1:1 ratio for a total of 586 treated with GA 20 mg/day and 569 treated with GA 40 mg/day. In this trial GA 40 mg/mL failed to show superiority and the study was terminated early during the open-label (OL) phase. The mean number of confirmed relapses was 0.28 for subjects on GA 20 mg/day and 0.27 for subjects on GA 40 mg/day during the DB phase. Both the GA9006 and FORTE trial were submitted as part of this application to support safety of the 40 mg/mL formulation.

SONG trial and GLOW trials
The SONG trial then compared GA 20 mg/0.5 mL to GA 20 mg/mL in a superiority trial designed to show patient satisfaction with a smaller volume injection. Although the new formulation showed marginal improvement in patient satisfaction this application received a Complete Response as it was felt the efficacy of GA 20 mg/day could not be relied on to predict the efficacy of a more concentrated formulation which might be absorbed differently. The sponsor was advised that an efficacy trial was necessary for the more concentrated formulation and recommended a superiority trial of Copaxone 20 mg/0.5 mL compared with placebo. The pivotal GLOW trial was started with a plan to enroll 1400 subjects, but was terminated on August 6, 2012. Instead the sponsor chose to continue development of the GA 40 mg/1mL TIW dosage alone.

2.5.2 Regulatory history relevant to Copaxone 40 mg/mL TIW

MS- GA-301 GALA trial
The GALA trial was submitted to IND 27998 on February 8, 2010. This is the double-blind, placebo-controlled, superiority trial submitted in this application to support the new dosage of GA 40 mg/mL TIW.

preNDA Meeting
At the pre-sNDA meeting on October 31, 2012 the sponsor proposed submitting an NDA for the new formulation and dosing of Copaxone, but the Agency recommended that it be submitted as a supplement instead. It was agreed that the GALA trial serve as the single pivotal efficacy trial and the FORTE trial and GA9006 trial supplement safety data. It was also agreed that the remainder of the clinical and non-clinical data, including the Drug Substance data, would be cross-referenced from NDA 020622 as the drug substance is identical to that used in the 20 mg/mL product. CMC felt that there was sufficient information provided regarding the manufacturing process to file the application. Microbiology asked that filter validation and sterility test verification studies be part of the sNDA to support the increased drug productconcentration.

FDA requested additional descriptive efficacy data from the FORTE trial. Regarding safety, the FDA advised the sponsor to clarify the extent of exposure of the GA 40 mg/ml daily dosing and the three times a week dosing. Additionally the FDA did not recommend a pooled analysis of all GA 40 mg doses, regardless of frequency, as the sponsor proposed, but instead recommended a separate analysis for each dose studied.

At the meeting the time of the database lock was confirmed to be June 4, 2012, after the SAP was last amended on March 22, 2012. The format of the sNDA was discussed in detail. Labeling was considered a review issue, but in principal the Agency agreed to include both the 20 mg/day and the 40 mg TIW in the label.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Although inspections were not performed, data integrity appeared intact. Checks for data integrity performed by this reviewer were several-fold. CRFs from three subjects were selected at random, and variables in these CRFs were verified in the datasets to make sure that they accurately reflected what was in the CRF. This reviewer also checked the efficacy datasets for missing data and it appeared limited. Efficacy and safety data was checked to determine if certain centers were vastly underreporting compared to others, and overall most centers appeared to be reporting sufficiently without driving the results of the study.

There were problems in data quality that made analysis difficult. In order for the reviewer to be able to confirm efficacy and safety data it is necessary to be able to easily open and use the appropriate datasets. When multiple datasets are provided with the same name or with names that do not adequately describe what data they contain, it can be confusing. Because some of the datasets were quite large, such as ADAE, and took 18 minutes to open, without an identifying name to the dataset that was unique, it was a major impediment in working with the data. It was unclear from looking at the names of the datasets if they contained information from the DB phase, the OL phase, or both. Once it was established that many datasets contained both DB and OL data, it was problematic that there was not an EPOCH variable to easily separate data into Pool 1 and Pool 2 for analysis. Another complicating fact was that Legacy data was collected and the sponsor converted it to an SDTM-like format, but without several critical variables. Consequently some Agency software could not be easily used, such as JReview and MAED without a lot of manipulation of the datasets. Upon request the sponsor was able to provide new analysis datasets that were easier to use and which contained an EPOCH variable.

The reviewer's guides did not initially help to clarify how the data was analyzed because two guides were provided, both entitled MS-301-GALA, and none seemed to be labeled Integrated Summary of Safety (ISS). After an information request the sponsor did provide an explanation that the reason there were two reviewer's guides entitled MS-301-GALA and no reviewer's guide entitled ISS was because all efficacy data came from the MS-301-GALA trial. One of the MS-301-GALA reviewer's guides described the Integrated Summary of Efficacy (ISE) which was composed of a single dataset from June 4, 2012 that was used for the double-blind analysis of efficacy. The second reviewer's guide described data used for the ISS analysis, and the guide included safety data collected until the time of the database lock of safety data on November 1, 2012. Because efficacy data had not changed they also entitled the second guide MS-GALA-301, even though this dataset was to be primarily used to evaluate safety.

Components of the submission were inadequately addressed by the sponsor. Despite the fact that data was collected on immunogenicity of the GA 40 mg/mL TIW dose in the GALA pivotal trial, the results were not provided nor was there any justification for why immunogenicity of the new formulation did not need to be addressed at this time. When the sponsor was directly asked about this they said that they would provide the study report for the immunogenicity data in a later submission. They failed to mention in the ISE or ISS that they had submitted an immune-analytical report associated with Study GA-9006 for the 40 mg/day dose, and the report was only discovered accidentally upon review of the submission.

Some inconsistency of how investigators coded some of the withdrawals was noted. Withdrawals that were within days of SAEs and AEs were sometimes coded as failed to return for follow-up visit or failed to sign informed consent rather than attributed to the AE, despite the proximity of events.

Although narratives were provided in the submission, it was time-consuming to access them as they were not linked to subjects mentioned in the text of the submission nor were there direct links for the various categories of narratives such as withdrawals, deaths, SAEs; instead all the narratives were linked in a single document that was in sequential numeric order. This meant that every time one wanted to review a particular AE it was a multi-step process to find the relevant narrative.

This reviewer also noted that the narratives had some inconsistencies in how investigators coded the various SAEs. The syndromes of immediate post-injection reaction (IPIR) and hypersensitivity reactions were not always clearly distinguished. The Investigator's Brochure and the protocols did not do an adequate job distinguishing between these overlapping syndromes to aid investigators with their coding.

3.2 Compliance with Good Clinical Practices

The sponsor reports that all three trials used to support this NDA were conducted in full accordance with the Good Clinical the Good Clinical Practice (GCP) as described in the Consolidated Guideline approved by the International Conference on Harmonization (ICH) as well as FDA regulations, the Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314 and any other applicable national and local laws. For studies 9006 and 9016 the sponsor also specified that they followed the Standard Operating Procedures for clinical investigation and documentation at Teva Pharmaceutical Industries Ltd. For study 9016 they followed Directive 2001/20/ED of the European Parliament and the Council of the European Union.

At each site there were two principal investigators (PI) who were responsible for the conduct of the trial. Each subject was consented before starting the trial. One PI had overall responsibility to lead the site study team and aspects of the study at the respective site. This investigator recruited new subjects, collected data and guarded the conduct of the study. The second PI, the treating neurologist/physician, who was blinded to treatment assignment, was responsible for evaluating subject eligibility, supervising drug administration, recording Adverse Events (AE) and monitoring safety assessments including MRI and laboratory testing. The treating physician also qualified relapses and decided whether or not the relapses needed treatment. An additional neurologist/physician was the examining neurologist who was blinded to all treatment assignments and safety assessments and who was used for the neurological exams performed during the DB PC portion of the study. A medical monitor followed up on emergent safety issues and referred them to the Data Monitoring Committee (DMC), if necessary. A Steering Committee was available to offer expert opinion if warranted on aspects of clinical trial design. Periodic teleconferences were held to assess and guide the study. All subjects who entered the study were consented initially as well as if they had a significant increase in the Expanded Disability Status Scale (EDSS) and they were reminded of the standard-of-care medications available to them.

3.3 Financial Disclosures

The sponsor provided adequate financial disclosures for Trial MS-GA-301. In that study four of the investigators disclosed their financial interests on form 3455. This included the following three investigators: (b) (6), MD received fees in excess of $25,000 for payment to his laboratory research investigating T-regulatory cells, (b) (6) (b) (6) MD received $55,000 to serve on the speaker's bureau and to serve as a consultant, (b) (6), MD received $26,500 to serve as an expert witness, to serve on the speaker's bureau and to serve as a consultant and (b) (6), MD, PhD received $26,000 to serve as an educator and faculty member/consultant for other TEVA products, namely (b) (6). For the

remainder of the investigators and subinvestigators there was nothing to disclose as documented on form 3454 signed by the Senior Director of Regulatory Affairs for Teva. Financial disclosures were not deemed necessary for Trials GA-9006 or the FORTE trial because they were not efficacy trials supporting approval nor was there any single participating investigator who made a significant contribution to safety; safety data came from many sites with patients widely distributed.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the review of Kavitas Vyas, Ph.D. which was not available at the time of this review.

4.2 Clinical Microbiology

The product was recommended for approval by the Agency microbiology reviewer, Jessica Cole, Ph.D. Please refer to her review dated July 17, 2013.

4.3 Preclinical Pharmacology/Toxicology

No new data was presented in this application.

4.4 Clinical Pharmacology

No new data was presented in this application directly applicable to GA 40 mg/mL TIW. An immunogenicity report related to GA 40 mg/mL daily was included in the submission and was reviewed by Clinical Pharmacology reviewer, Xinning Yang, Ph.D. His comments are discussed in section 7.4.6.

4.4.1 Mechanism of Action

The mechanism of action by which GA works in patients with MS is unknown.

4.4.2 Pharmacodynamics

No new data was presented in this application.

4.4.3 Pharmacokinetics

No new data was presented in this application.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The path to CDER Electronic Document Room for this submission can be found at:
\\Cdsesub1\evsprod\NDA020622\0083

Trials that contributed to efficacy analysis

Study Number	Study Design	Treatment Regimens
MS-GA-301	Pivotal Phase 3 trial randomized, multicenter, 12 month DB, placebo-controlled study	GA 40 mg TIW Placebo

Trials that contributed to safety analysis

Study Number	Study Design	Treatment Regimens
MS-GA-301 GALA	Phase 3, randomized, multicenter, 12 month DB parallel group followed by OL	GA 40 mg TIW (DB) Placebo (DB) GA 40 mg TIW (OL)
9016 FORTE	Phase 3, randomized, multicenter, 12 month DB parallel group followed by OL	GA 40 mg TIW (DB) GA 20 mg/day (DB) GA 40 mg TIW (OL)
9006	Phase 2, randomized, multicenter, 36 weeks DB parallel group study	GA 40 mg TIW (DB) GA 20 mg/day (DB)

5.2 Review Strategy

The primary emphasis of the review was on the GALA trial as this was the only trial that contributed new data to the efficacy portion of the label. Special attention was paid to the blinding of the study, randomization procedures, the withdrawal rate, cause of withdrawal, and amount of missing data to determine if the primary outcome of the trial could be relied upon for providing substantial evidence. Relapse rates of the various sites were evaluated to determine if there were any sites that were driving the primary outcome that should be excluded in a sensitivity analysis. The results of Trial 9006 and 9016 were not used to substantiate the efficacy of Copaxone 40 mg TIW.

The safety review was conducted by reviewing all of the narratives that contributed to the Integrated Summary of Safety (ISS) serious adverse events (SAEs),

discontinuations, and deaths and comparing them to the safety findings of the laboratory data and vital signs to look for discrepancies, particularly with regard to subjects that may have withdrawn from the trials. Once a potential signal was detected, Empirical Signal was checked to determine if there was any evidence for a signal in the post-marketing setting. This is a query and reporting software that is derived from AERS data but which excludes likely duplicate reports as well as standardizes drug names and uses the latest MedDRA coding. A relative reporting is reported which tells how many times more frequent than expected an event is. The EBGM or Empirical Bayes Geometric Mean is an estimate of the relative reporting ratio when large amounts of data accumulate and additionally a 90% confidence interval from 5% to 95% is also provided. The reviews of the past NDA submissions were inspected to see if the identified potential signals may have been detected in the past. In the case of a single AE, namely breast cancer, when it appeared that a signal may have been detected, a safety reviewer, Dr. Gerald Boehm, then conducted a more thorough epidemiologic evaluation of this finding across other MS treatments to determine if this was indeed a signal specific to this drug or this disease.

The efficacy and safety results of the pivotal trial were then compared to those of the marketed product, as described in the label, since no direct comparisons exist. The safety findings were able to be compared within the trials contributing to the ISS to get a sense of how the marketed product compared with the new dose and formulation. This was also helpful to determine if there was a dose response to safety side effects.
This review has incorporated data from the 4-month Safety Update Report of the ongoing open- label (OL) phase of the MS-GALA trial up to the cut-off date of May 12, 2013 as well as all responses to FDA requests for clarification of data submitted to the FDA as of November 7, 2013.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 MS-GA-301 GALA study

Title*:* A multinational, multicenter, randomized, parallel-group study performed in subjects with RRMS to assess the efficacy, safety and tolerability of GA injection 40 mg administered three times a week compared to placebo in a double-blind design.

Study centers and number of patients: This was a multinational study with 1404 randomized subjects which included 155 sites in 17 countries including: Bulgaria, Czech Republic, Germany, Estonia, UK, Georgia, Croatia, Hungary, Israel, Italy, Lithuania, Poland, Romania, Russia, Ukraine, USA, and South Africa. A total of 86 (6.1%) were from the US.

Publication: Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. A multinational, multicenter, randomized parallel-group study to assess efficacy, safety, and tolerability of Glatiramer Acetate 40 mg injection three times a week in subjects with RRMS: Baseline Patient Characteristics of the GALA Study. (Abstract P912) Multiple Sclerosis 2012; 18(4 Suppl):414. [Presented at: 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. October 10-13, 2012. Lyon, France.]

***Duration*:** 12 months followed by an open-label ongoing extension period

- Placebo-controlled phase: June 22, 2010-May 08, 2012
- Open-Label phase: Ongoing

Objectives: *To assess the efficacy, safety and tolerability of GA injection 40 mg administered three times a week (TTW) compared to placebo in a double-blind study design as measured by number of confirmed relapses in a 12 month period.*

Study Design: *This was a randomized, DB, PC study. Eligible subjects with RRMS were randomized in a 2:1 ratio and assigned to one of the following treatment arms:*

- GA 40 mg three times a week
- Placebo three times a week

There were three phases to this study. The phases included the 1 month screening phase, the 12 month DB, PC phase and the OL extension phase which is ongoing. The OL phase was divided into two periods: During period 1 as subjects concluded DB treatment they entered OL treatment and this period concluded when all subjects had finished the DB phase. Period 2 followed where only OL treatment was an option.

Relapse evaluation took place on schedule visits as well as unscheduled visits. In the PC phase of the study the Examining Neurologist/Physician assessed the subjects and the Treating Neurologist was responsible for supervising drug administration, monitoring AEs and safety assessments and confirming a relapse based on the evaluation performed by the Examining Neurologist. All study personnel were blinded to subject treatment as were subjects until all had completed the DB phase of the trial. Once the DB phase was complete all further examinations and treatment were performed by the single Study Physician/Neurologist. A Steering Committee oversaw the study and offered expert opinion about clinical aspects of the protocol and a Data Monitoring Committee (DMC) oversaw the emerging safety data as well as the progress of the trial. A central MRI reading center in New York evaluated and quantified all MRI data.

Placebo-controlled phase (PC)
In the PC phase there were 7 scheduled visits at months -1 (screening), 0 (baseline), 3, 6,9,12 (end of PC or early termination). During this phase the subjects underwent

MRIs at months 0, 6, and 12 of the study. The study schedule can be found in Appendix 1.

After the PC phase was complete subjects were offered entry into the OL extension phase and all subjects were placed on GA 40 mg TIW. The following categories of subjects were excluded from the OL phase.

1. Premature discontinuation from the PC phase of the study
2. Pregnancy or breast feeding
3. Subjects with unstable medical condition, excluding acute MS exacerbations

Open-label phase (OL)
The OL phase of the study is still ongoing and the schedule can be found in the Appendix 1.

The termination visit of the PC phase served as the baseline visit of the OL phase (month 12 of DB = baseline OL). The OL phase included visits every 3 months x 1 year (months 15, 18, 21, 24) and then every 6 months as well as at termination. An MRI was optional at the terminal visit of the OL phase. The termination visit date could vary by country and is contingent upon the commercial availability of the approved product or upon withdrawal of the product by the sponsor. Subjects who complete the termination visit activities were considered completers.

Number of subjects (randomized, completed): R = 1404, C = 1289.

***Key Inclusion Criteria**:*

1. Subjects must have a confirmed and documented MS diagnosis as defined by the Revised McDonald criteria with a relapsing-remitting disease course.
2. Subjects must be ambulatory with an EDSS score of 0-5.5 in both screening and baseline visits.
3. Subjects must be in a relapse-free, stable neurological condition and free of corticosteroid treatment [intravenous (IV), intramuscular (IM) and/or per OS (PO)] or ACTH 30 days prior to screening (month -1) and between screening and baseline (month 0) visits.
4. Subjects must have experienced one of the following:
    - At least one documented relapse in the 12 months prior to screening or
    - At least two documented relapses in the 24 months prior to screening, or
    - One documented relapse between 12 and 24 months prior to screening with at least one documented T1-Gd enhancing lesion in an MRI performed within 12 months prior to screening.
5. Subjects must be between 18 and 55 years of age, inclusive.
6. Women of child-bearing potential must practice an acceptable method of birth control.

Key Exclusion Criteria:

1. Subjects with progressive forms of MS.

2. Use of experimental/investigational drugs, immunosuppressive agents or cytotoxic agents within the 6 months prior to screening.
3. Use of natalizumab or any other monoclonal antibodies, or cladribine within 2 years prior to screening.
4. Previous treatment with immunomodulators (including interferon β 1a and 1b, and intravenous [IV] immunoglobulin) within 2 months prior to screening.
5. Previous use of GA or any other glatiramoid.
6. Chronic (more than 30 consecutive days) systemic (IV), per OS (PO) or intramuscular (IM) corticosteroid treatment within 6 months prior to screening visit.
7. Previous total body irradiation or total lymphoid irradiation.
8. A known history of sensitivity to Gd, inability to successfully undergo MRI, or known drug hypersensitivity to mannitol.

Concomitant Medications:

Symptomatic MS drugs, short-term treatment with IV corticosteroids for acute relapse for a maximum of 1 gram/day for a maximum of 5 days, topical and inhaled steroids at discretion of the treating physician.

Test product, dosage and mode of administration:

- Investigational drug
  GA 40 mg in 1 ml for subcutaneous (sc) injection in a pre-filled syringe (PFS) administered TIW. Each PFS also contains 40 mg mannitol dissolved in water for injections. Batch numbers: K-42887 and K-45185.

- Placebo
  Matching placebo injection (40 mg mannitol dissolved in 1ml water for injections) for SC injection in a PFS administered TIW. Batch numbers: PL9002 and PL9005.

Blinding:

To maintain the blind all subjects were injected with a pre-filled syringe TIW containing placebo or Copaxone. Blinding was maintained for all subjects until the last subject completed the PB controlled phase.

Criteria for Early Treatment Discontinuation:

A subject may withdraw or be withdrawn from the study for the following reasons:
1) Death
2) Adverse Event
3) Subject withdrew consent

4) Request of primary care physician or Investigator
5) Refusal to sign the re-consent form
6) Non-compliance
7) Protocol violation
8) Pregnancy
9) Teva requested subject to be withdrawn
10) Lost to follow-up/failure to return

Outcome Measures:

Clinical Efficacy

Primary endpoint

- The total number of confirmed relapses during the PC treatment phase (those relapses confirmed by the treating neurologist)

Secondary endpoint:

- The cumulative number of new/enlarging T2 lesions taken at Month 6 and Month 12 (end of PC phase)
- The cumulative number of enhancing lesions on T1-weighted images taken at Months 6 and 12 (end of PC phase)
- Brain atrophy as defined by the Percent Brain Volume Change (PBVC) from baseline to Month 12 (end of PC phase)

Exploratory Endpoints:

- The time to the first confirmed relapse during the PC phase
- The proportion of relapse-free subjects during the PC phase
- The total number of confirmed relapses during the PC phase, requiring hospitalization and/or IV steroids
- The proportion of subjects with confirmed EDSS progression during the PC phase
- Change from baseline to Month 12 in EDSS score
- Change from baseline to Month 12 in Ambulation Index (AI)
- The volume of T2 lesions at Month 12
- The cumulative number of new/enlarging hypointense lesions on T1 scans at Months 6, 12
- The volume of hypointense lesions on T1 scans at Month 12
- The cumulative number of new hypointense lesions on T1 scans at Months 6, 12
- The cumulative number of enlarging hypointense lesions on T1 scans at Months 6, 12
- The cumulative number of new T2 lesions at Months 6, 12
- The cumulative number of enlarging T2 lesions at Months 6, 12
- Brain atrophy as defined by the percentage change from baseline to Month 12 in

normalized gray matter volume and in normalized white matter volume
- General health status as assessed by the European Quality-of-Life (EuroQoL) Questionnaire (EQ-5D)
- Assessment of the effect of general health and symptom severity on work, using the Work Productivity and Activities Impairment - General Health (WPAI-GH) Questionnaire

Clinical Safety
Outcome measures included adverse events (AEs), serious adverse events (SAEs), AE leading to death or withdrawal, pregnancy, clinical laboratory parameters, vital signs measurements, and electrocardiograms (ECG). MedDRA 15.0 was used to code AEs. AE with missing onset data were included, except for those that were time-dependent. Different verbatim terms for the same subject coded to the same PT with overlapping or consecutive dates were considered as one, whereas if the duration of one of these AEs was recorded as less than a day, the AE was considered a different one.

The analyses that the sponsor planned to present included:
- Incidence tables in decreasing order of the rate ratio where this is defined as the event rate (ER) for GA 40 mg TIW/event rate for placebo per PT. The ER is the number of events reported/100 subject years based on calculation of exposure to actual treatment.
- Frequency and Incidence tables of AE by treatment group, gender, severity, causal relationship with the study drug
- Hazard rate analysis by treatment group

Relapse Definition and Evaluation, Treatment:
Definition of a confirmed relapse: Relapses are a new or recurrent neurologic symptom not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings found on the evaluation of the examining neurologist. New or recurrent neurologic symptoms that evolved gradually over months were to be considered disease progression, not an actual relapse. The findings of the examining neurologist would then be evaluated by the treating neurologist who would confirm the relapse. New or recurrent neurologic symptoms that occurred fewer than 30 days following the onset of a relapse as defined above were to be considered part of the same relapse and not a new event.

Procedure to be followed if a suspected relapse occurred:
Subjects were to contact the treating provider within 48 hours of the onset of symptoms to complete a telephone questionnaire to determine if an unscheduled relapse assessment should occur. If required, the subject was then to be evaluated by the examining neurologist within 7 days. The relapse assessment documented the event in the source documents and the eCTD which included the Functional System Scale (FS), Ambulatory Index (AI) and the Expanded Disability Status Scale (EDSS). The treating neurologist determined whether a relapse had occurred, based on the neurological

examination performed by the examining neurologist. A formal relapse assessment was necessary for determining if treatment with corticosteroids was needed.

Endpoints:

Kurtzke Expanded Disability Status Scale (EDSS)

The EDSS provides a disability score for MS subjects from 0 to 10. The steps of the EDSS are scored based on both ambulation and the Functional System Scores (FS). The FS represent eight different functions of the central nervous system (CNS) including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, mental or other. Each system is rated on a 5 or 6 point scale except for "other' which is rated dichotomously as none or other neurological findings attributed to MS.

Ambulation Index (AI)

The Hauser AI is a semi-quantitative rating scale to assess mobility by evaluating the time and degree of assistance required to walk 25 feet. Scores range from 0 to 10. The subject is asked to walk a marked 25-foot course as quickly as possible and is timed. Use of any assistive devices is noted.

MRI Parameters

MRIs were to be performed on all subjects and data transferred to a central MRI reading center so that a blinded reader could evaluate each study. MRIs were performed at baseline, month 6 and month 12. MRIs were not to be performed within 30 days of receiving IV steroids. The following key measures were obtained:

Number of T1-Weighted Gadolinium (Gd) –Enhanced Scan

T1-weighted Gd-Enhanced scans were used as a measure of disease activity through the quantification of the number or volume of contrasting-enhancing lesions. This measure is felt to correlate with relapse frequency. Gd is a contrast agent known to pass through the blood brain barrier when there are alterations in this barrier due to acute inflammation.

Number of new/newly enlarging, recurrent and persistent T2 –weighted hyperintense lesions

The T2 –weighted lesions are thought to represent established lesions, both old and new whose total volume can be equated with measuring the disease burden. Appearance of new T2 –weighted lesions can indicate disease activity and scans were compared to the previous scan.

Brain Atrophy (SIENAX Technique)

The SIENAX technique is an automated computerized technique that measures the change in brain volume over time. Normalized brain volume at baseline was obtained as well as the percent brain volume change.

***Volume* of T2 hyperintense lesions** -assessed at baseline and month 12.

***Number* of new hypointense lesions on T1-weighted MRI scans-** assessed.

Patient reported outcomes

- ***EuroQoL (EQ5D)***
  This is a standard measure of health outcome applied to a wide range of health conditions and treatments. It is self-administered and takes approximately 65 minutes. It is cognitively simple to complete and measures the economic impact of illness.

- ***The Work Productivity and Activities Impairment (WPAI-GH) Questionnaire***
  This instrument assesses productivity losses by measuring the effect of health on work as well as activities of daily living. There are 6 questions regarding activities as well as the time missed from work. It is self-administered and takes approximately 5 minutes to complete.

Ancillary tests

- Anti-GA antibodies and their titers were measured in order to evaluate the difference in antibody titers and kinetics between the two treatment arms.

Peripheral blood lymphocytes (PBL) proliferation profiles were compared between the two treatment arms. The sponsor plans to evaluate the proliferation patterns differences from those who are treated with daily GA 20 mg injections. Other immunological parameters will be collected as well in a subset of 100 patients.

Statistical Methods Analysis Plan:
The database was locked on June 4, 2013 after the last randomized subject had completed the PC phase.

Analysis Populations

- **Intent-To-Treat (ITT) Population**: consists of all subjects who have been randomized to the study. Assignment was based upon the treatment to which subjects were randomized regardless of which treatment they actually received. This is the population used for all primary and secondary efficacy endpoints.
- **Safety (ST) Population:** consists of all randomized subjects who receive at least one dose of randomized study medication.
- **Completers (CO) Population**: consists of all subjects who have been randomized to the study and completed the PC phase.
- **Evaluable (EV) Population**: This population is a subset of the CO population. It consists of all subjects who have been randomized to the study, completed the PC phase and complied with major protocol requirements.

Robustness of the primary efficacy analysis will be demonstrated by the sensitivity analyses evaluating the ITT population along with the CO and EV populations.

Sample Size Justification
The expected annualized relapse rate (ARR) in an untreated subject is 0.35 relapse/year. Treatment with GA 40 mg TIW is expected to reduce the ARR by 30% or more when compared with placebo. That is, the expected ARR in treated patients is expected to be 0.245 relapse/year. It is anticipated that 15% of subjects will drop out of treatment. Hence in a study that has 1350 subjects, 900 on GA 40 mg TIW and 450 on placebo, there will be approximately 90% power to detect a statistically significant difference in the total number of confirmed relapses between the treatment group and the placebo group.

The subjects' country was added as a covariate to all analyses. Centers within a country were pooled. Because some countries had a very low number of subjects they were pooled into one geographic region based on geographic proximity and similar standard of care. Of the 17 countries involved in this study pooling occurred in the following countries:

- Estonia and Lithuania
- Israel, UK, and Italy
- Hungary and the Czech Republic

Subgroup analyses were not planned.

Primary Efficacy Analysis
The primary efficacy endpoint was the total number of confirmed relapses during the PC treatment phase. A negative binomial regression was applied to the ITT population with an "offset" based on the log of the subject's exposure to treatment. The model also included the following covariables:

- Baseline EDSS
- Log of the prior 2-year number of relapses
- Volume of T2 lesions at baseline
- Status of Gd-enhancing T1 activity at baseline
- Country or geographic region

Sensitivity analyses of the primary endpoint were done with the CO and EV populations in addition to the ITT population. Repeat of the primary analysis was done without introducing the covariates except for the treatment group. Repeat of the primary analysis was also done with the volume of the T2 lesions at baseline as an additional covariate. The robustness of the primary analysis and their sensitivity to missing data was done by comparing the ITT population results to the CO population results.

Further sensitivity analyses took into account the reason for the missing data such as missing completely at random (MCAR), missing at random (MAR), and not missing at

random (NMAR). Death, pregnancy, withdrawal of consent not due to study treatment is considered MCAR. A subject who withdrew for a reason independent of the number of confirmed relapses is considered MAR and this might include those who withdrawal due to AE, protocol violations, as well as other reasons.

Analysis of secondary endpoints

The endpoints were tested in a prespecified hierarchal order in order to control for multiplicity.

- The cumulative number of new/enlarging T2 lesions taken at month 6 and month 12 (end of PC phase).
- The cumulative number of enhancing lesions on T1-weighted images taken at months 6 and 12 (end of PC phase).
- Brain atrophy as defined by the PBVC from baseline to month 12 (end of PC phase).

Cumulative number of new/enlarging T2 lesions at month 6 and month 12

In these analyses an offset employing the log of the proportion of the number of the available post-baseline scans was employed. For example, if data was missing from month 12, then the data was imputed from the difference between month 6 and baseline and an offset log (0.5) was introduced. If data was missing from month 6, but month 12 was done, then the difference from month 12 was compared to the baseline and an offset of 0 was introduced. In the case of missing data for a subject at months 6 and 12, data was not imputed but subjects were excluded from the analysis. In all other cases of missing data an offset of 0 will be used.

In addition, for the cumulative number of new and enhancing T2 lesions the model will also include the following covariates:

- Number of enhancing lesions on the T1-weighted image at baseline
- Country or geographical region (CGR)

Cumulative number of enhancing lesions on T1-weighted images at months 6 and 12

This was based on the outcome of a comparison between GA 40 mg TIW and placebo derived from a baseline-adjusted Negative Binomial Regression with an “offset” employing the log of the proportion of the number of the available post-baseline scans to adjust for missing MRI scans. If a subject was missing both month 6 and month 12 scans they were excluded from the analysis. The model included two covariates: the number of enhancing lesions on T1-weighted images at baseline and the country or geographical region (CGR).

Brain atrophy as defined by the percent brain volume change from baseline to month 12

The percentage change in normalized brain volume from baseline to month 12 was based on the outcome of a comparison between GA 40 mg TIW and placebo derived from a baseline-adjusted analysis of covariance. Subjects with a missing measurement

at month 12 were excluded from this analysis. In addition to the treatment group, the model also included the following covariates:

- Sienax normalized brain volume at baseline
- The number of enhancing lesions on T1-weighted image
- Country or Geographical Region (CGR)

Exploratory Endpoints

Exploratory endpoints were only to be performed for the ITT population. Each was analyzed at a significance level of 5%.

Safety Analyses

AEs with missing onset date were included in all AE analyses, except for those that might be time-dependent. Different verbatim terms (VT) for the same subject if coded to the same preferred term (PT) with overlapping or consecutive dates were considered as one. If such an AE was recorded as lasting less than a day, then this was considered a different one. Only AEs that begin after the treated was started were included.

Protocol Amendments

Amendment 1 summary (July 8, 2010)

The MRI definition of new T2 lesions and new hypointense T1 lesions were changed to include lesions shown previously that enlarged in volume as well as lesions not seen in previous scans. This change led to a change in the respective exploratory outcomes as well as the first secondary endpoint which was rephrased from "the number of new T2 lesions at month 12 compared to baseline" to "the cumulative number of new/enlarging T2 lesions measured at month 6 and month 12".

1. The ancillary study of antiGA antibodies was conducted in only 400 subjects rather than all subjects.
2. Ampyra, no longer an experimental treatment, was taken off the disallowed list of concomitant medications.
3. A single pharmacogenetic sample was felt to be sufficient rather than the two planned.
4. Patients who had undergone experimental treatment for MS, namely, endovascular treatment of chronic cerebrospinal venous insufficiency, were excluded from this study.

Amendment 2 summary (January 1, 2012)

1. There were alterations to the statistical analysis. The sponsor justified these changes based on the results seen in the literature as well as their recently completed BRAVO study for laquinimod where the percentage of subjects with at least one Gd-enhancing T1 lesion at baseline was higher in the laquinimod group than in the placebo group. This factor was a strong predictor of the rate of relapse that was not controlled for. As the randomization process for the GALA trial did not stratify according to the baseline MRI activity, the sponsor added the baseline volume of T2 lesions as a continuous variable and Gd-enhancing T1

lesions at baseline as an indicator variable to the primary analysis model of the primary endpoint, in addition to those already pre-specified.

Efficacy Results
See section 6, the ISE, for the efficacy results.

Safety Results
See section 7 for the full safety results of the GALA trial which are incorporated into Pool 1 (DB) and Pool 2 (OL). A short summary of the safety results relate exclusively to the GALA trial will be provided here. Consistent with the known AE profile of GA, the most common AEs in both study phases (PC and OL) of the trial were injection site reactions (ISR) and symptoms associated with Immediate Post-Injection Reaction (IPIR).

The overall incidence of serious adverse events (SAEs) was similar on placebo (4.6%) and GA 40 mg TIW (4.5%), with some differences noticed between SOCs. There were more subjects on Copaxone 40 mg TIW with SAEs due to infection than there were on placebo. There were also more having neurological, psychiatric, gastrointestinal, hepatobiliary, musculoskeletal and skin complaints on Copaxone. Many of these complaints were not directly attributed to drug or were AEs already identified in the label. The incidence of AEs leading to early discontinuation was higher in the GA 40 mg TIW group (3.1%) than the placebo group (1.3%), but the overall rate of AEs and dropouts were low in both groups than previously seen in the clinical trials described in the label. The most common reasons for discontinuation in the GA 40 mg TIW group were ISR in 1% and IPIR in 0.5% according to the company core data sheet definition and 0.1% according to the US definition. No specific AE predominated in the placebo group. In both treatment groups, the majority of AEs were mild or moderate in severity, and the incidence of AEs with sequelae was low (<2.5%), according to the sponsor. There were two deaths in the DB phase, one on placebo and a second accidental death. A third sudden death in sleep took place during the OL phase to a subject on GA 40 mg TIW who had a cardiovascular history. All were thought unlikely to be related to Copaxone.

The incidence of AEs considered by the investigator as having a reasonable possibility of being related to study drug was notably higher in the GA 40 mg TIW group (47.9%) than in the placebo group (15.8%) according to the sponsor. As requested by the FDA, the following AEs were assessed in addition to ISRs and IPIR: lipoatrophy, chest pain, hypersensitivity/anaphylaxis, thrombocytopenia, hepatitis and liver injury, breast cancer, and thromboembolic events. Their incidence was generally similar between placebo TIW and GA 40 mg TIW. Breast cancer appeared at increased frequency in those treated with Copaxone, but a further safety analysis revealed that breast cancer appears to be increased among multiple sclerosis patients in general and is not specific to those treated with Copaxone.

Blood biochemistry analysis did not identify any new safety signals for GA 40 mg TIW. Two subjects, both in the GA 40 mg TIW group, had SAEs associated with potentially clinically significant increases in liver transaminases in conjunction with elevated bilirubin. The narratives were inconclusive, but the SAEs suggested that the events may have been due to drug-induced liver injury (DILI) and in both cases, liver function values decreased after discontinuation of Copaxone. No new safety signals associated with vital signs or ECG were observed. See section 7 for further details of the safety results from this trial.

5.3.2 GA/9006

This was a pilot trial where 20 mg/day of GA was compared to 40 mg/day of GA in subjects with RRMS during a 36 week trial. The primary endpoint was an MRI endpoint.

Title
A Multi-Center, Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy, Tolerability and Safety of 40 mg of GA in the Treatment of Relapsing-Remitting Multiple Sclerosis Patients

Study Centers and Number of Subjects
A total of 18 US sites were involved with a total of 90 randomized subjects in a 1:1 ratio of GA 40 mg/day and Ga 20 mg/day.

Publications based on this Study
Cohen JA, Rovaris M, Goodman AD, Filippi M, and the MRI-AC Study Group, and the 9006 Study Group. Results of a randomized, double-blind, parallel-group study assessing safety and efficacy of 40 mg vs.20 mg of glatiramer acetate on MRI-measured disease activity in RRMS. (Abstract S61.001) Neurology 2006; 67(1):185.

Duration
A single phase of DB, PC conducted October, 2003 until September, 2005.

Objectives
To evaluate the efficacy of GA 40 mg/day compared to the marketed GA 20 mg/day administered by daily subcutaneous injection, as reflected primarily by MRI. Secondary objectives include evaluation of secondary MRI parameters, relapse rate, as well as tolerability and safety compared to the 20 mg formulation.

Study Design
This was a phase 2 double-blind, parallel group trial designed to investigate the efficacy, tolerability and safety of GA 40 mg/day in the treatment of RRMS as compared it to the marketed product, GA 20 mg/day. A total of 90 eligible subjects were randomized in a 1:1 ratio. They were treated for 36 weeks. Subjects were those with a diagnosis of

Clinically Definite MS according to Posner criteria with disease duration of at least 6 months. All had had at least one relapse in the preceding year, a baseline EDSS of 0-5 and at least 1-15 Gd-enhancing lesions on the screening MRI. Efficacy was measured using a primary endpoint of total number of T1-Gd enhancing lesions measured at months 7, 8, and 9. Secondary endpoints included total number of new T1-Gd enhancing lesions at months 9 and 9, total number of new T2 lesions at months 8 and 9, change in the total volume of T2 lesions from, baseline to termination, relapse rate and change from baseline of the Timed 25-ft. Walk test. Various other MRI endpoints and change from baseline EDSS were measured on an exploratory basis as well as the safety and tolerability of both products. Scheduled visits were at screening, baseline, and months 1, 3, 6, 7, 8, and 9. Blood samples were collected for immunological testing.

Schedule
Located in Appendix 1.

Demographics
A total of 44 subjects on GA 20 mg and 46 subjects on GA 40 mg were enrolled in this trial. Most subjects were female in both arms (between 71-80%). The mean age in both groups was 37. MS baseline characteristics were comparable, according to the sponsor, including baseline EDSS score of 2 and prior 1 year relapse rate of 1.5. Most subjects completed the trial with the exception of 6 subjects in each treatment arm that terminated early. Early withdrawal due to AE was 2.3% on GA 20 mg and 8.7% on GA 40 mg.

Efficacy
In the ITT cohort the primary endpoint showed a 38% reduction in cumulative T1-Gd enhancing lesions at months 7, 8, and 9 on the 40 mg dose compared with the 20 mg dose ($p = 0.0898$). A post-hoc analysis of the risk of relapse was reduced by 50% on the 40 mg dose ($p = 0.0183$). The proportion of relapse-free subjects increased from 52.3% on 20 mg/day to 76.1% on 40 mg/day. The total number of relapses was reduced by 41% on the higher dose ($p = 0.102$).

Safety
Data from this trial contributed to Pool 1 (DB) and Pool 2 (OL) and will be reviewed in more detail in section 7. According to the sponsor injection site reactions were reported with at least a 5% higher incidence on 40 mg/day than on a dose of 20 mg/day. These reactions included burning, mass, pain, and urticaria. Immediate post injection reactions (IPIR) were also higher and more severe on the 40 mg dose (32.6%) then on the 20 mg dose (22.7%). All events resolved without sequelae in this 36 week trial. The largest difference between the two groups in the IPIR symptoms were palpitations reported by 10.9% of subjects on GA 40 mg and only 2.3% of subjects on GA 20 mg.

5.3.3 GA/9016 FORTE

Based on the positive results of the GA/9006 trial this pivotal trial was performed comparing GA 40 mg/day to GA 20 mg/day in a superiority designed trial. This multinational, double-blind, controlled trial randomized 1155 patients in a 1:1 ratio on the two doses of Copaxone for a year. The inclusion and exclusion criteria were similar to the GA-301 study but the definition of relapse was a bit stricter and symptoms had to persist for more than 48 hours rather than 24 hours. After the first 12 months of the trial the subjects were offered an extension trial where all were treated with GA 40 mg/day. The extension trial was terminated early after GA 40 mg/day failed to demonstrate superiority of the rate of confirmed relapses during the 12-month double-blind period.

Title: A multinational, multicenter, randomized, parallel-group, double-blind study to compare the efficacy, tolerability and safety of GA injection 40 mg/mL to that of GA 20 mg/mL administered once daily by subcutaneous injection in subjects with RRMS.

Publication:
Comi G, Cohen J, Arnold D, Wynn D, Filippi M, Phase III Dose-Comparison Study of Glatiramer Acetate for Multiple Sclerosis Ann Neurology 2011 Jan;69 (1): 75-82.

Duration:
Double-blind phase: September 14, 2006-May 20, 2008
Open-Label phase November 19, 2008 ended

Objectives:
To compare the efficacy of daily subcutaneous injections of GA 40 mg/day to that of GA 20 mg/day in RRMS patients as determined by the rate of confirmed relapses during the 12-month double-blind phase, and to evaluate the long-term safety of GA 40 mg/day.

Design:
This trial was a randomized, double-blind, actively controlled two arm multinational trial comparing the efficacy of daily subcutaneous GA 20 mg/mL to GA 40 mg/mL as determined by the rate of confirmed relapses. Eligible subjects with RRMS according to the Revised McDonald criteria were stratified by center and randomized in a 1:1 ratio and assigned to one of the following treatment arms for 12 months:

- GA 40 mg/mL daily
- GA 20 mg/mL daily

Subjects were ages 18-55, ambulatory, and had EDSS scores between 0-5 with disease duration of at least 6 months prior to screening. Inclusion criteria were similar to those used in the GA 301 trial. There were two phases to the trial, a 12 month DB phase and a 12 month OL phase which followed. Study visits occurred at screening, randomization and months 1, 2,3,6,9 and 12. Following completion of the DB phase all subjects were switched to 40 mg/mL and further visits occurred during the OL phase at months 15, 18, 21, and 24 or early termination.

The primary endpoint was the rate of confirmed relapses during the 12 month DB phase. MRI was conducted in all subjects at baseline and at the end of 12 months. A group of 234 subjects deemed the "frequent MRI cohort" had MRI performed additionally at months 2,3,6,9 and 24 (termination or early discontinuation. Magnetization Transfer (MT) and Magnetization Resonance Spectroscopy (MRS) were performed at baseline and month 12. Blood samples for anti-GA antibodies were collected at baseline, months 1, 3, 6,9,12 18, and 24 (termination or early discontinuation). Safety was also monitored.

Schedule:
Schedule is found in Appendix 1.

Demographics:
The trial was conducted in 20 countries worldwide with a total of 136 sites represented. US subjects represented 22.8% or 263 of the 1155 randomized subjects. Of those, 586 subjects were treated with GA 20 mg and 569 subjects were treated with GA 40 mg. The two cohorts were well balanced for baseline demographics, according to the sponsor. They were 95% Caucasian, 71.7% female, had a mean of 2 relapses in the preceding 2 years, and had a mean onset of disease 1.5 years earlier. A total of 1024 subjects completed the DB phase and 1005 of those subjects entered the OL phase, but not all completed the OL phase as the trial was terminated early. Early termination from the DB phase was greater in those on GA 40 mg (79, 13.9%) than in those on GA 20 mg (52, 8.9%). The most common cause for termination was AE (GA 40 mg (51, 9.0%) and GA 20 mg (28, 4.8%). There was one death in the study due to traffic accident and five subjects withdrew due to pregnancy.

Efficacy:
The primary endpoint for the trial was the rate of confirmed relapses during the 12 month, double-blind phase. This trial failed to show superiority of GA 40 mg/day over the marketed product, GA 20 mg/day: both treatment arms appeared similar in their ability to reduce the number of relapses in subjects. The trial was terminated early in the OL phase. The mean (SD) number of confirmed relapses was 0.28 (0.58) for subjects on GA 20 mg/day and 0.27 (0.54) for those on GA 40 mg/day during the DB phase. The rate ratio (RR) [95%] of the 40 mg dose over the 20 mg dose was 1.0732 [0.8799, 1.3090]; p value =0.4859. The MRI endpoints as well as other exploratory endpoints also failed to show a significant difference between the two doses. Immunogenicity results were not included in the clinical study report.

Safety:
Safety data from this study contributed to Safety Pools 1 and 2 and will be reviewed in more detail in section 7. According to the sponsor, the total exposure to study drug during the DB phase was between 3 days to 13 months and in the OL phase between 2 days to 12 months. The mean [SD] exposure was 11.0 [2.6] months in the DB phase and 6.8 [2/1] months during the OL phase. During the DB phase the incidence of AEs

was similar between both doses of GA. The incidence of AEs in the DB phase was 85.2% on the GA 20 mg/day dose and 86.2% on the GA 40 mg/day dose (incidence rate 90.9% and in the OL phase the incidence of AEs was 90.9% on GA 20 mg/day and 95.9% on GA 40 mg/day. The most common AEs were injection site reactions (ISR) and immediate post-injection reactions (IPIR). ISRs were reported by 55.6% of subjects (IR=59.4) on GA 20 mg and 58.0% of subjects (IR=64.4) on GA 40 mg. In the DB phase, IPIRs were reported by 19.6% of subjects (IR=21.0) on GA 20 mg and by 20.6% of subjects (IR=22.8) on GA 40 mg. The most common AEs leading to early termination in both phases were IS reactions, IPIR symptoms, skin reactions, and edema. One death (due to a road traffic accident) occurred during the DB phase in the GA 40 mg group. Similar rates of SAEs were reported in both dose groups during the DB phase: 25 subjects (4.3%; IR=4.6) on GA 20 mg and 24 subjects (4.2%; IR=4.7) on GA 40 mg. No significant changes in laboratory measurements, ECG, or vital signs parameters related to treatment were apparent.

6 Review of Efficacy

Efficacy Summary

Study MS-GA-301 (GALA) was a 1404-patient, prospective, randomized, parallel-group, double-blind, placebo-controlled, multinational study performed in subjects with RRMS to assess the efficacy, safety and tolerability of GA 40 mg/ml TIW injected subcutaneously for one year followed by an open-label extension phase. The placebo-controlled phase of the study consisted of a 1-month screening phase followed by a 12-month treatment phase. The primary clinical endpoint was the number of confirmed relapses. Following completion of the placebo-controlled phase, subjects were offered the opportunity to enroll in a single-group ongoing OL phase and continue taking GA 40 mg TIW until it was commercially available or until development was stopped by the Sponsor. There were 461 subjects in the placebo group and 943 subjects in the GA 40 mg TIW group. The study was conducted at 155 sites in over 17 countries.

6.1 Indication

GA (b) (4) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

6.1.1 Methods

See section 5.3.1

6.1.2 Demographics

The arms of the study were well balanced with respect to sex, race, age, and BMI as is displayed in Table 4. As seen, the mean age in the placebo group was 38.1 years and in the GA 40 mg TIW the mean age was 37.4 years. In general 68% of both the drug-treated and placebo-treated group were female and they were almost exclusively Caucasian, as might be expected in a trial populated by predominantly Eastern Europeans.

Table 4 Distribution of Subject Demographics and BMI in the ITT population

GALA (MS-GA-301)		Placebo (N=461)	GA 40 mg TIW (N=943)	All (N=1404)
Sex				
All	n (%)	461 (100)	943 (100)	1404 (100)
Female	n (%)	313 (67.9)	641 (68.0)	954 (67.9)
Male	n (%)	148 (32.1)	302 (32.0)	450 (32.1)
Race				
American Indian or Alaska Native	n (%)	0	1 (0.1)	1 (0.1)
Asian / Oriental	n (%)	0	2 (0.2)	2 (0.1)
Black or African American	n (%)	3 (0.7)	12 (1.3)	15 (1.1)
Caucasian	n (%)	455 (98.7)	916 (97.1)	1371 (97.6)
Other	n (%)	3 (0.7)	12 (1.3)	15 (1.1)
Age (years)				
	Mean (SD)	38.1 (9.2)	37.4 (9.4)	37.6 (9.3)
	Median	38.4	36.9	37.3
	Min, Max	18.0, 55.9	18.0, 55.9	18.0, 55.9
BMI				
	Mean (SD)	24.4 (4.8)	24.4 (4.7)	24.4 (4.7)
	Median	23.8	23.6	23.7
	Min, Max	15.9, 43.2	15.4, 45.3	15.4, 45.3

CSR MS- GALA p 103

The group were well matched for baseline disease characteristics with a median EDSS score of 2.5, range between 0-5.5, mean time from first symptom of 7.7 years, mean time from diagnosis of 3.8 years, mean time of last relapse 0.5 years and mean number of relapses in the past 2 years of 1.9 as displayed in Table 5.

Baseline MRI lesions were also assessed, and there were slight differences between the two arms. The number of T1 Gd + lesions, number of T2 lesions, number of T1 hypointense lesions, the volume of T2 lesions, and T1 Gd+ lesions were all greater in those receiving GA 40 mg TIW than in those receiving placebo as demonstrated in Table 6.

Table 5 Distribution of Baseline MS Characteristics (ITT Population)

GALA (MS-GA-301)		Placebo (N=461)	GA 40 mg TIW (N=943)	All (N=1404)
Time from first Symptom (Years)				
	Mean (SD)	7.6 (6.4)	7.7 (6.7)	7.7 (6.6)
	Median	6.1	5.7	5.9
	Min, Max	0.4, 31.0	0.3, 38.8	0.3, 38.8
Time from Diagnosis (Years)				
	Mean (SD)	3.9 (4.7)	3.7 (5.0)	3.8 (4.9)
	Median	1.8	1.4	1.5
	Min, Max	0.0, 26.7	0.0, 38.8	0, 38.8
Time from Onset of Last Relapse (Years)				
	Mean (SD)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
	Median	0.4	0.4	0.4
	Min, Max	0.1, 2.2	0.1, 2.1	0.1, 2.2
No. of Relapses in the Last Year				
	Mean (SD)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
	Median	1.0	1.0	1.0
	Min, Max	0.0, 4.0	0.0, 6.0	0.0, 6.0
No. of Relapses in the Last 2 Years				
	Mean (SD)	1.9 (0.9)	1.9 (0.9)	1.9 (0.9)
	Median	2.0	2.0	2.0
	Min, Max	1.0, 6.0	1.0, 11.0	1.0, 11.0
Baseline EDSS score				
	Mean (SD)	2.7 (1.2)	2.8 (1.2)	NA
	Median	2.5	2.5	NA
	Min, Max	0.0, 5.5	0.0, 5.5	NA

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Table 6 Distribution of Baseline MRI parameters (ITT Population)

GALA (MS-GA-301)		Placebo (N=461)	GA 40 mg TIW (N=943)	All (N=1404)
Number of T_1 GdE Lesions at BL	Mean (SD)	1.4 (3.7)	1.7 (4.7)	1.6 (4.4)
Proportion of Subjects with No T_1 GdE Lesions at BL	N (%)	307 (66.6)	607 (64.4)	914 (65.1)
Proportion of Subjects with One T_1 GdE Lesion at BL	N (%)	53 (11.5)	126 (13.4)	179 (12.7)
Proportion of Subjects with Two T_1 GdE Lesions at BL	N (%)	29 (6.3)	52 (5.5)	81 (5.8)
Volume T_1 GdE Lesions (mL) at BL	Mean (SD)	0.1 (0.5)	0.2 (0.8)	0.2 (0.7)
Number of T_2 Lesions at BL	Mean (SD)	36.7 (26.7)	38.0 (26.3)	37.5 (26.5)
Volume T_2 Lesion (mL) at BL	Mean	17.4 (17.4)	19.7 (20.7)	19.0 (19.7)
Number of T_1 Hypointense Lesions at BL	Mean (SD)	20.4 (18.1)	23.7 (21.9)	22.6 (20.7)
Volume T_1 Hypointense Lesions (mL) at BL	Mean (SD)	4.7 (6.6)	5.3 (7.7)	5.1 (7.3)

CSR MS- GALA 301 p. 105

Reviewer's Comment

The baseline differences between those treated with Copaxone and those treated with placebo were minimal, but favored placebo.

6.1.3 Subject Disposition

A total of 1524 subjects were screened, 1404 were randomized, and 1289 completed. Of those 92% who completed, 91.09% were on drug and 93.28% were on placebo. Of those randomized for the study, 461 were assigned to placebo and 943 were assigned to GA 40 mg TIW. A total of 17 countries and 155 sites were involved as seen in Table 7. Only 6.1% (186) of subjects were from the US, and 86.25% (1211) subjects were from Eastern Europe.

Table 7 Distribution of Randomized subjects by Country; DB phase

Country	Number subjects	% of Total
Bulgaria	214	15.2%
Czech Republic	18	1.3%
Germany	40	2.8%
Estonia	14	1.0%
UK	6	0.40%
Georgia	25	1.8%
Croatia	111	7.9%
Hungary	12	0.9%
Israel	3	0.2%
Italy	16	1.1%
Lithuania	26	1.9%
Poland	268	19.1%
Romania	145	10.3%
Russia	166	11.8%
Ukraine	236	16.8%
USA	186	6.1%
South Africa	18	1.3%
Total # subjects	1404	100%

Reviewer's Comment
Most of the patients that were randomized completed the trial and those who did drop-out were well balanced between GA and placebo, suggesting that blinding was preserved. The completion rate compares favorably to other pivotal trials for immunomodulators including the two trials that lead to GA's approval (See Appendix 2). This trial was only 12 months in duration compared to the more typical two year pivotal efficacy trials, and that might account in part for the lower discontinuation rate.

Discontinuations
The sponsor's analysis of withdrawals was reviewed and is cited in Table 8. According to the sponsor, discontinuations were few; there were a total of 31 (6.72%) in the placebo group and 84 (8.91%) in the Copaxone group. The most common cause of discontinuation was withdrawal of consent, 3.69% in the placebo group and 3.61% in the Copaxone group.. According to the sponsor discontinuation due to AE was only

1.3% in the placebo group and 3.08% in those on Copaxone in the GALA trial. In the GALA trial other causes of discontinuation were negligible as seen in the following Table.

Table 8 Discontinuations from MS GA 301 during the DB PC phase

GALA (MS-GA-301)	Placebo (N=461)		GA 40 mg (N=943)		All (N=1404)	
	N	%	N	%	N	%
Total Number of Randomized Subjects	461	100.0	943	100.0	1404	100.0
Total Number of Subjects Completed PC phase	430	93.28	859	91.09	1289	91.81
Total Number of Treatment Discontinuation	31	6.72	84	8.91	115	8.19
Death	1	0.22	.	.	1	0.07
Adverse Event	6	1.30	29	3.08	35	2.49
Subject Withdrew Consent	17	3.69	34	3.61	51	3.63
Request of Primary Care Physician or Investigator	1	0.22	1	0.11	2	0.14
Non-Compliance with Study Drug	.	.	2	0.21	2	0.14
Protocol Violation	.	.	2	0.21	2	0.14
Pregnancy	4	0.87	7	0.74	11	0.78
Failed to Return / lost to follow-up	1	0.22	5	0.53	6	0.43
Refused to Re-Sign Informed Consent after Relapse	1	0.22	4	0.42	5	0.36

CSR MS-301-GALA Table 7 p 101

It was noted that the sponsor's analysis lacked withdrawal due to relapse and that few subjects either on drug or placebo withdrew due to AE. Many withdrew due to "subject withdrew consent" which was categorized separately from "refused to re-sign informed consent after relapse". The sponsor was asked to submit a new analysis of withdrawal that included "withdrawal due to lack of efficacy".

In their submission, dated July 30, 2013, the sponsor stated that this would need to be analyzed post-hoc as all three studies did not collect this information. The sponsor's new analysis is shown in Table 9. For the new analysis the sponsor performed a search within the comments of those who discontinued for reasons other than "death", "adverse events" and "pregnancy". From the sponsor's presentation it appears that withdraws due to lack of efficacy is comparable in those on placebo and those on GA 40 mg TIW.

Table 9 DB Cohort Withdrawals due to Lack of Efficacy

GA9006 GA9016 and MS-GA-301 - DB phase	GA9006 and GA9016				MS-GA-301			
	GA 20 mg/day (N=630)		GA 40 mg/day (N=615)		Placebo TIW (N=461)		GA 40 mg TIW (N=943)	
	N	%	N	%	N	%	N	%
All cases of "Lack of Efficacy"	8	1.3	13	2.1	5	1.1	11	1.2

Sponsor submission dated July, 2013

In an analysis done by this reviewer all of the discontinuations for MS-301-GALA were reviewed and the results can be found in Table 10. Even with this new analysis, discontinuations due to AE remain much lower than reported for the marketed product.

Table 10 Reclassification of Withdrawals Summary

GALA (MS 301)	Placebo TIW (N=461)		GA 40 mg TIW (N = 943)		All (N= 1404)	
	N	%	N	%	N	%
Total # randomized	461	100.00	943	100.00	1404	100.00
Total who completed PC phase	430	93.28	859	91.09	1289	91.81
Total discontinuations	31	6.72	84	8.91	115	8.19
Discontinuations due to death	1	0.22	0	0	1	0.07
Discontinuations due to AE	7	1.5	33	3.5	40	2.8
Discontinuations due to withdrew consent	11	2.4	21	2.2	32	2.3
Failed to return/loss to follow-up	1	0.22	3	0.32	4	0..28
Discontinuations related to relapse, disease progression	6	1.3	15	1.6	21	1.5
Discontinuation due to pregnancy	4	0.87	7	0.74	11	0.78
Protocol violation	0	0	2	0.21	2	0.14
Request of PI	1	0.22	1	0.11	2	0.14
Noncompliance	0	0	2	0.21	2	0.14

Protocol Violations
Protocol violations were well balanced between those on drug and those on placebo. A total of 41 subjects in the placebo group (8.9%) and 73 subjects on drug (7.7%) had at least one major violation during the PB controlled phase.

Treatment Compliance
According to the sponsor treatment compliance was excellent in both groups, 99.3% (+/- 7.2) for those on placebo and 98.5% (+/- 8.6) for those on GA 40 mg TIW. [3]

Prior Treatment History -Not collected by the sponsor.

3 Treatment compliance was defined as the number of used syringes divided by the number of total syringes expected to be used in those undergoing treatment who returned for follow-up visit. If did not include those who went off of medication. If the percentage of used syringes was less than 75% than what was expected, then the patient was considered non-compliant.

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis was performed on the ITT population and sensitivity analyses were performed on the CO and EV populations as defined below.

- **Intent-To-Treat (ITT) Population**: consisted of all subjects who were randomized to the study, a total of 461 on placebo and 943 on GA 40 mg TIW for a combined total of 1404. The ITT and **Safety (ST) population** were identical in this study as there were no reported drug dispensing errors.
- **Completers (CO) Population**: consisted of all subjects who were randomized to the study and completed the PC phase: 430 in the placebo group and 859 in the GA 40 mg TIW group for a total of 1289.
- **Evaluable (EV) Population**: This population is a subset of the CO population. It consisted of all subjects who had been randomized to the study, completed the PC phase and had no protocol violations for a total of 403 on placebo, 816 on GA 40 mg TIW and 1219 overall.

.
The primary efficacy analysis was derived from the total number of confirmed relapses over the PC phase which was the first 12 months of treatment (Table 12). This table shows the distribution of the number of confirmed relapses by treatment. The majority of subjects on both GA and placebo had no relapses in the 12 month period. Very few subjects on either placebo or GA 40 mg/mL TIW had more than two relapses in a year.

Table 11 Distribution of the number of Confirmed Relapses during the PC phase of the GALA trial

GALA (MS-GA-301)	Placebo (N=461)		GA 40 mg (N=943)	
	N	%	N	%
All	461	100.0	943	100.0
0	302	65.5	726	77.0
1	119	25.8	171	18.1
2	29	6.3	31	3.3
3	9	2.0	10	1.1
4	2	0.4	5	0.5

CSR MS GALA p 466

A baseline adjusted negative binomial regression with an *offset* based on the log of the subject's exposure to the treatment was performed for the PC phase and is seen in Table 13. This adjustment provided a RR of 0.0656 with a $p < 0.0001$ and an adjusted mean number of confirmed relapses of 0.331 for GA 40 mg TIW and 0.505 for placebo at 12 months.

Table 12 Total number of confirmed relapses- negative binomial regression

GALA (MS-GA-301)	No. of Subjects	Estimate	SE	Lower Confidence Limit	Upper Confidence Limit	P-Value
GA 40 mg Adjusted Mean	943	0.331	0.028	0.280	0.392	
Placebo Adjusted Mean	461	0.505	0.049	0.418	0.609	
GA 40 mg vs Placebo Risk Ratio	1404	0.656	0.066	0.539	0.799	<.0001

CSR MS- 301- GALA p 467

Reviewer's Comments

The ARR and RR of GA 40 mg TIW is comparable to past controlled trials with GA as well as other immunomodulators.

In addition the sponsor then used pre-specified covariates including the baseline EDSS score, the log of the prior 2-year number of relapses, the volume of the T2 lesions at baseline, the status of the Gd-enhancing T1 activity at baseline, and the country or binomial regression and that is displayed for the principal analysis of the ITT population in Table 13. Table 13 also displays the results of the analyses that were repeated without the introduction of the covariates except for the treatment group where the RR was 0.669. Previously with all the covariates it was 0.656. Both of these analyses were highly significant with a p value < 0.0001. Table 14 shows the results from the alternative analysis models, the ANCOVA, the Wilcoxon-Mann Whitney test and the Poisson regression, all of which were highly significant and supportive of the primary analysis.

Table 13 Summary of Analyses of Relapse for the ITT population

Analysis Model	Covariates	Adjusted Mean Estimates	Treatment effect GA 40 mg vs. Placebo [95% CI]	P-value
Principal Analysis				
Total No. of Confirmed Relapses: Negative Binomial Regression (Principal Model)	1) EDSS at BL 2) Status of GdE T_1 activity at BL 3) Volume T_2 lesions at BL 4) Log of prior 2-year number of relapses 5) CGR	GA 40 mg TIW=0.331 Placebo=0.505	Risk Ratio: 0.656 [0.539; 0.799]	<0.0001
Robustness Analyses				
Total No. of Confirmed Relapses: Negative Binomial Regression (Unadjusted)	Treatment only	GA 40 mg TIW=0.322 Placebo=0.482	Risk Ratio: 0.669 [0.546; 0.821]	0.0001
Total No. of Confirmed Relapses: Quasi-Likelihood (Over-Dispersed) Poisson Regression	1) EDSS at BL 2) Status of GdE T_1 activity at BL 3) Volume T_2 lesions at BL 4) Log of prior 2-year number of relapses 5) CGR	GA 40 mg TIW=0.327 Placebo=0.497	Risk Ratio: 0.657 [0.553; 0.780]	<0.0001
Individual Annualized Relapse Rate: ANCOVA	1) EDSS at BL 2) Status of GdE T_1 activity at BL 3) Volume T_2 lesions at BL 4) Log of prior 2-year number of relapses 5) CGR	GA 40 mg TIW=0.469 Placebo=0.635	Adjusted Mean Difference: -0.166 [-0.262; -0.070]	0.0007
Individual Annualized Relapse Rate: Wilcoxon's test	NA	NA	NA	<0.0001

CSR MS 301 GALA p 109 Table 11 (CGR = country/geographic area)

In order to explore the robustness of the primary endpoint further, pre-specified sensitivity analyses were performed by the sponsor on the CO and EV populations. All were consistent with the primary analysis and statistically significant. The EV population was a subset of the CO population who did not have protocol violations which included 403 on placebo and 816 on GA 40 mg TIW for a total of 1219. The CO was 430 subjects on placebo and 859 subjects on GA 40 mg for a total of 1289. The analyses performed found in Table 14 include the following:

- Repeat principal analysis on the CO and EV populations
- Analysis of covariance (ANCOVA) with individual ARR was response variable
- Wilcoxon-Mann Whitney test with the individual ARR as the response variable
- A quasi-likelihood (over-dispersed) Poisson regression was also performed, both adjusted for the covariates as well as unadjusted
- A randomization distribution test

Table 14 Sensitivity Analyses of the Primary Endpoint for the CO and EV population

Endpoint Analyses	Treatment Effect: GA 40 mg vs. Placebo		
	RR	**CO Population**	**EV Population**
Total Confirmed Relapses: Negative Binomial Regression (Principal Model)	Risk Ratio (95% CI)	0.619 (0.505; 0.759)	0.617 (0.499; 0.763)
	P value	<0.0001	<0.0001
Total Confirmed Relapses: Negative Binomial Regression (Unadjusted)	Risk Ratio (95% CI)	0.636 (0.514;0.786)	0.628 (0.503; 0.784)
	P value	<0.0001	<0.0001
Total Confirmed Relapses: Quasi-Likelihood (Over-Dispersed) Poisson Regression	Risk Ratio (95% CI)	0.623 (0.522; 0.744)	0.621 (0.517; 0.746)
	P value	<0.0001	<0.0001
Individual Annualized Relapse Rate: ANCOVA	Adjusted Mean Difference	-0.178 (-0.253; -0.102)	-1.73 (0.249; -0.097)
	P value	<0.0001	<0.0001
Individual Annualized Relapse Rate: Wilcoxon's test	NA	NA	NA
		P < 0.0001	P < 0.0001

Summarized multiple sponsor sources including: CSR MS 301 GALA p 110-111

The FDA requested that the sponsor do a sensitivity analysis of confirmed and unconfirmed relapses during the PC phase. According to the sponsor this analysis also yielded highly significant results which were confirmed by the Agency statistician. The RR [95% confidence interval] was 0.685 [0.568; 0.828] which demonstrated a 31.5% reduction in the mean number of confirmed and unconfirmed relapses in the GA 40 mg TIW group ($p < 0.001$) compared with the placebo group. According to the Agency statistician 51 subjects treated with Copaxone and 22 subjects treated with placebo had at least one relapse that was not confirmed. When these events were included in the analysis the combined annualized relapse rate was 0.592 for the placebo group and 0.406 for the Copaxone group.

Finally the sponsor did a sensitivity analysis for missing data patterns to include missing completely at random (MCAR), missing at random (MAR) and not missing at random (NMAR). This was a predefined analysis as recommended by the European Medicines Agency 2009 guideline on missing data in confirmatory clinical trials.

- MCAR – conditions where the premature withdrawal is independent from the number of confirmed relapses that could occur in the rest of the trial to include death, pregnancy, and withdrawal of consent not related to study treatment such as moving or planning pregnancy.

- MAR – conditions where the premature withdrawal is conditionally independent of the number of confirmed relapses that might have occurred in the remainder of the trial such as AE.

- NMAR – conditions which are neither MCAR nor MAR such as refused to sign the re-consent form, protocol violation, failed to return for follow-up visit.

Some reasons for withdrawal required a case by case designation such as subject withdrew consent, request of the investigator or other reasons.

Table 15 Missing Data Analysis

GALA	Placebo		GA 40 mg TIW	
	N	%	N	%
All	461	100.0	94.3	100.0
MAR	6	1.3	29	3.2
MCAR	11	2.4	25	2.7
MNAR	14	3.0	30	3.2
None	430	93.3	85.9	91.1

GALA CSR Table 15.7.1.7.1 0 487

There were similar proportions of subjects with MCAR data missing, 2.4% in the placebo group, and 2.7% in the GA 40 mg TIW group. In the NMAR group they were

also evenly proportioned with 3.0% in the placebo group and 3.2% in the GA 40 mg TIW group. Both of these groups should have occurred at random if there was true blinding, and there is every indication that this occurred. Only in the MAR group there were 1.3% in the placebo group and 3.1% in the GA 40 mg TIW group; more on drug withdrew prematurely which may have been conditional on an experimental factor such as adverse event, but not because of a relapse. Despite this the sponsor then went on to show that the distribution of p-values from 150 imputed datasets where their mean estimates of relapse in a risk ratio is robust to any value of δ regardless of the missing data pattern.

Reviewer's Comments
Every sensitivity analysis that the sponsor performed confirmed the primary analysis and was highly significant. In addition the efficacy of the primary endpoint was in line with prior efficacy trials for GA 20 mg/day.

6.1.5 Analysis of Secondary Endpoints(s)

As was specified in the statistical plan, if the primary endpoint was achieved, the three secondary endpoints would be tested inferentially in hierarchical fashion. Statistically significant treatment effects were seen for the cumulative number of new or enlarging T2 lesions and the cumulative number of enhancing lesions on T1-weighed images taken at months 6 and 12, but not for brain atrophy as define by the percent brain volume change (PBVC) from baseline to month 12. Table 16 is a summary of MRI endpoints for the ITT population.

Table 16 Summary of MRI-based secondary and exploratory efficacy endpoints ITT population GALA trial

GALA (MS-GA-301)			
Secondary and Exploratory Endpoint	**Adjusted Mean Estimates**	**Treatment Effect GA 40 mg TIW vs Placebo [95% CI]**	**P-value**
Secondary Endpoints			
No 1: The Cumulative No. of New/Enlarging T_2 Lesions Taken at Month 6 and Month 12	GA 40 mg TIW=3.650 Placebo=5.592	Risk Ratio: 0.653 [0.546; 0.780]	<0.0001
No. 2: The Cumulative No. of Enhancing Lesions on T_1-Weighted Images Taken at Month 6 and Month 12	GA 40 mg TIW=0.905 Placebo=1.639	Risk Ratio: 0.552 [0.436; 0.699]	<0.0001
No. 3: Brain Atrophy as Defined by the Percent Brain Volume Change from BL to Month 12	GA 40 mg TIW=-0.706 Placebo=-0.645	Adjusted Mean Difference: -0.061 [-0.154; 0.033]	0.2058

NDA 020622 ISE p37

Cumulative number of new/enlarging T2 lesions taken at month 6 + month 12
At 6 and 12 months there were cumulatively 3.65 new or enlarging T2 lesions on GA 40 mg TIW and 5.592 lesions on placebo.. This demonstrated a statistically significant treatment effect with risk ratio [95% CI] of 0.653 [0.546, 0.780], which accounted for a 34.7% reduction in the cumulative number of new and enlarging T2 lesions in the GA 40 mg TIW group ($p < 0.001$) compared with the findings in the placebo group. According to a post-hoc analysis of the data by the Agency statistician, the mean number of new or enlarging T2 lesions at month 12 was 1.8 for GA 40 mg TIW and 2.8 for placebo ($p < 0.0001$).

Cumulative number of enhancing lesions on T1-weighted images taken at months 6 and 12
There were 0.905 enhancing T1 lesions on GA 40 mg TIW and 1.639 on placebo cumulatively at 6 and 12 months. This demonstrated a statistically significant treatment effect with the risk ratio [95% CI] of 0.552 [0.436; 0.699], which accounted for a 44.8% reduction in the cumulative number of enhancing lesions on T1-weighted images in the GA 40 mg TIW group ($p < 0.001$) compared with the findings in the placebo group.

Brain atrophy as defined by the PBVC from baseline to month 12
The percent change of brain volume showed no appreciable difference from baseline to Month 12 between those treated with GA 40 mg TIW and those treated with placebo. The adjusted mean difference [95%] was minimal, -0.061 [-0.154; 0.033], ($p = 0.2058$).

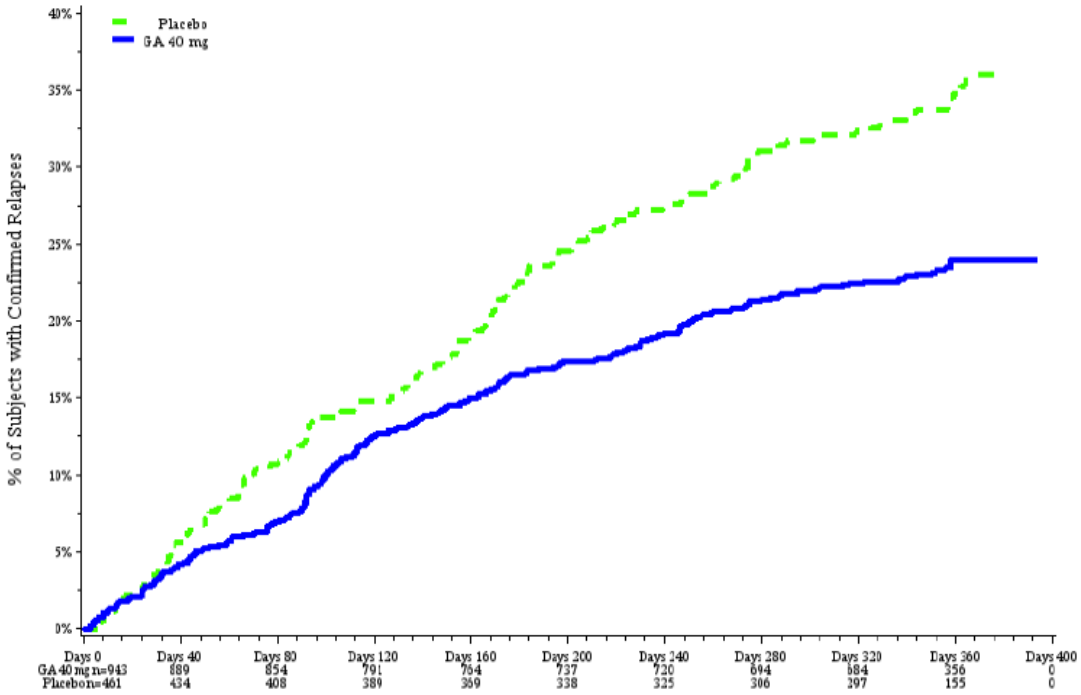
Reviewer's Comments
Further substantiation of the primary endpoint and reduction of the relapse rate comes from evaluating the effect on reducing both T2 new or enlarging lesions and T1 enhancing lesions, signs of disease activity in MS. A treatment effect was not seen for brain atrophy as defined by the PBVC.

6.1.6 Other Endpoints

Relapse-Related Exploratory Endpoints:

Time to First Confirmed Relapse during the PC phase:
According to the sponsor there was a significant effect for GA 40 mg TIW over placebo demonstrated by a 39.4% reduction in the hazard for first relapse during the PC phase ($p<0.0001$) as seen in Figure 1.

Figure 1 Time to First Confirmed Relapse during the PC phase



CSR GALA trial Figure 3 page 117

Proportion of Relapse-Free Subjects during the PC phase:
There was also a favorable effect for GA 40 mg TIW over placebo in the odds of being relapse-free during the PC phase of the trial. There was almost a 2-fold increase in the odds during the PC phase ($p<0.0001$) on GA 40 mg TIW compared with placebo. According to the sponsor the adjusted proportions/means estimate was 0.756 on GA and 0.617 on placebo for an odds ratio of 1.928 (CI 1.491; 2.494).

The Total Number of Severe Relapses defined as Confirmed Relapses Requiring Hospitalization and/or IV Steroids during the PC Phase:
The most severe relapses were assessed using this measure. There was a favorable effect for GA 40 mg TIW over placebo as demonstrated by a 35.6% reduction in the total number of confirmed severe relapses during the PC phase ($p<0.0001$). According to the sponsor the adjusted proportions/means estimate was 0.301 for GA and 0.466 for placebo for a risk ratio of 0.644 (CI 0.526; 0.790).

Reviewer's Comment
All three of these related endpoints to relapse rate were highly significant which lends further credence to the treatment effect of the product. Time to first relapse is noted to be

an endpoint that is increasingly being used as a primary endpoint in trials that minimize time on placebo.

Disability-Related Exploratory Endpoints:

Change in EDSS scores and proportion of those with confirmed EDSS progression:

No significant difference between the GA 40 mg TIW and placebo treatment groups was seen for either the proportion of subjects with confirmed EDSS progression, or change from baseline to Month 12 EDSS score (p≥0.2449) as seen in Table 17 according to the sponsor.

Change in Ambulatory Index (AI) scores:

No significant difference between the GA 40 mg TIW and placebo treatment group was seen in the change from baseline to Month 12 score (p= 0.6339) as seen in Table 17 according to the sponsor.

Table 17 Disability Related Endpoints for the GALA trial – DB, PB –controlled phase

Disability Related Endpoints	**Placebo N=461**	**GA 40 mg TIW N = 943**
N (%) of patients who progressed Estimated % from the logistic model Odds Ratio (OR)	17 (3.7%) 3.0%	42 (4.5%) 3.5% OR = 1.182 (p = 0.5726)
Change from Baseline in EDSS Mean (Median) unadjusted Estimate mean from ANCOVA	 0.1 (0.0) 0.193	 0.0 (0.0) 0.161 (p = 0.2449)
Change from Baseline in AI Mean (Median) unadjusted Estimate mean from ANCOVA	 0.1 (0.0) 0.171	 0.0 (0.0) 0.157 (p=0.6339)

CSR GALA trial adapted from Table 16

Reviewer's Comment

Copaxone was not found to have a positive treatment effect on reducing disability progression in either past trials with GA 20 mg/day or in the current trial with GA 40 mg TIW. The CombiRx trial, an NIH sponsored trial, which compared GA 20 mg/day, beta interferon, and combined treatment with GA 20 mg/day and beta interferon[4] also did not show a significant treatment in this regard.

4 Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, Salter AR, Gustafson T, Wolinsky JS, CombiRx Investigators Randomized study combining interferon and glatiramer acetate in multiple sclerosis Ann Neurol 2013 Mar, 73 (3): 327-40.

MRI-Based Exploratory Endpoints:
Table 18 displays numerous MRI endpoints provided in the ISE evaluated by the sponsor in this trial.

Table 18 Exploratory MRI endpoints GALA study ITT population

Exploratory Endpoints			
The Cumulative No. of New/Enlarging Hypointense Lesions on T_1 Scans at Months 6 and 12	GA 40 mg TIW=1.745 Placebo=2.618	Risk Ratio: 0.666 [0.549; 0.808]	<0.0001
The Cumulative No. of New Hypointense Lesions on T_1 Scans at Months 6 and 12	GA 40 mg TIW=1.508 Placebo=2.293	Risk Ratio: 0.658 [0.540; 0.800]	<0.0001
The Cumulative No. of Enlarging Hypointense Lesions on T_1 Scans at Months 6 and 12	GA 40 mg TIW=0.218 Placebo=0.308	Risk Ratio: 0.707 [0.525; 0.953]	0.0228
The Volume of Hypointense Lesions on T_1 Scans at Month 12	GA 40 mg TIW=4.867 Placebo=5.019	Adjusted Mean Difference: -0.152 [-0.328; 0.024]	0.0895
The Cumulative No. of New T_2 Lesions at Months 6 and 12	GA 40 mg TIW=2.518 Placebo=3.978	Risk Ratio: 0.633 [0.528; 0.759]	<0.0001
The Cumulative No. of Enlarging T_2 Lesions at Months 6 and 12	GA 40 mg TIW=1.088 Placebo=1.574	Risk Ratio: 0.691 [0.564; 0.847]	0.0004
The Volume of T_2 Lesions at Month 12	GA 40 mg TIW=18.031 Placebo=18.593	Adjusted Mean Difference: -0.563 [-0.978; -0.147]	0.0080
Percentage Change from BL to Month 12 in Normalized Gray Matter Volume	GA 40 mg TIW=-1.001 Placebo=-0.961	Adjusted Mean Difference: -0.040 [-0.221; 0.140]	0.6610
Percentage Change from BL to Month 12 in Normalized White Matter Volume	GA 40 mg TIW=-0.245 Placebo=-0.293	Adjusted Mean Difference: 0.049 [-0.129; 0.226]	0.5920

Number of new/enlarging hypointense lesions on T1 scans:
There was highly significant benefit for GA 40 mg TIW over placebo in reducing the number of new and enlarging hypointense lesions on T1 scans. There was a 33.4% reduction in the cumulative number of new/enlarging lesions at Months 6 and 12 (p <0.0001).

Number of new hypointense lesions on T1 scans:
There was a highly significant benefit for GA 40 mg TIW over placebo to reduce these cumulative lesions on T1 scans at Months 6 and 12 by 34.2% (p <0.0001).

Number of enlarging hypointense lesions on T1 scans:
There was a significant benefit for GA 40 mg TIW over placebo to reduce these cumulative lesions on T1 scans by 29.3% at Months 6 and 12 (p =0.0228).

Number of new T2 lesions:
There was a highly significant effect for GA 40 mg TIW over placebo with a 36.7% reduction in the cumulative number of new T2 lesions at Months 6 and 12 (p <0.0001).

Number of enlarging T2 lesions:
There was a favorable effect for GA 40 mg TIW over placebo with a 30.9% reduction in cumulative number of enlarging T2 lesions at Months 6 and 12 (p =0.0004).

Volume of T2 lesions:
There was a significant effect for GA 40 mg TIW over placebo in the volume of T2 lesions with a mean difference of -0.563 ml in volume at Month 12 (p =0.0080).

Volume of hypointense lesions on T1 scans:
There was no significant difference between treatment groups noted for the volume of hypointense lesions at Month 12 (p = 0.0895).

Gray matter and white matter volume:
There was no appreciable difference in brain volume changes (normalized gray matter or normalized white matter) noted between GA 40 mg TIW and placebo from baseline to Month 12 (p = 0.6610 for gray matter volume and p = 0.5920 for white matter volume).

Reviewer's comment
The number and volume of T1-weighted lesions and mean number of T2 lesions are used frequently as confirmatory endpoints in phase 3 MS trials; however no single MRI measure captures all aspects of MS pathology or serves as a surrogate to predict relapse rate or disease progression. Thus, when several different MRI measures all have statistically significant outcomes this serves as supportive evidence of the primary clinical outcome. In this case, the number of new or enlarging lesions on T1 scans, the "black holes" at months 6 and 12 showed a significant reduction. This finding is frequently correlated with a reduction in axonal loss and neurodegeneration. The number of new T2 lesions at months 6 and 12 were significantly reduced, as well as the volume of such lesions. The T2 volume often is used as an estimate of disease burden.

These MRI findings are consistent with those in the studies described in the label. Previously, in the 9 month MRI study, the total number of cumulative T1 Gd-enhancing lesions was reduced on Copaxone. In the time to first relapse study in those with a first clinical episode, there were fewer new T2 lesions and reduced lesion volume on Copaxone.

Patient Reported Outcomes
Patient reported outcomes were assessed using two instruments that were self-reported, the EQ-5D measured on a visual analogue scale and the WPAI-GH questionnaire.

General health status (EQ-5D):
This was assessed with an instrument that assessed (1) mobility, (2) self-care, (3) routine activities, (4) pain and discomfort and (5) anxiety and depression. There were three possible responses for each of the five items. There was no significant difference ($p > 0.05$) in any of the five individual dimensions and results were similar across treatment groups according to the sponsor. There was also no significant difference noted in the overall health using the EQ-5D-VAS between the GA 40 mg TIW and placebo groups at Month 12. Both relied on the visual analogue scale with scores ranging between 0-100.

Effect of general health and symptom severity on work (WPAI-GH questionnaire):
This questionnaire had 6 questions related to general health and symptom severity related to work and according to the sponsor there were no appreciable differences in answers were noted between the GA 40 mg TIW and placebo groups at Month 12 ($p>0.05$).

6.1.7 Subpopulations

Subgroup analysis was not performed by the sponsor for region, gender, or ethnicity as the population demographics were too homogenous to allow for a meaningful analysis. A total of 98% of the study was Caucasian, 70% female and 82% Eastern European. The statistical reviewer did perform a subgroup analysis of efficacy for the primary endpoint on those from the US and those outside the US because of concerns about differences in the practice of medicine and how relapses might be evaluated outside the US. This analysis was performed, and Croatia was found to be a major outlier with more relapses then elsewhere including the US. Except for Croatia, all sites with at least 30 subjects had consistent relapse rates. When Croatia was removed from the analysis the relapse rate in the US was a bit lower that the rest of the world as seen in Table 19. There was no evidence for underreporting of relapses in those in Eastern Europe compared with the US or any evidence that the results would not be referable to the US population. Due to the small treatment groups it is difficult to draw any definitive conclusions.

Table 19 Summary of relapse analysis by region

Country	Placebo N=461	GA 40 mg N=943
US		
N	25	61
Estimated ARR	0.294	0.230
Risk Ratio (nominal p-value)		0.785 (p=.688)
Non-US (including Croatia)		

N	436	882
Estimated ARR	0.494	0.320
Risk Ratio (nominal p-value)		0.647 (p<.0001)
Croatia		
N	39	72
Estimated ARR	0.305	0.397
Risk Ratio (nominal p-value)		1.304 (.465)

Sharon Yan, Ph.D. Statistics Reviewer

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Although the sponsor did not perform a specific dose-finding study, prior to their pivotal trial, they did perform two studies with a dose of GA 40 mg/day as compared to the marketed dose, namely study 9006 and 9012 (FORTE), which contributed to the safety database in this submission. These were both superiority studies where GA 40 mg was compared to GA 20 mg given daily. The GA 40 mg daily was not found to be superior to the marketed dose. Efficacy of both doses appeared similar. The rate of confirmed relapses was 0.28 on GA 20 mg/day and 0.27 on GA 40 mg/day for a RR of 1.0732.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This was not assessed in the pivotal trial submitted in this application and no long term efficacy data is available for the 40 mg three times a week dose of GA. The OL phase of the GALA trial is ongoing and efficacy data has not yet been assessed.

7 Review of Safety

Safety Summary

This analysis of safety data reviews the results of two safety cohorts that composed the ISS, Pool 1 which was a DB, PC cohort with 2649 subjects and Pool 2 an OL cohort of 2258 subjects. Additionally attention was given to the safety data from the pivotal MS-301-GALA trial. In Pool 1 those on a dose of 20 mg/day of GA, 630 subjects, had 575.0 years of exposure, on a dose of 40 mg a day of GA 615 subjects had 539.6 years of exposure, on a dose of GA 40 mg TIW 943 subjects had 875.0 years of exposure, and on placebo 461 subjects had 437.7 years of exposure as summarized in Table 22. The extension study as seen in Table 23 observed 2258 subjects of whom 1253 were exposed to GA 40 mg TIW, (282.0 years of exposure for those on the product less than a year and 572.0 years of exposure for those exposed for greater than a year), 1005 were exposed to GA 40 mg/day (295.4 years for those with less than a year of exposure and 273.8 years for those with more than a year of exposure).

The treatment groups studied were well matched for drug compliance, dropout rate, baseline characteristics including sex, race, and age as well as MRI and disease characteristics. Of note, however, the patient population was mostly from Eastern Europe and Caucasian and may reflect a less heterogeneous population than a population with primarily US subjects. Specifically in the MS-301-GALA trial, approximately 6% of the subjects were from the US and Canada, whereas in the GA/9006 and GA9016 trials, approximately 30% were from the US and Canada.

Although no direct comparison between GA 20 mg/day and GA 40 mg TIW can be made, review of the DB, PB-controlled cohort suggests that GA 40 mg TIW is not only safe for the treatment of MS, but also similar in side effect profile to the approved product without new risk. The incidence of the well-known complications of Copaxone use are actually less with the 40 mg TIW dosing than with the approved 20 mg/day dosing.

In the blinded portion of the trials 72% of subjects on GA 40 mg TIW had AE and 86.2% on the approved product had AE. Deaths and serious AE were approximately the same on both products (no deaths in either group, serious AE 4.5% on GA 40 mg TIW, and 4.1% on GA 20 mg/day). Withdrawals due to AEs were also similar but slightly higher in the GA 20 mg/day group (4.9% vs. 3.1%). Some of the most frequent AE for all doses of GA were the high level term (HLT) Injection Site Reactions (ISR) and its components which appears to be dose-related (35.5% on GA 40 mg TIW and 57.5% on GA 20 mg/day, and higher yet on GA 40 mg/day, 59.2%). Other AEs were very similar across many preferred terms (PT) suggesting the similarity between products. Immediate post-injection reaction (IPIR) occurred in 6.5% of those on GA 20 mg/day, and 1.5% of those on GA 40 mg TIW, and 8.5% of those on GA 40 mg/day. Other infrequent AE that appeared dose-related were fatigue, upper respiratory tract infection and depression.

7.1 Methods

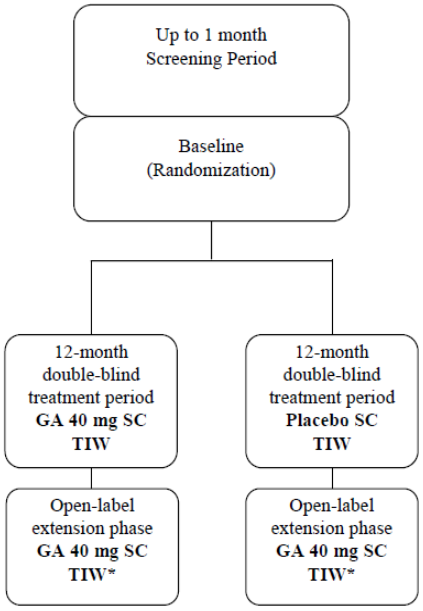
By prior agreement the safety review was performed on two populations, Pool 1, from the DB phase and Pool 2, from the OL phase. Special attention was placed on the results from the MS-301-GALA study as this was the only study to evaluate the GA 40 mg TIW dose in a controlled fashion compared to placebo. The incidence of AEs associated with each dose was compared, both by evaluating and confirming AEs, laboratory results, vital signs and ECG results reported in the datasets and checking them against patient narratives.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Integrated Summary of Safety (ISS) is primarily focused on a single trial, MS-301 GALA, a study where GA 40 mg TIW was compared to placebo in a randomized,

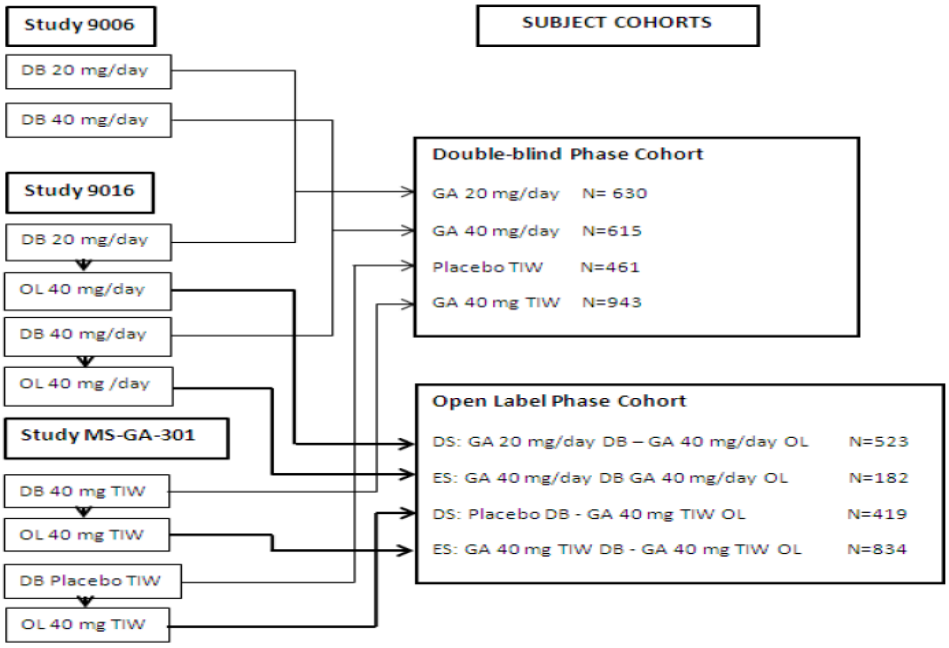
double-blind trial lasting for 12 months that was followed by an open-label period which is still on-going. There was no comparison to the marketed product in this trial. A total of 1404 subjects were in this portion of the safety database, 943 on GA and 461 on placebo. This safety cohort is depicted in Figure 2.

Figure 2 Diagram of MS-GALA- 301 Treatment DB and OL phases



Two additional trials contributed to the ISS as supportive data and they were GA/9006 and GA/9016-FORTE both of which evaluated the use of the GA 40 mg dose on a daily basis to the GA 20 mg dose. The ISS safety cohorts are outlined in Figure 3.

Figure 3 Diagram of Subject Cohorts in Safety Analysis



Abbreviations: GA, glatiramer acetate; DB, double-blind; OL, open-label; TIW, three times per week; ES, early start if the subjects had received GA 40 mg (either daily or TIW) during the DB phase; DS, delayed start if subjects had received GA 20 mg/day or placebo TIW during the DB phase and had not started GA 40 mg (either daily or TIW) until the OL phase.

Cut-off Dates:

- Study GA/9006: all data included; database lock date was November 24, 2005
- Study GA/9016 (FORTE): data was included for the completed DB phase and for the OL extension phase terminated by the Sponsor on November 19, 2008; database lock was January 29, 2009.
- Study GA-MS-301 (GALA): data was included for the completed PC phase (database lock-date: 4 June 2012) and up to a cutoff date of 01 November 2012 for the ongoing OL extension.

7.1.2 Categorization of Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence in a subject administered a pharmaceutical product. The MedDRA dictionary (Version 15.0) was used to code adverse events. AEs were classified by severity, seriousness and the relationship to the study drug by the sponsor. Only new or worsening events were considered AEs. AEs could include an unfavorable sign such as a laboratory test, symptom, or disease temporally associated with the use of the investigational product.

A new or worsening condition was considered an AE, but not a stable condition. Worsening of the disease, such as a relapse or increasing disability as measured by the EDSS were recorded as an AE if the outcome was more serious than would normally be expected from the normal course of the disease in a particular subject. AEs were characterized as:

- Mild – easily tolerated
- Moderate – interferes with daily activity
- Severe - prevents normal activity

Laboratory data were considered abnormal and reported as AEs if they led to a subject's withdrawal, were associated with a serious adverse event (SAE), were associated with signs or symptoms, or were considered clinically significant by the clinician.

Even though AEs were collected from the time that subjects signed the Informed Consent until 30 days following the last dose of drug, only those that began after the study drug was administered were included in the tables of AEs such as treatment emergent adverse events (TEAE). Since subjects may have had different verbatim terms (VT) to describe the same preferred term (PT) the coder converted different VT to PT that had overlapping or consecutive dates so that they were considered a single AE. Syndromes were generally not used as VT. This was helpful as the definition for the most common syndrome associated with this product had different definitions in the US and Europe, where the study was performed. VTs that were part of syndromes were converted to multiple related PTs, if known. AEs that were missing the onset date were included in all analyses, unless they were time dependent.

Serious Adverse Event (SAE)
A SAE is defined as an AE that results in any of the following:

- Death
- Life-threatening
- Requires hospitalization or prolongs existing inpatients' hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- An important medical event which requires medical intervention to prevent any of the above outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There were two safety pools evaluated in the ISS, the DB Phase cohort and the OL Phase cohort.

Safety Pool 1: the DB phase pool included 2649 subjects in the following four cohorts:

- GA 20 mg/day: all subjects in studies GA/9006 and GA/9016 DB phase who were randomized to GA 20 mg daily (N=630).
- GA 40 mg/day: all subjects in studies GA/9006 and GA/9016 DB phase who were randomized to 40 mg daily (N=615).
- Placebo TIW: all subjects in the GALA PC phase who were randomized to placebo three times a week (N=461).
- GA 40 mg TIW: all subjects in the GALA PC phase who were randomized to GA 40 mg three times a week (N=943).

Of this safety pool the disposition is noted in Table 20.

Table 20 Pool 1 Disposition

DB cohort	GA 20 mg/day (N = 630)		GA 40 mg/day (N = 615)		Placebo TIW (N = 461)		GA 40 mg TIW (N = 943)	
	N	%	N	%	N	%	N	%
Randomized	630	100.0	615	100.0	361	100.0	943	100.0
Completed according to protocol	561	89.0	522	84.9	430	93.3	869	91.1
Prematurely terminated	69	11.0	93	15.1	31	6.7	84	8.9

Safety Pool 2: the OL phase pool was a total of 2258 subjects consisting of four cohorts. All subjects were from the OL phase of studies GA-9016 and MS-301. The groups were designated with the label ES for early start that were on 40 mg for the duration of the studies, namely exposure on this dose for more than a year, and DS for delayed start (that is those on placebo or Copaxone 20 mg during the DB phase who switched to OL Copaxone).

- DS GA 40 mg/day group: all subjects in the GA/9016 study who were randomized to 20 mg/day during the DB phase and received at least one dose of GA 40 mg/day during the OL phase (N=523).
- ES GA 40 mg/day group: all subjects in the GA/9016 study who were randomized to GA 40 mg/day during the DB phase and received at least one dose of GA 40mg/day during the OL phase (N=482).
- DS GA 40 mg TIW group: all subjects in the GALA study who were randomized to placebo TIW during the DB phase and received at least one dose of GA 40 mg TIW during the OL phase (N=419).
- ES GA 40 mg TIW group : all subjects in the GALA study who were randomized to GA 40 mg TIW during the DB phase and received at least one dose of GA 40 mg TIW during the OL phase (N=834).

Those who entered the OL phase have their disposition summarized in the following table.

Table 21 Pool 2 Disposition

Disposition of OL Cohort (Pool 2)	Delayed Start GA 40 mg/day (N = 523)		Early Start GA 40 mg/day (N = 482)		Delayed Start GA 40 mg TIW (N = 419)		Early Start GA 40 mg TIW (N = 834)	
	N	%	N	%	N	%	N	%
Randomized	523	100.0	482	100.0	419	100.0	834	100.0
Completed according to protocol	12	2.3	11	2.3	N/A*	N/A	N/A	N/A
Ongoing	N/A	N/A	N/A	N/A	381	90.9	796	95.4
Prematurely terminated	511	97.7	471	97.7	38	9.1	38	4.6
Teva Requested subject be withdrawn**	465	88.9	426	88.4	N/A	N/A	N/A	N/A

*Ongoing study
**Extension phase was terminated early as failed to meet primary endpoint during DB phase

7.2 Adequacy of Safety Assessments

There were a total of 1362 exposures to GA 40 mg TIW and 1138 exposures to GA 40 mg/day for a total of 2500 exposures to the GA 40 mg dose. Of these at least 834 were exposed to GA 40 mg TIW for a year and 482 were exposed to GA 40 mg on a daily basis for a year. This provides more than adequate exposure to a 40 mg dose to meet ICH recommendations. In addition, according to the sponsor, there have been more than 1.75 million subject-years of exposure to Copaxone at all doses. As of December, 2012, a total of 8524 subjects with 16779 subject-years of treatment were treated within clinical trials.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Extent of Exposure in Pool 1
The exposure to study drug in subject-years was calculated from the date of first study drug administration to the last date of the study drug administration during the DB period and is summarized in the table that follows. For all three trials the mean extent of exposure was 10.8 months.

Table 22 Descriptive Statistics of Exposure to Study Medication in Pool 1

Exposure to Study Drug in Years	GA 9006 and GA 9016		MS-GA-301	
	GA 20 mg/day N = 630	GA 40 mg/day N = 615	Placebo TIW N = 461	GA 40 mg TIW N = 943
# Subjects	630	615	461	943
Mean	0.9	0.9	0.9	0.9
SD	0.2	0.2	0.1	0.2
Min	0.0	0.0	0.1	0.0
Median	1.0	1.0	1.0	1.1
Max	1.1	1.1	1.0	1.1
Sum	575.0	539.6	437.7	875.0

Based on Table 25 page 21 of the ISS

Extent of Exposure in Pool 2
The exposure to study drug in subject-years was calculated from the date of the first study drug in the OL phase until the last dose during the OL phase. For the GA9016 trial the mean exposure in the OL phase was 7.2 months and for the GA-301 trial the mean exposure was 8.4 months. The data from the GA-301 was being collected in an ongoing fashion at the time of this NDA and was cut off on November 1, 2012.

Table 23 Descriptive Statistics of Exposure to Study Medication in Pool 2

Exposure to Study Drug in Years	GA 9016		MS-GA-301	
	Delayed Start GA 40 mg/day N = 523	Early Start GA 40 mg/day N = 482	Delayed Start GA 40 mg TIW N = 419	Early Start GA 40 mg TIW N = 834
# Subjects	523	482	419	834
Mean	0.6	0.6	0.7	0.7
SD	0.2	0.2	0.2	0.2
Min	0.0	0.0	0.0	0.0
Median	0.5	0.5	0.7	0.7
Max	1.0	1.0	1.1	1.1
Sum	295.4	273.8	282.0	572.0

Based on Table 26 page 22 of the ISS

Extent of Exposure in Study GA- 301- GALA
The safety population for the GA-301-GALA study was the same as the ITT population of the efficacy trial and extent of exposure is seen in Table 22. Exposure to GA 40 mg TIW increased at the time of the 120 day safety update with a median of 12 months of exposure in the delayed start and 13.2 months in the early start groups with a maximum of 19.2 months in both groups. The exposure data at the time of the cut-off is presented below in Table 24.

Table 24 Exposure as of the 120 day safety update for those in GA-301-GALA Pool 2

MS-GA-301 - OL phase		Delayed Start GA 40 mg TIW (N=419)	Early Start GA 40 mg TIW (N=834)
Exposure to Study Drug (Years)*	Number of Subjects	419	834
	Mean	1.0	1.1
	SD	0.3	0.3
	Min	0.0	0.0
	Median	1.0	1.0
	Max	1.6	1.6
	Sum	438.7	904.5

Selection Criteria
All patients in the GALA and the FORTE study had a diagnosis of RRMS as defined by the Revised McDonald criteria. The protocols excluded subjects with less than 1 relapse in the preceding 12 months prior to screening, or less than 2 relapses in the preceding 24 months, or less than 1 relapse between 12-24 months prior to screening with MRI evidence of Gd-enhancing lesions within the prior 12 months. Subjects were ambulatory with an EDSS of 0-5.5 at baseline in the GALA study and 0-5 in the FORTE study. They had to have a relapse-free period in the 30 days prior to screening. They could not be treated chronically with Copaxone or other immunomodulators nor could other immunomodulators or chronic steroids be used during the studies. Subjects were ages 18-55.

In the phase 2 study GA 9016 subjects had clinically definite MS defined by Poser with disease duration of at least 6 months, at least one documented relapse in the prior year to study entry, and at least one but not more than 15 Gd enhancing lesions on screening MRI. Subjects had to have been relapse-free at least 30 days prior to screening. The EDSS score had to be between 0-5. Other immunomodulators or immunosuppressive agents were not allowed during the study.

Demographics and baseline characteristics of the population in MS studies
Pool 1
In the DB pool the demographic characteristics were very similar to those of the average MS patient. Both groups were primarily Caucasian, between 95-99%, the mean age ranged from 36.3 to 38.1 years and 68% to 72% of subjects were female. Subjects were recruited worldwide. In the GA9006 and GA9016 studies approximately 30% were from the USA and Canada whereas in the pivotal GALA study only 6% were from the USA and Canada, the remainder was largely from Eastern Europe.

The MS disease characteristics at baseline were similar in all treatment groups within each of the studies. The median duration of MS since the first symptoms was between 4.5 to 6.1 years, the mean number of exacerbations in the past year was 1.3-1.5 and in the past two years 1.9-2.0.

Pool 2
In the OL pool the demographic characteristics of the pool were again very similar to those of the average MS patient across treatment groups and studies. Between 67-72.2% of subjects were female, between 94.8 to 98.8% were Caucasian and the mean age was between 37.5 to 39.4 years. The median duration of MS since the first symptoms was between 7.5 to 8.8 years (see Tables 4, 5).

7.2.2 Explorations for Dose Response

Daily use of GA 20 mg/day was approved in 2005 and has been demonstrated to be well tolerated and effective in four completed pivotal trials that were randomized DB, PC trials as described in the label. Prior to approval a dose-finding study was not performed.

The sponsor chose to explore a higher dose of GA with a pilot trial, 9006, submitted in this application, where the efficacy, safety and tolerability of GA 40 mg/day was compared to GA 20 mg/day for 9 months. This appeared to show that the 40 mg/day dose compared favorably to the 20 mg/day in reducing MRI-inflammatory activity. The sponsor then evaluated the 40 mg/day dose in the FORTE trial, also part of this application. This was a superiority trial where GA 40 mg/day was compared with GA 20 mg/day. The relapse rates were similar on both doses of Copaxone and the 40 mg/day dose was not found to be superior.

As injection site reactions and aversion to frequent injections are thought to limit the use of daily Copaxone, the sponsor next explored the use of three times a week dosing. This was done in the pivotal trial GALA presented in this submission where GA 40 mg/mL TIW was compared with placebo in a randomized, double-blind fashion. Both appear to be effective, although have not been compared directly. The sponsor plans to continue marketing both products should the 40 mg TIW dose be approved to give patients treatment options.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

The safety assessment for each study was based on AE reports, clinical laboratory parameters, physical examinations, and vital signs which took place at screening, baseline, months 1, 3, 6, 9, unscheduled visits, and month 12 for the two longer studies. ECGs were performed at baseline, unscheduled visits, and month 12. At these visits serum for antiGA antibodies was also obtained. Drug compliance was assessed. Laboratory measurements were presented according to SI units. MRIs were performed at baseline, months 6, and month 12 (for the longer studies). AEs were to include SAE, AE leading to withdrawal, and any deaths or pregnancies. Laboratory testing included the tests found in Appendix 3.

There were a total of 428,148 laboratory tests recorded for the DB safety cohort. This cohort consisted of 2649 subjects in the safety population which was identical to the ITT population as everyone randomized took study medication. The criteria for normal laboratory findings in the NDA application are found in Appendix 4.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not assessed in this application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other drugs in this drug class at the present time.

7.3 Major Safety Results

7.3.1 Deaths

Double-blind phase
There were a total of two deaths in the DB phase of the studies. One took place on placebo TIW and the other on GA 40 mg/day. They are described below. No deaths took place during the DB period on GA 40 mg TIW.

- 301-592301 Sudden death Placebo TIW GALA trial
  This 47 year old male died suddenly. The patient received placebo TIW for 145 days. He was a smoker without cardiac history who experienced diaphoresis, intermittent fever, dyspnea, weakness about two weeks after a relapse treated with IV methylprednisolone. Within a day of reporting symptoms he died suddenly. His death certificate listed acute cardiovascular and pulmonary insufficiency and the sponsor attributed the death to an acute cardiopulmonary event. No autopsy report is available. Review of this individual's AEs prior to death reveal AEs of

anemia, iron deficiency, and vitamin B12 deficiency but none related to cardiopulmonary complaints.

- 9016-55101 Motorcycle injury GA 40 mg/day FORTE trial
  This 34 year old male died from injuries related to a motorcycle accident. He had received GA 40 mg/day. He collided with a moose while riding a motorcycle and sustained multiple injuries including exsanguination from aortic and cardiac rupture resulting in death. His death is deemed not related to the treatment.

Open-label phase

There was a single death in the OL cohort in a patient treated with GA 40 mg TIW for a total of 489 days. This sudden death was attributed by the sponsor to a myocardial infarction (MI) based on past history as well as autopsy findings compatible with prior MI. No seizures were witnessed at any time. The autopsy report did not mention the presence of pulmonary embolism.

- 301-582612 Sudden death, most likely MI GA 40mg TIW GALA Extension
  This 40 year old male was treated with GA 40 mg TIW in the DB phase for 364 days and 125 in the OL phase before his death for a total exposure of 489 days. He had a history of myocardial infarction (at age 26 in 1991), obesity, and smoking. He had stable vital signs, ECGs and laboratory tests during the study. He died suddenly in his sleep. Prior to expiring the patient's wife noted a change in his breathing rhythm and she was unsuccessful rousing him from his sleep. His autopsy showed evidence for post-infarction cardiosclerosis associated with his previous MI. The cause of death was unknown but thought to be related to acute heart failure. Review of this subjects AE reports reveal only a complaint of hemorrhoids prior to his death. His medications during the trial are listed below in Table 25. His vital signs were reviewed. His temperatures and pulses were always in a normal range and his systolic blood pressure (SBP) was never measured above 138 mmHg. His diastolic blood pressure (DBP) was never measured above 90 mmHg during the trial as seen in Table 26.

Table 25 Concomitant Medications for Subject 301/582612

Medication	Indication	Dose/Route	Start	End	Epoch
METHYLPREDNISOLONE	MS RELAPSE	1000 mg IV	2010-07	2010-07	SCREENING
IPIDACRINE	MS RELAPSE	IM	2010-07	2010-07	SCREENING
CYANOCOBALAMIN	MS RELAPSE	IM	2010-07	2010-07	SCREENING
RANITIDINE	GASTRIC PROTECTION	PO	2010-07	2010-07	SCREENING
METHYLPREDNISOLONE	MS RELAPSE	1000 mg IV	2011-03-11	2011-03-15	DB TREATMENT
OMEPRAZOLE	GASTRIC PROTECTION	20 mg PO	2011-03-11	2011-03-15	DB TREATMENT
CAPIVEN	HAEMORRHOIDS	1 tablet PO	2011-11-30	2011-12-09	DB TREATMENT
NEFLUAN	HAEMORRHOIDS	1 patch to skin	2011-11-30	2011-12-09	DB TREATMENT
METHYLPREDNISOLONE	MS RELAPSE	1000 mg IV	2011-06-17	2011-06-21	DB TREATMENT
OMEPRAZOLE	GASTRIC PROTECTION	20 mg IV	2011-06-17	2011-06-21	DB TREATMENT

Table 26 Vital Signs for Subject 301/582612 who died during the study

VISIT NUMBER	SBP	DBP
-1	122 mmHg	79 mmHg
0	135 mmHg	87 mmHg
0	130 mmHg	84 mmHg
0	132 mmHg	86 mmHg
1	137 mmHg	87 mmHg
2	130 mmHg	82 mmHg
3	134 mmHg	81 mmHg
4	138 mmHg	90 mmHg
5	133 mmHg	86 mmHg
unscheduled*	133 mmHg	84 mmHg
unscheduled	136 mmHg	84 mmHg
unscheduled	129 mmHg	85 mmHg
unscheduled	128 mmHg	87 mmHg
unscheduled	131 mmHg	82 mmHg

*Unscheduled visits were for drug dispensing.

120 Day Safety Update

No new deaths occurred during this time period.

Reviewer's Comments

In the ISS analysis there was one sudden death on placebo and two sudden deaths on Copaxone. Of the two on drug, one was treated with 40 mg/day during the DB phase and one was treated with a dose of 40 mg TIW during the OL phase. Neither appears likely to be related to the use of Copaxone.

Sudden death is not uncommon in MS. Episodes of demyelination can cause seizure, arrhythmias and autonomic instability (which may be the case in the subject that was on placebo). Not all sudden death is directly related to disease. Some drugs, such as fingolimod, may exert a direct effect on the heart conduction system[5] and have been associated with the risk for asystole and sudden death[6,7] and direct effect of drug is always a consideration.

It is noted that Copaxone's labeling does not make any reference to pharmacodynamic effects on the cardiovascular system. A search of postmarkteing data in Empirica Signal was performed and there did not appear to be any likely causal association of GA and myocardial

5 Yadav V, Bourdette D, New Disease-Modifying therapies and New Challenges for MS Current Neurology and Neuroscience Reports, 2012 October 21012; 12(5):489-491.
6 Yadav, V., Vourdette, D New Disease-modifying therapies and new challenges for MS Current Neurol Neurosci Rep 2012 Octl 12 (5): 489-91.
7 Villaba, Lourdes FDA Review Fingolimod PSUR

infarction or sudden death. A literature search on this topic was also performed and no articles or case reports were found.

Regarding the subjects on Copaxone that died in this study, the accidental death in the subject on GA 40 mg/day is unrelated to treatment. Only the death of the 40 year old male who died after 489 days of exposure to Copaxone may have had a causal relationship. According to Riudavets[8] who did a case series of 50 cases of MS who experienced unexpected death 18% were due to CV disease, 6% were due to PE, 2% pneumonia, 2% a metabolic disorder, 42% neurological complications related to MS, 18% accidents, suicides, and murder, 10% intoxications, and 2% thermal injuries. This death took place suddenly in sleep in a patient with cardiac risk factors and with an autopsy showing evidence of prior myocardial infarction. Although a cardiovascular death is the most likely cause of death for this patient, it is not the only possible cause. Sudden death does not need to be cited in the label as there is only a single case where causality cannot be determined, but is unlikely to be related to Copaxone.

7.3.2 Nonfatal Serious Adverse Events

Pool 1

In all three trials in the DB phase the sponsor identified a total of 208 non-fatal SAE of which 165 were on GA and 43 were on placebo. The SAEs were primarily of mild or moderate severity in all groups. Of these events, 115 individuals had SAE, 94 in individuals on GA and 21 in individuals on placebo. The incidence of subjects with SAEs was 4.2% (26) for GA 40 mg/day, 4.1% (26) for GA 20 mg/day, 4.5% (42) for GA 40 mg TIW, and 4.6 % (21) for placebo TIW. This suggests that SAEs were as likely to occur on placebo as on any dose of GA. The most common SAEs were in the Infection and Infestation and the Nervous System categories where there was no clear dose response. Table 27 shows the breakdown of SAE by primary organ system (SOC) by number of events, number of subjects, and percent of subjects.

Table 27 Pool 1 Frequency and Incidence of Serious Adverse Events by SOC

Primary System Organ Class r number of SAE n number of subjects % of subjects	GA 20 mg/day N = 630 r n (%)	GA 40 mg/day N = 615 r n (%)	Placebo TIW N = 461 r n (%)	GA 40 mg TIW N = 943 r n (%)
Any class	44 26 4.1%	49 26 4.2	43 21 4.6	72 42 4.5
Infections and infestations	4 4 0.6	3 2 0.3	4 3 0.7	15 11 1.2
Nervous system disorders	4 4 0.6	7 7 1.1	5 3 0.7	11 9 1.0
Gastrointestinal disorders	4 3 0.5	5 3 0.5	1 1 0.2	4 4 0.4
Hepatobiliary disorders	2 2 0.3	1 1 0.2	1 1 0.2	4 4 0.4
Skin and subcutaneous tissue disorders	0 0 0	2 2 0.3	1 1 0.2	6 4 0.4
Musculoskeletal and	3 3 0.5	1 1 0.2	0 0 0	5 3 0.3

8 Riudavets, et al. Cause of death in patients attending MS clinics. Neurology, 1991 Aug; 41 (8): 1193-6.

connective tissue disorders				
Neoplasms benign, malignant and unspecified	5 4 0.6	1 1 0.2	2 2 0.4	1 1 0.1
Psychiatric disorders	1 1 0.2	3 2 0.3	0 0 0	3 2 0.2
Ear and labyrinth disorders	2 2 0.3	0	0	2 2 0.2
General disorders and administration site conditions	2 2 0.3	4 4 0.7	1 1 0.2	2 2 0.2
Surgical and medical procedures	5 4 0.6	1 1 0.2	4 4 0.9	2 2 0.2
Immune System disorder	1 1 0.2	3 3 0.5	0 0 0	2 2 0.2
Eye Disorders	0 0 0	0	0 0 0	1 1 0.1
Metabolism and nutritional disorders	0 0 0	1 1 0.2	0 0 0	2 1 0.1
Cardiac disorders	1 1 0.2	5 4 0.7	3 3 0.7	5 2 0.2
Vascular disorders	2 2 0.3	0 0 0	0 0 0	1 1 0.1
Renal and urinary disorders	1 1 0.2	0 0 0	7 2 0.4	1 1 0.1
Pregnancy, puerperium and perinatal conditions	0 0 0	1 1 0.2	2 2 0.4	1 1 0.1
Reproductive system and breast disorders	1 1 0.2	0 0 0	2 2 0.4	1 1 0.1
Injury, poisoning and procedural complications	5 2 0.3	3 2 0.3	7 3 0.7	2 1 0.1
Respiratory, thoracic and mediastinal disorders	1 1 0.2	5 5 0.8	2 1 0.2	0 0 0
Investigations	0 0 0	3 1 0.2	1 1 0.2	1 1 0.1

ISS PostText Table 43 adapted
A serious AE (SAE) is defined as any event that was fatal or immediately life-threatening, resulting in or prolonged a hospitalization, was permanently or significantly disabling, was a congenital anomaly or required medical or surgical intervention or to prevent permanent sequelae or any of the previously mentioned outcomes.

Pool 2

This cohort included those in the extension OL phase treated with GA for either an extended period (ES) over a year, or delayed start (DS) treated first with placebo or GA 20 mg/day followed by GA after the first year. SAE were again reasonably well balanced. SAEs were reported by 2.9% of those in the DS GA 40 mg TIW group, 2.5% of those in the ES GA 40 mg TIW group, 1.3% of those in the DS GA 40 mg/day group, and 2.4% of those in the ES GA 40 mg/day group. The SAEs for Pool 2 are summarized in Table 28.

Table 28 Pool 2 Frequency and Incidence of SAE by SOC

Primary System Organ Class	**Delayed Start GA 40 mg/day N = 523** r n (%)	**Early Start GA 40 mg/day N = 482** r n (%)	**Delayed Start GA 40 mg TIW N = 419** r n (%)	**Early Start GA 40 mg TIW N = 834** r n (%)
Any class	13 7 1.3	16 12 2.5	28 12 2.9	24 20 2.4
Infections and infestations	2 2 0.4	0	9 5 1.2	2 2 0.2

Nervous system disorders	2	1	0.2	2	1	0.2	1	1	0.2	4	3	0.4
Gastrointestinal disorders	3	3	0.6	0	0	0	2	2	0.2	0	0	0
Hepatobiliary disorders	0	0	0	0	0	0	0	0	0	1	1	0.1
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	1	1	0.2	1	1	0.1
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	0	0	0	1	1	0.1
Neoplasms benign, malignant and unspecified	1	1	0.2	6	5	1.0	0	0	0	1	1	0.1
Psychiatric disorders	0	0	0	1	1	0.2	2	2	0.5	0	0	0
General disorders and administration site conditions	1	1	0.2	1	1	0.2	0	0	0	0	0	0
Surgical and medical procedures	1	1	0.2	2	2	0.4	2	2	0.5	2	2	0.2
Immune System disorder	0	0	0	1	1	0.2	1	1	0.2	0	0	0
Eye Disorders	0	0	0	0	0	0	0	0	0	1	1	0.1
Cardiac disorders	0	0	0	0	0	0	0	0	0	1	1	0.1
Vascular disorders	2	2	0.4	0	0	0	1	1	0.2	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	0	0	0	1	1	0.1
Pregnancy, puerperium and perinatal conditions	0	0	0	0	0	0	0	0	0	1	1	0.1
Reproductive system and breast disorders	0	0	0	2	1	0.2	0	0	0	2	2	0.2
Injury, poisoning and procedural complications	0	0	0	1	1	0.2	1	1	0.2	0	0	0
Respiratory, thoracic and mediastinal disorders	1	1	0.2	0	0	0	2	2	0.5	1	1	0.1
Investigations	0	0	0	0	0	0	1	1	0.2	0	0	0
Blood and Lymphatic	0	0	0	0	0	0	0	0	0	1	1	0.1
Congenital Familial Genetic	0	0	0	0	0	0	1	1	0.2	0	0	0

Infections and Infestations
Pool 1

Infections and infestations were noted to be the most frequent SOC with SAEs reported during the DB phase, with highest incidence on GA 40 mg TIW dose. There were 4 cases on GA 20 mg/day (0.6%), 2 cases on GA 40 mg/day (0.3%), 3 cases on placebo (0.7%), and 11 cases on GA 40 mg TIW (1.2%) as displayed in Table 29. The types of infection experienced leading to SAE were diverse. Previously infection, influenza, rhinitis, bronchitis, gastroenteritis, vaginal candidiasis have been described in the label as occurring more frequently than on placebo. In this cohort some atypical infections were seen, a possible case of osseous TB which was not verified with biopsy, and a case of herpes zoster. A case of latent TB was also noted in a patient that previously had a fever workup and was treated for ear infection and sinusitis. Narratives are provided in Table 30.

Table 29 Pool 1 Infections and Infestations SOC related PTs

Preferred Term	GA 20 mg/day N = 630 N	%	GA 40 mg/day N =615 N	%	GA 40 mg TIW N = 943 N	%	Placebo TIW N = 461 N	%
ALL subjects	4	0.6	2	0.3	11	1.2	3	0.7
Tuberculosis	0		0		2	0.2	0	
Bronchitis	0		2	0.3	0		0	
Candidiasis	1	0.2	0		0		0	
Device Related Infection	1	0.2	0		0		0	
Gallbladder Empyema	0		0		1	0.1	0	
Gastroenteritis Rotavirus	0		0		1	0.1	0	
Herpes Zoster	1	0.2			1	0.1		
Influenza	0		1	0.2	1	0.1	0	
Injection Site Abscess	0		0		1	0.1	0	
Nail Infection	0		0		1	0.1	0	
Pneumonia	0		0		2	0.2	0	
Pyelonephritis Acute	0		0		1	0.1	0	
Pyelonephritis Chronic	1	0.2	0		0		2	0.4
Sinusitis	0		0		1	0.1	0	
Sepsis	0		0		1	0.2	1	0.2
Viral Infection	0		0		1	0.1	0	
Vestibular Neuronitis					1	0.1		

Table 30 Pool 1 Infections and Infestations SOC Narratives for SAEs

Patient ID	Age, Sex, PT	Time onset	Comments
GA 20 mg/day (n = 630)			
9016322204	51 F Device related infection	78 days	Developed breast cancer, complete mastectomy and reconstruction with an expander. Expander needed to be removed on day 78 due to infection. Discontinued study drug day 94. *May be related to study medication.*
9016500204	22 F Pyelonephritis chronic	103 days	History of chronic pyelonephritis admitted to hospital and treated due to recurrent symptoms. Study drug not interrupted. *Cannot rule out relationship to study medication but most likely related to MS.*
9016520503	25 F Candidiasis	114 days	Hospitalized for acute cholecystitis and candidiasis. Treated with antibiotics and antifungal medications. Discontinued study drug. *Cannot rule out relationship to study medication*
9016530107	24 M Herpes Zoster		Developed herpes zoster of leg and admitted to the hospital for IV acyclovir. No change in study drug. *Probably related to the study medication with reactivation of herpes zoster.*

GA 40 mg/day (n = 615)			
9016102806	26 M Bronchitis Influenza	320 days	Developed a cough and sore throat, fever and MS exacerbation. Nasal swab positive for influenza type A. Given IV antibiotics. No change in study medication. *Cannot rule out relationship to study medication.*
9016102905	54 F Bronchitis	28 days	Developed fever and symptoms of bronchitis. No change in study medication. *Cannot rule out related to study medication.*
GA 40 mg TIW (n = 943)			
301130303	40 F Latent Tuberculosis	3 months	Diabetic from USA with history of benign gastric neoplasm who had a normal CXR at enrollment. After starting GA 40 mg TIW developed intermittent pyrexia after finishing treatment for ear infection, sinusitis with levofloxacin. Investigation of pyrexia revealed neck CT which showed a prominent LN. The node was not biopsied .QuantiFERON-TB gold test was positive after the pyrexia resolved. Latent TB was diagnosed. The CXR remained normal. Patient was treated with TB medication and was able to complete study DB study. *May be related to study medication.*
301506109	30 F Gastroenteritis	9 days	Hospitalized with gastroenteritis with positive stool sample for rotovirus, continued in study *Cannot rule out related to study medication.*
301506404	52 F Injection site abscess Staph sepsis Bone tuberculosis	5 months	History of sciatica which reoccurred in this patient from Russia. Hospitalized and received IV dexamethasone, analgesics, diclofenac and other medications. Injection site abscesses were found and severe in both hips and left gluteal region. Developed fever and pyelonephritis and was treated with oral azithromycin and amoxicillin/clavulanic acid followed by IV ciprofloxacin and metronidazole. Blood cultures were positive for staph aureus and sepsis was severe. After approximately 6 weeks symptoms resolved but within 2 weeks she developed fever and was hospitalized with severe pain in the lumbar region, right hip. CT showed spondylitis L4-L5, inflammation of the right iliac and iliopsoas muscles. Received more IV antibiotics (amoxicillin/clavulanic acid). Three weeks later she had severe lumbar radiculopathy. Thought to have tuberculous spondylitis but no biopsy or testing performed. Terminated from the study and started on TB medication. *Cannot rule out related to study medication.*
301522105	28 F Influenza Sinusitis	4 months	Hospitalized for both symptoms and treated with IV antibiotics which resolved, continued treatment. *Cannot rule out related to study medication.*
301522306	44 M Nail infection	1 month	Hospitalized and given IV antibiotics, continued treatment. *Cannot exclude related to study medication.*
301536913	47 F Viral infection	10 weeks	Hospitalized with MS exacerbation and viral infection, study drug briefly interrupted and then resumed. *Cannot rule related to study medication.*
301537307	44 M Pneumonia	3 days	Subject was sick upon enrollment with nasopharyngitis which resolved in 3 days, then three days later hospitalized with fever, cough, positive chest X-ray. Received IV antibiotics. No change in study drug. *Not likely related to study medication.*
301537321	50 M	4 months	Developed fever and had a Chest X-ray compatible

	Pneumonia		with pneumonia, treated with IV antibiotics. Study drug briefly interrupted and then resumed. *May be related to study medication.*
301538203	49 F Herpes Zoster Ophthalmic	11 months	Smoker with history of depression, spondylosis, developed acute pain in right eye and diagnosed by general practitioner. Treated with acyclovir. No change in study medication. *Probably related to study medication with reactivation of herpes zoster.*
301543402	27 F Pyelonephritis Acute	5 months	Diabetic, history of urethrotomy, hospitalized due to painful urination and lumbar pain. Treated with oral antibiotics. No change in study medication. *Unlikely related to study medication.*
301583903	35 F Gallbladder Empyema	Day 26	Abdominal pain with an abdominal ultrasound that showed an acute calculus cholecystitis and gallbladder empyema treated with IM and oral antibiotics. No change in medication. *Unlikely relate to study medication*

Pool 2

No atypical infections occurred during the OL phase. Of the infections that did occur, none appeared likely to have been related to Copaxone (see Table 31). There were two cases of appendicitis. Subject 301-506103 was a complicated case of peritonitis, caecitis, appendicitis with abscess and rupture as well as salpingitis, and it is possible that Copaxone usage may have contributed to the persistence of her infection. The other case of appendicitis, 301-522504 was uncomplicated. The SAE classified as gastroenteritis actually had colitis and did not have positive stool samples or any evidence of an active infection. Case 9016-311001 was of interest as this 39 year old male had a history of pulmonary TB, but during this study had an episode of pneumonia without any recurrence of his TB.

Table 31 Pool 2 Infections and Infestations SOC related PTs

SOCT	PTT	DS GA 40 mg TIW	DS GA 40 mg/day	ES GA 40 mg TIW	ES GA 40 mg/day
Infections And Infestations	Appendiceal Abscess	1	0	0	0
	Appendicitis	1	0	0	0
	Appendicitis Perforated	1	0	0	0
	Bronchitis	0	0	1	0
	Gastroenteritis	1	0	0	0
	Helicobacter Infection	1	0	0	0
	Infectious Peritonitis	1	0	0	0
	Pneumonia	0	1	0	0
	Salpingitis	1	0	0	0
	Sinusitis	0	1	0	0
	Urinary Tract Infection	2	0	0	0
	Viral Infection	0	0	1	0

Reviewer's Comment
SAEs due to Infection and Infestation were highest in the Copaxone 40 mg TIW cohort but no type of infection markedly predominated and most could not be directly attributed to the product, nor did there appear to be a dose response. Because there was a case of presumptive TB and another with latent TB, a search using Empirica Signal was done of the post-marketing reports looking at TB, pulmonary TB, disseminated TB, bony TB and TB in lymph nodes and no signal was detected.

Nervous System Disorders
Nervous system disorders as SAEs were slighter greater on the GA 40 mg TIW dose, 9 subjects (1.0%) and GA 40 mg/day, 7 subjects (1.1%), compared with GA 20 mg/day , 4 subjects (0.6%), and placebo, 3 subjects (0.7%). The SAE narratives were reviewed and revealed no specific pattern that can be linked to drug treatment. Migraine and syncope which were seen in subjects in these trials have previously been described in the label as occurring with some frequency. SAEs reported for MS relapses were most frequent in those who took Copaxone 40 mg TIW. A summary of the PTs associated with these SAEs is summarized in Table 32 and a line listing for each subject is provided in Table 33

Table 32 Nervous System SOC by PT for Pool 1

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N = 461 N %
ALL subjects	4 0.6	7 1.1	9 1.0	3 0.7
Apallic Syndrome	0	0	0	1 0.2
Aphasia	0	1 0.2	0	0
Cerebral Haemorrhage	0	0	0	1 0.2
Convulsion	1 0.2	0	0	0
Haemorrhage Intracranial	0	0	0	1 0.2
Headache	1 0.2	0	0	0
Ischaemic Stroke	0	0	1 0.1	0
Loss Of Consciousness	0	1 0.2	0	0
Lumbar Radiculopathy	0	0	1 0.1	0
Radiculitis Lumbosacral	0	0	1 0.1	0
Migraine	1 0.2	0	0	0
MS Relapse	0	1 0.2	5 0.5	1 0.2
Paraesthesia	2 0.4	1 0.2	0	0
Presyncope	0	1 0.4	0	0
Radicular Syndrome	0	1 0.2	1 0.1	0
Sciatica	0	0	1 0.1	0
Syncope	0	0	2 0.2	2 0.4
VIIth Nerve Paralysis	0	1 0.2	0	0

Table 33 Pool 1 Line listing of those with Nervous System SOC

SUBJID	GR	PTT	SEX/AGE	SEVERITY	ACTION TAKEN	ONSET DAY	DURATION
90061403	GA 20 daily	Convulsion	F 48	SEVERE	No Change	262	Ongoing
9016105305	GA 20 daily	Paraesthesia	F 26	SEVERE		350	17
9016340907	GA 20 daily	Headache	F 33	SEVERE	Drug Interrupted	357	2
9016340912	GA 20 daily	Migraine	F 36	SEVERE	No Change	307	2
301327202	GA 40 TIW	Syncope	M 34	MOD	No Change	363	1
301505602	GA 40 TIW	Relapse Hospitalized	F 37	MOD	No Change	218	46
301506404	GA 40 TIW	Lumbar Radiculopathy	F 52	SEVERE	Drug Withdrawn	200	Ongoing
301583319	GA 40 TIW	Ischaemic Stroke	M 48	SEVERE	No Change	360	23
301592604	GA 40 TIW	Relapse Hospitalized	F 42	MOD	No Change	363	14
301593005	GA 40 TIW	Radiculitis LS	F 22	SEVERE	No Change	356	6
301600907	GA 40 TIW	Relapse Hospitalized	M 29	MILD	No Change	362	8
301600936	GA 40 TIW	Relapse Hospitalized	F 47	SEVERE	Drug Withdrawn	211	71
301601212	GA 40 TIW	Relapse Hospitalized	F 45	MOD	Drug Interrupted	356	7
9016104911	GA 40 daily	Relapse Hospitalized	F 41	SEVERE	No Change	357	5
9016105307	GA 40 daily	Paraesthesia	F 27	SEVERE	No Change	356	Ongoing
9016321205	GA 40 daily	7th Nerve Paralysis	F 49	SEVERE	No Change	357	Ongoing
9016321801	GA 40 daily	Aphasia	F 43	SEVERE	No Change	361	1
9016511003	GA 40 daily	Presyncope	F 36	SEVERE	Drug Withdrawn	105	<1 Day
9016530502	GA 40 daily	LOC	M 44	SEVERE	Drug Withdrawn	48	<1 Day
9016540801	GA 40 daily	Radicular Syndrome	F 48	MODERATE	No Change	357	13
301505701	Pb TIW	Relapse	F 28	SEVERE	No Change	364	18
301537017	Pb TIW	Apallic Synd. Cerebral Hemorrhage	M 47	SEVERE	No Change	323	Ongoing
301600901	Pb TIW	Syncope	F 52	MILD	No Change	358	<1 Day

Since there was an imbalance in SAEs due to relapse, 5 individuals on GA 40 mg TIW and only 1 on placebo this was explored in more detail by looking at all AEs reported as MS relapse and not just SAEs. It was determined that there were a total of 41 AEs due to relapse. This represented 36 unique events among 35 subjects. Table 34 displays the frequency of unique relapses for each dose of Copaxone by severity. Doing the analysis in this fashion reveals that 1.9% of patients on placebo reported relapse and 2.0% of patients on GA 40 mg TIW reported relapse as an AE. Both cohorts predominantly had moderate relapses which limited activities of daily living. Severe relapses were no greater on GA 40 mg TIW than on placebo. All of the relapses deemed SAEs resulted in hospitalization even though the relapses were predominantly considered moderate and not severe.

Table 34 Number of unique relapses that are AEs by treatment cohort

Dose	N	Mild Relapses	Moderate Relapses	Severe Relapses	Total Relapses
GA 20 mg /day	630	1	2	0	3 0.05 %
GA 40 mg/day	615	0	5	1	6 1.0 %
GA 40 mg TIW	943	2	16	1	19 2.0%
Placebo	416	1	6	1	8 1.9 %
Total Unique Relapses		4	29	3	36

Pool 2
Review of the narratives for the neurological SAEs appeared unrelated to Copaxone. A summary of the findings is found in Table 35. A patient that was reported to have epilepsy and brain edema actually had a seizure after gamma knife surgery for an AVM which was unrelated to Copaxone.

Table 35 Pool 2 Nervous System SOC related PTs

SOC	PTT	DS GA 40 mg TIW	DS GA 40 mg/day	ES GA 40 mg TIW	ES GA 40 mg/day
Nervous System Disorders	Brain Edema	0	0	1	0
	Dizziness	2	0	0	0
	Epilepsy	0	0	2	0
	Headache	0	1	0	0
	MS Relapse	0	0	1	0
	Paralysis Flaccid	0	0	0	1
	TIA	0	1	0	0
	7^{th} Nerve Paralysis	0	0	0	1

Reviewer's Comment
Most of the neurologic events that occurred had no clear relationship to treatment. Although the SAEs due to relapse, all of which resulted in hospitalization, were greatest on Copaxone 40 mg TIW compared to placebo, individuals who had relapses considered them moderate and not severe. It is reassuring that relapses were no more frequent a cause of AE on drug than on placebo, and the increase in the SAE rate appears to be due to the fact that more happened to be hospitalized when treated with Copaxone than when treated with placebo, rather than the episodes actually being deemed more serious.

Gastrointestinal Disorders
Pool 1
The incidence of gastrointestinal disorder SAEs was similar on all doses of Copaxone and greater than placebo. Nausea, vomiting and dysphagia are previously described in the drug label as occurring in >2% in the marketed product. Narratives for the cases in Pool 1 are described below and a summary of PT are found in Table 36.

Table 36 Pool 1 Gastrointestinal SOC related PTs

System Organ Class Preferred Term	GA 20 mg/day N = 630 N	 %	GA 40 mg/day N = 615 N	 %	GA 40 mg TIW N = 943 N	 %	Placebo TIW N = 461 N	 %
ALL subjects	3	0.5	3	0.5	4	0.4	1	0.2
Abdominal Pain	1	0.2	1	0.2	1	0.1	0	
Constipation	0		1	0.2	0		0	
Diarrhoea	0		1	0.2	0		1	0.2
Gastric Ulcer Haemorrhage	0		0		2	0.2	0	
Inguinal Hernia	0		0		1	0.1	0	
Intestinal Obstruction	1	0.2	0		0		0	
Nausea	0		1	0.2	0		0	
Palatal Oedema	1	0.2	0		0		0	
Pancreatitis	0		0		1	0.1	0	
Swollen Tongue	2	0.4	0		0		0	
Vomiting	0		1	0.2	0		0	

- 9016-322103 A 35 year old female on Ga 20 mg/day with a history of cholelithiasis who was admitted to the hospital on day 317 for a cholecystectomy due to symptomatic gallstones. History of gallstones preceded study. *This was unlikely to be related to treatment with Copaxone.*

- 9016-322307 A 49 year old female on GA 20 mg/day who had an episode of feeling hot, four hours after injection that occurred on day 5 of treatment. In addition she had chills, fever up to 40C, elevated blood pressure, nausea, diarrhea, tongue and palatal edema. She briefly stopped the study medication and the symptoms resolved but then discontinued several weeks later. *Her symptoms may be related and may represent an allergic reaction.*

- 9016-321801 A 43 year old female subject was assigned to GA 40 mg/day. She had an episode of shortness of breath, back pain, inability to speak, chills, diarrhea, and vomiting on day 150 of treatment. Four days later she was hospitalized with diffuse pain in her hands, arms, hip, knees and a slight headache. She did have a mild temperature of 37.9, leucocyte count of 14, 3, elevated CRP of 41.4, and increased IgE of 790 mcg/L. She was diagnosed with an allergic reaction and Voltaren was prescribed. She completed the DB phase but did not continue into the OL phase. *Symptoms may be related to the study medication.*

- 9016-380602 A 29 year old male who chronically used baclofen for muscles cramps and also had a history of intestinal volvulus. He developed headache, chills and vomiting on day 5 of therapy with GA 40 mg/day. He discontinued medication on day 117 because of injection site reactions. Two days after he discontinued he was admitted to the hospital with abdominal pain and constipation. He was treated with an enema and medication and after a month his symptoms resolved. *More likely this is a complication related to his use of baclofen.*

- 301-130606 A 45 year old male nonsmoker with a history of rheumatoid arthritis who uses ibuprofen. Four months after starting GA 40 mg TIW he had a syncopal episode. He was found to have a bleeding gastric ulcer and treated with proton pump inhibitors. Helicobacter test was positive. A week later he was readmitted to the hospital with an episode of syncope. His gastric bleeding required gastroscopy and surgery. *His ulcer and GI bleed is likely related to his use of ibuprofen and positive helicobacter.*

- 301-537004 A 42 year old overweight female on simvastatin for hypercholescerolemia. She was being treated with GA 40 mg TIW. After an injection she had an episode of headache, nausea, dyspnea and flushing. This resolved, but two weeks later she had an episode of nausea, severe abdominal pain and diarrhea. Her symptoms resolved within a day. *Cannot rule out related to study medication.*

- 301-592703 A 28 year old overweight male GA assigned to 40 mg TIW. He was hospitalized for the repair of an inguinal hernia. *This is unlikely to be related to Copaxone.*

- 301-601004 A 38 year old female who smoked and who was assigned to GA 40 mg TIW. She also took many daily vitamins including A and B complex, Vitamin C and Omega 3 oil, monthly cyanocobalamine, and also took ketoprofen for her migraines. Shortly after undergoing plastic surgery she got hospitalized for cholelithiasis and acute pancreatitis. She had endoscopic surgery and a calculus was extracted. There were actually multiple stones noted in the biliary tract. During her hospitalization she was noted to have erosive gastritis. *Both the gastritis and the pancreatitis are unlikely to be related to Copaxone and are more likely related to the ketoprofen use and the cholelithiasis.*

Pool 2

There were two cases of pancreatitis, both on DS GA 40 mg, but neither seemed likely to be related to the use of Copaxone. There was also one report of severe hemmorhoids on ES GA 40 mg TIW, and one report of vomiting on DS GA 40 mg/day.

Reviewer's Comment

As reported in past trials nausea and vomiting appeared related to use of this product. Other gastrointestinal symptoms reported here are common occurrences most likely unrelated to treatment with Copaxone.

Hepatobiliary Disorders
Pool 1
Hepatobiliary complaints, though infrequent as SAEs, were greatest in those on GA 40 mg TIW. There were four subjects (0.4%) on GA 40 mg TIW, two subjects (0.3%) on GA 20 mg/day, one subject on GA 40 mg/day (0.2%), and one subject (0.2%) on placebo as displayed in Table 37 and 38 who had hepatobiliary complaints. Cholecystitis and cholelithiasis occurred both in those on Copaxone and on placebo and are known to occur frequently in middle aged females.

There were two cases of possible drug-induced liver injury (DILI), one with labs that appeared to meet Hy's Law criteria described below and one who had polypharmacy including prolonged treatment with steroids that might have played a role in the transaminase elevations. The cases are discussed further in section 7.3.4.

Table 37 Pool 1 Hepatobiliary SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N = 461 N %
ALL subjects	2 0.3	1 0.2	4 0.4	1 0.2
Biliary Dyskinesia	0	1 0.2	0	0
Cholecystitis	0	0	1 0.1	0
Cholecystitis Acute	1 0.2	0	0	0
Cholelithiasis	1 0.2	0	1 0.1	1 0.2
Drug-Induced Liver Injury	0	0	1 0.1	0
Hepatitis Toxic	0	0	1 0.1	0

Table 38 Line listings of those with Hepatobiliary SOC- Pool 1

SUBJID	GR	PTT	SEX/AGE	DAY TX	SEVERITY	TREATMENT	RECOVERY	DURATION
9016-322103	GA 20 daily	Cholelithiasis	F 34	359	SEVERE	No Change	R	8
9016-520503	GA 20 daily	Cholecystitis Acute	F 24	110	MODERATE	Drug Withdrawn	R	11
301-506012	GA 40 TIW	Drug-induced Liver Injury	F 33	107	MODERATE	No Change	R	57
301-583903	GA 40 TIW	Cholecystitis	F 34	355	SEVERE	No change	R +Sequelae	2
301-592408	GA 40 TIW	Hepatitis Toxic	M 46	31	SEVERE	Drug Withdrawn	R	*NR
301-601004	GA 40 TIW	Cholelithiasis	F 38	362	MODERATE	No change	R	7
9016-105906	GA 40 daily	Biliary Dyskinesia	F 33	55	SEVERE	No Change	R	6

301-537904	Pb TIW	Cholelithiasis	M 40	354	SEVERE	No Change	R	76

- 301-592408 A 46 year old male was treated with 40 mg TIW. He was hospitalized with symptoms of jaundice including yellow sclera and dark urine after a month on Copaxone. His symptoms probably started 10 days earlier. He was noted to have liver function elevations including an AST of 347 IU/L, ALT 577 IU/L, and total bilirubin 168.9 mmol/L. The following day his labs revealed an AST of 545 IU/L, Alt 378 IU/L, and total bilirubin 114.5 mmol/L. The patient was noted to have a slightly enlarged liver and mild monocytosis. Abdominal ultrasound was normal and serologies for hepatitis were unremarkable. Information about alcohol use, illicit drugs, herbs, dietary supplements and serology for autoimmune hepatitis were not available. Treatment with Copaxone was discontinued and treatment with hepatoprotective silybum marianum began. Six days later liver functions returned to near normal with AST of 66 IU/L, ALT 231 IU/L, and total bilirubin 49 mmol/L. At his early termination visit 2 weeks after hospitalization his labs revealed AST 18 U/L (WNL), ALT 57 U/L (1.2 x ULN) and bilirubin of 41 umol/L (1.9 x ULN). According to an information request with the sponsor the labs were not thought to meet Hy's Law criteria as the reference range for the hospital laboratory where the blood was sent were not provided and the recovery was thought to be too rapid for DILI.

- 301-506012 A 34 year old female was treated with 40 mg TIW. She was treated with BCP chronically. She had a relapse one month into the study and was treated with IV steroids for five days and then oral steroids. Treatment with steroids was for over a month (a protocol violation). Several weeks later her liver functions rose to ALT 528 IU/l (11x ULN), AST 324 IU/l (7.7 x ULN), ALP 160 IU/l (1.3 x ULN), total bilirubin 25 umol/L (1.1 x ULN) and direct bilirubin 9 umol/L (1.5 x ULN). Despite these changes she remained on study medication. One week later liver functions rose further to AST 542.4 (17 x ULN), ALT 494 (15.9 x ULN). Serology for infectious hepatitis was negative and information regarding alcohol, herbs, dietary supplements, autoimmune hepatitis was unknown. Jaundice was evident and abdominal ultrasound showed hepatomegaly, chronic cholecystitis, and diffuse changes suggestive of chronic hepatitis. The gastroenterologist thought that this represented a case of drug induced liver dysfunction and drug was permanently discontinued on day 129. Liver functions returned to normal. The subject was terminated from the study because of protocol violation, the excessive use of steroids, and not for the adverse event. At early termination the ALT was 91 IU/l (1.9 X ULN), AST 54 IU/l (1.3 X ULN), total bilirubin 24 umol/L (1.1 X ULN) and direct bilirubin 9 umol/L (1.5 X ULN). ALP was within normal limits, 50 IU/l. Several months later the patient had another relapse and received steroid treatment again. She was noted to have mild elevation in transaminase levels with an ALT of 113 U/l and AST 55 U/l.

Pool 2

There was a single case of cholelithiasis in subject 301-538102 on ES GA 40 mg TIW.

Reviewer's Comment

Two subjects treated with GA 40 mg TIW had SAEs related to elevated transaminase levels that potentially were drug induced. The first case, 301-592408, may represent a case meeting Hy's Law criteria. Even though the reference range of the lab where the blood work was sent is not known, the high values are very suggestive as are the symptoms of jaundice and yellow sclera. Two week later, upon recovery, the patient's bilirubin was still elevated at 1.9 x ULN at the study laboratory suggesting that earlier the bilirubin may have been quite a bit higher. Rapid recovery from DILI is possible when the offending agent is stopped and does not necessarily indicate a viral etiology. The patient was never rechallenged with Copaxone and causality is unknown. Nonetheless, a single case possibly meeting Hy's Law criteria, in light

of minimal evidence in the post-marketing literature for DILI, does not suggest a need to add this to the label. The second case, 301-506012, was on BCP and received a prolonged course of steroids, both known to cause DILI. When rechallenged with steroids at a later date off of Copaxone, she again had modest transaminase elevations, making it unlikely that Copaxone alone was responsible for the initial elevations observed. The remaining cases of hepatobiliary problems such as cholelithiasis were present both on Copaxone as well as placebo and are common in middle aged women; there is no evidence to strongly suggest that the AE is related to Copaxone.

Skin and Subcutaneous Tissue Disorders
Cohort 1
Slightly more subjects on GA 40 mg TIW had skin and subcutaneous tissue disorders leading to SAEs as seen in Table 39 than on other doses or placebo. Rash, pruritus, urticarial, and other skin disorders are already described in the label as being associated with Copaxone. The narratives of those with SAEs due to skin and subcutaneous disorders are provided below.

Table 39 Pool 1 Skin and subcutaneous tissue SOC and related PT

System Organ Class Preferred Term	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N =461 N %
ALL subjects	2 0.3	4 0.4	1 0.2
Angioedema	1 0.2	2 0.2	0
Erythema	0	1 0.1	0
Pruritus	0	1 0.1	0
Rash	0	1 0.1	0
Swelling Face	1 0.2	0	0
Urticaria	0	1 0.1	1 0.2

- 301-522718 A 37 year old female on GA 40 mg TIW develop a rash on day 12 of therapy. Three days later she had an anaphylactic reaction with injection including generalized rash, pruritus, flushing, vomiting, abdominal pain and a drop in blood pressure to 70. After treatment she fully recovered and discontinued early. *Rash is a symptom of an allergic reaction and felt to be causally related to treatment.*

- 301-537306 A 26 year old female with multiple SAEs reported angioedema 1 minute after drug injection of her dose of GA 40 mg TIW. *This is felt to be related to treatment.*

- 301-537329 A 49 year old obese female had IPIR 5 months after starting GA 40 mg TIW and symptoms included pruritus, erythema, dyspnea, anxiety and urticaria. Six months later she had a second episode and at that time interrupted therapy briefly. She then completed the study but did not enter the OL period. *This symptom appears to be causally related.*

- 301592801 A 52 year old female developed injection site inflammation, erythema, and edema after her first injection of GA 40 mg TIW. This reoccurred two months into the study and she terminated early. *This symptom appears to be causally related.*

- 9016103903 This was a 44 year old female who had injection site reactions from the first day of the study. On day 119 after taking GA 40 mg/day she experienced swelling of the face, dyspnea, and nausea. Symptoms resolved after a trip to the ER where she received steroids and diphenylhydramine for an allergic reaction. The patient reports that she has had similar episodes in the past when taking oxycodone. She had undergone surgery just 9 days before this allergic reaction for a tubal ligation, but was not thought to have been administered oxycodone. *This episode is probably related to treatment.*

- 9016351309 This 34 year old female developed chest erythema and pruritus on day 29 of treatment with GA 40 mg/day. This was followed by eyelid edema that resolved. There was no dysphagia, dyspnea tachycardia or hypotension. *This is most likely related to treatment.*

Pool 2

One subject, 301-537137, had an exacerbation of a preexisting psoriasis, and a second subject, 301-537303 who had a history of asthma, developed urticaria.

Reviewer's Comment

Many of the symptoms reported as skin disorders appear related to use of Copaxone and appear to be allergic reactions and are consistent with what is already known about the product from the label. Most were able to remain on the study medication except for one suggestive of anaphylactic shock and another with recurrent episodes of edema and erythema associated with injection site inflammation; both discontinued.

Musculoskeletal and Connective Tissue

Pool 1

According to Copaxone's label, > 2% of those using the product have experienced back pain. Back pain did occur in these trials as well as other nonspecific musculoskeletal symptoms that lead to SAEs as seen in Table 40. Narratives are also provided below.

Table 40 Pool 1 Musculoskeletal and Connective Tissue SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %
ALL subjects	3 0.5	1 0.2	3 0.3
Arthralgia	1 0.2	0	0
Back Pain	0	1 0.2	1 0.1
Chondropathy	1 0.2	0	0
Disc Disorder	0	0	1 0.1
Muscular Weakness	1 0.2	0	0

Myositis	0	0	4 0.4
Spondylitis	0	0	1 0.1

- 9016-104109 A 38 year old female treated with GA 20 mg/day had an episode of bilateral extremity muscle weakness and numbness on day 62 of therapy. Without treatment these improved spontaneously and resolved with minimal residual deficit within three days. She was diagnosed with an MS exacerbation. *These symptoms appear unrelated to Copaxone.*

- 9016-301806 A 49 year old female who had a history of a right knee injury was hospitalized due to a grade III right knee chondropathy. She received physiotherapy, iontophoresis and was ultimately discharged from the hospital but remained on the GA 20 mg/day. *The symptoms appear unrelated to Copaxone.*

- 9016-322307 A 49 year old female on GA 20 mg/day who experienced arthralgias, hotness four hours after injection of study medication on day 6. The next day after injection she developed a fever of 40C and other symptoms consistent with IPIR. *The patient's symptoms appear related to study medication.*

- 9016-321801 A 43 year old female treated with GA 40 mg/day. She experienced ISRs. On day 150 of the trial she developed dyspnea, tachycardia, chills, back pain aphasia, vomiting and diarrhea. Symptoms resolved within 2 hours. Her symptoms were felt to be an allergic reaction. *Her symptoms probably were related to treatment.*

- 301-506404 A 52 year old overweight female treated with GA 40 mg TIW had a history of sciatica developed recurrent sciatic and got hospitalized. In the hospital she had multiple complications with abscesses and sepsis treated with antibiotics and dexamethasone, and ultimately was diagnosed with osseous TB. During her illness she had symptoms of muscle pain or myositis as well as spondylitis. *The subject's symptoms appear related to TB which may be related to treatment.*
- 301-538012 A 44 year old male on GA 40 mg TIW had a previous history of disc disease, recurrent sciatica and disc surgery at L4-5 and L5-S1. He got hospitalized for intervertebral disc disorder and recovered, but when pain reoccurred he underwent spinal decompressive surgery. *This is most likely unrelated to treatment given his previous history.*

- 301571006 A 41 year old male experienced low back pain approximately 6 months after starting. GA 40 mg TIW which resolved. The patient continued his study medication. *This is unlikely to be related to treatment.*

Pool 2

There was a single SAE for back pain in subject 301-592615 on ES GA 40 mg TIW.

Reviewer's Comment

In addition to the back pain described in the literature, other complaints of pain occurred in patients with MS who use Copaxone. Most are nonspecific, sporadic, or related to IPIR or their underlying disease. There does not appear to be evidence for a dose response.

Neoplasms benign, malignant and unspecified

Cohort 1

Neoplasia was found in all treatment arms and is probably unrelated to treatment in these trials of no more than a year's duration. Breast cancer is discussed further in section 7.3.4. Table 41 provides a summary of the findings for Pool 1.

Table 41 Pool 1 Neoplasms SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N = 461 N %
ALL subjects	4 0.6	1 0.2	1 0.1	2 0.4
Breast Cancer	2 0.4	1 0.2	0	0
Fibroadenoma Breast	1 0.2	0	0	0
Metastases Lymph nodes	1 0.2	0	0	0
Oesophageal Carcinoma	0	0	0	1 0.2
Thyroid Cancer	0	0	0	1 0.2
Uterine Leiomyoma	1 0.2	0	1 0.1	0

This is a brief summary of the cases.

- 301-132104 GA 40 mg TIW This 42 year old obese female was treated with GA 40 mg TIW. One year after starting the drug she had a total abdominal hysterectomy for a uterine leiomyoma.
- 9016-322411 GA 20 mg/day Uterine Leiomyoma
- 9016-520304 GA 20 mg/day Fibroadenoma of Breast
- 301-537604 Placebo Prior history of treated goiter now biopsy proven for thyroid cancer
- 9016-321406 GA 20 mg/day Breast Cancer with metastases to Lymph Nodes see section 7.3.4
- 9016-322204 GA 20 mg/day Breast Cancer see section 7.3.4
- 9016-341201 GA 40 mg/day Breast Cancer see section 7.3.4

Pool 2

A listing of those subjects with neoplasia in the OL phase is found in Table 42. In the OL period the subject with malignant melanoma, 9016-311901, actually first noticed the skin lesion on day 61, too soon to be likely to be related to Copaxone, but diagnosis was made during the OL period. Liver metastases due to an unknown primary were detected in a single subject during the OL period, but she had symptoms of her cancer earlier in the DB period when she presented with an abnormal urinalysis and hypercalcemia. A subject, 9016-103605 with a leiomyoma, had a lengthy history of dysmenorrhea preceding the trial. Another subject, 9016-530804, had both a leiomyoma and a benign ovarian tumor. A further subject was diagnosed with liver metastases due to an unknown primary, but her symptoms began early in the DB phase.

Table 42 Pool 2 Neoplasm SAEs and related PTs

SOC	PTT	DS GA 30 Mg TIW	DS GA 40 Mg/day	ES GA 40 Mg TIW	ES GA 40 Mg/day
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Ovarian Tumour	0	0	0	1
	Breast Cancer	0	0	1	2
	Malignant Melanoma	0	0	0	1
	Metastases To Liver	0	2	0	0
	Uterine Leiomyoma	0	0	0	2

Reviewer's Comment
The cases of neoplasia detected probably are unrelated to treatment in these trials as they were either in subjects with preexisting history or detected too soon after starting treatment to be related. The only exception that is explored further in section 7.3.4 is breast cancer.

Psychiatric Disorders
Pool 1
Anxiety and nervousness are already described in the Copaxone label as occurring in > 2% of patients who take this product and were detected in this cohort as well. Anxiety can accompany IPIR as well as ISR, although it may also occur independently. SAEs were only observed in those with anxiety on Copaxone and none were observed in those on placebo. Table 48 summarizes the findings for Cohort 1 and this is followed by a line listing of some of the pertinent cases.

Table 43 Pool 1 Psychiatric SOC by PT

Systems Organ Class Preferred Term	GA 20 mg/day N = 630 N	%	GA 40 mg/day N = 615 N	%	GA 40 mg TIW N = 943 N	%
ALL subjects	1	0.2	2	0.3	2	0.2
Anxiety	0		2	0.4	1	0.1
Depression	0		0		1	0.1
Panic Attack	1	0.2	0		0	
Psychotic Disorder	0		1	0.2	0	
Suicidal Ideation	0		0		1	0.1

- 9016-311502 A 36 year old female with a history of agoraphobia who developed acute psychosis on day 226 of the study. She had been assigned to a dose of GA 40 mg/day. Symptoms resolved after psychiatric hospitalization and treatment. The study drug was discontinued for a month. *It is unlikely that this is due to the study medication.*

- 9016-322004 A 55 year old male assigned to GA 20 mg/day who had anxiety associated with chest pressure, vertigo around the time of an injection. He had a second episode a day later that resolved. He was able to continue the medication. *The anxiety and panic reaction are probably related to study medication.*

- 301-131801 A 23 year old female with a history of anxiety, depression prior to enrollment. She was chronically on paroxetine, alprazolam, and Vicodin prn. She was treated with GA 40 mg TIW. After 12 months on study medication she was hospitalized for a worsening depression and suicidality. *This is most likely related to preceding history.*

- 301537329 A 49 year old obese female assigned to GA 40 mg TIW who 5 months after enrollment had IPIR accompanied by anxiety. This resolved but reoccurred again a month later. Approximately 6 months later another episode occurred. The study drug was stopped. *This is most likely related to her treatment.*

Pool 2

Subject 9016-103302 treated with ES GA 40 mg/day had a 7 year history of alcohol abuse and went to get detoxified, Subject 301-131701 treated with DS GA 40 mg TIW had a lengthy history of depression and other psychiatric maladies, and subject 301-59211 treated with DS GA 40 mg TIW developed mania during this time interval and apparently had a past history unknown at the time of enrollment.

Reviewer's Comment

MS patients generally have more depression and psychiatric complaints than the general population. Specifically patients treated with Copaxone may have an increased amount of anxiety typically related to IPIR and ISR. There is nothing in the SAE reports to suggest that the other psychiatric complaints are causally related to the product.

Ear and Labyrinth Disorder

Pool 1

Labyrinth symptoms were not common on Copaxone, but did occur more frequently then on placebo. On GA 40 mg TIW one subject had hypoacusis and one had positional vertigo. On Ga 20 mg/day two subjects had vertigo. Causality cannot be determined.

- 9016-104109 A 38 year old female treated with GA 20 mg/day that had an episode of imbalance, and numbness and weakness of her lower extremities. This was diagnosed as an MS exacerbation on day 62 of treatment. On day 84 she had an episode of vertigo that resolved within 3 three days. *This is unlikely to have been related to treatment and is more likely to be related to MS.*

- 9016-322004 A 55 year old male had acute vertigo associated with a panic attack on day 11 of therapy with GA 20 mg/day. The vertigo began two hours after his injection and he also experienced chest pressure. He got better spontaneously. The patient's anxiety and chest pressure are mostly likely related to treatment; *causality cannot be determined for the vertigo.*

- 301592604 A 43 year old female randomized to GA 40 mg TIW was noted on day 326 of therapy to develop a mild influenza-like illness associated with vertigo. She was treated with antibiotics for a concomitant urinary tract infection. Her symptoms resolved and she continued therapy. The vertigo appears related to the influenza-like illness. *Although influenza can be related to Copaxone the vertigo does not appear to be directly related.*

- 301593903 A 51 year old female randomized to GA 40 mg TIW developed rhinitis and an URI associated with hypoacusis which required treatment with mannitol, vinpocetine and other IV fluids. After a while her symptoms resolved and she completed the study and entered the OL period. *The hyperacusis appears to be related to her URI and so indirectly may be related to treatment with Copaxone.*

Pool 2
No SAEs were filed under this SOC during the OL phase.
Reviewer's Comment
The cases that occurred during the DB phase appeared unlikely to be related to Copaxone and may have had more to do with underlying MS, viral illness or anxiety.

General Disorders and Administration Site Conditions
Pool 1
General and administration site conditions are well known for causing numerous symptoms associated with injection site reactions (ISR) and the following SAEs are no exception. These symptoms increased with dose as there were 2 subjects on GA 20 mg/day (0.3%) and 4 subjects on GA 40 mg/day (0.7%) who had such reactions (see Table 44 and 45). Narratives for the two on GA 40 mg TIW are provided.

Table 44 Pool 1 General and administration site conditions SOC

Systems Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N = 461 N %
ALL subjects	2 0.3	4 0.7	2 0.2	1 0.2
Chest Discomfort	2 0.4	0	0	0
Chest Pain	0	4 0.8	0	0
Face Oedema	0	2 0.4	0	0
Feeling Hot	0	0	1 0.1	0
Oedema	0	0	0	1 0.2
Pyrexia	2 0.2	1 0.2	1 0.1	0

- 301-130303 A 40 year old obese female with DM, treated with GA 40 mg TIW, with benign gastric neoplasm developed intermittent pyrexia three months into study thought to be related to her sinusitis and otitis media. This case was later found to have latent TB and was described previously under the Infection SOC.

- 301-537329 This was a 49 year old female assigned to GA 40 mg TIW. Five months into the study she experienced IPIR with dyspnea, pruritus, and urticaria. A second reaction took place 6 months later on study day 347. That episode was accompanied by anxiety, feeling hot, erythema, pruritus, and urticaria and resolved without treatment. She completed the DB phase but did not enter the OL phase. *This most likely is IPIR related to the study medication.*

Table 45 Pool 1 Line listings General Disorders, Administration Site Conditions

SUBJID	DOSE	PTT	AGE/SEX	AESEV	ACTION	OUTCOME	DAY ONSET	DURATION
9016322004	GA 20 daily	Chest Discomfort	55 M	SEVERE	No Change	R	11	<1 Day
9016322307	GA 20 daily	Pyrexia	48 F	SEVERE	Interrupted	R	7	2
301130303	GA 40 TIW	Pyrexia	40 F	MILD	No Change			41
301537329	GA 40 TIW	Feeling Hot	49 F	MOD	No Change	R	347	<1 Day
9016101601	GA 40 daily	Chest Pain	46 F	SEVERE	No Change	R	103	1
9016105602	GA 40 daily	Chest Pain	54 M	MOD	No Change	R	78	<1 Day
9016321801	GA 40 daily	Pyrexia	43 F	SEVERE	No Change	R	150	1
9016511003	GA 40 daily	Face Oedema	37 F	MOD	D/C	R	105	<1 Day
301537038	PB TIW	Oedema	39 F	SEVERE	D/C	R + Seq	162	7

Pool 2

Subject 9016-103701 had chest pain that was later attributed to pancreatitis. Subject 301-522504 was reported as having fatigue as an SAE, but this appears miscoded as the SAE narrative described an episode of appendicitis and appendectormy without complication. Subject 301-537303 had pyrexia associated with IPIR. Subject 301-582905 had chills and asthenia following an injection as well as dyspnea and pyrexia.

Table 46 Pool 2 General Disorders and Administration Site Conditions

SOC	PTT	DS GA 40 mg TIW	DS GA 40 mg/day	ES GA 40 mg TIW	ES GA 40 mg/day
General Disorders And Administration Site Conditions	Asthenia	1	0	0	0
	Chest Pain	0	2	0	2
	Chills	1	0	0	0
	Fatigue	1	0	0	0
	Pyrexia	1	0	0	0

Reviewer's Comment

Most of the SAEs reported in this SOC were related to symptoms associated with IPIR known to be related to Copaxone or were sporadic and not thought to be related to Copaxone. Chest pain, a feature of IPIR which was described in several SAEs is already described in the label.

Surgical and Medical Procedures
Pool 1
Surgical and Medical Procedures appeared generally unrelated to drug treatment and occurred with greatest frequency in those on placebo. Table 46 displays the various procedures done to subjects in these studies during the DB period. The two breast cancer cases are described further in section 7.3.4.

Table 47 Pool 1 Surgical and Medical Procedures SOC associated PTs

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N =943 N %	Placebo TIW N = 461 N %
ALL subjects	4 0.6	1 0.2	2 0.2	4 0.9
Appendectomy	0	0	1 0.1	0
Cervix Operation	0	0	0	1 0.2
Cholecystectomy	1 0.2	0	0	0
Coronary Arterial Stent	0	1 0.2	0	0
Inguinal Hernia Repair	0	0	1 0.1	0
Malignant Breast Lump Removal	1 0.2	0	0	0
Mastectomy	1 0.2	0	0	0
Spinal Laminectomy	1 0.2	0	0	0
Toe Amputation	0	0	0	1 0.2
Tonsillectomy	1 0.2	0	0	1 0.2
Ureteric Calculus Removal	0	0	0	1 0.2

Pool 2
A number of subjects had procedures which are listed in Table 48.

Table 48 Surgical and Medical Procedure SOC associated PTs for Pool 2

SOC	PTT	DS GA 40 Mg TIW	DS GA 40 Mg/day	ES GA 40 mg TIW	ES Ga 40 mg /day
Surgical And Medical Procedures	Appendectomy	1	0	0	0
	Bartholin's Cyst Sx	0	0	0	1
	Hysterectomy	0	0	0	1
	Knee Arthroplasty	0	0	1	0
	Pancreatectomy	0	1	0	0
	Perineoplasty (for incontinence)	0	0	1	0
	Thyroidectomy (for Thyroid Cancer after	1	0	0	0

	goiter biopsied)				

Reviewer's Comment
Review of the narratives for Pools 1 and 2 and those treated with Copaxone showed no evidence for a relationship to treatment.

Immune System disorder
Pool 1
Immune reactions which included anaphylactic reaction, shock, and hypersensitivity were the cause of SAEs in 0.2% in those treated with GA 40 mg TIW, 0.2% in those treated with GA 20 mg/day, 0.5% in those treated with GA 40 mg/day, and not seen in those treated with placebo in Pool 1. Hypersensitivity is already described in the label as an AE occurring in 3% on Copaxone 20 mg/day. Table 49 suggests that the symptoms appear to be dose related. Table 50 summaries the line listings and narratives provided for the two on GA 40 mg TIW. Both cases recorded as anaphylactic shock, may have had an anaphylactic reaction, no blood pressure measurement was mentioned in the narrative to suggest shock. Two cases that were called anaphylactic reaction actually were anaphylactic shock as they were accompanied by hypotension.

Table 49 Pool 1 Immune disorders SOC by PT

System Organ Class **Preferred Term**	**GA 20 mg/day** **N = 630** **N %**	**GA 40 mg/day** **N = 615** **N %**	**GA 40 mg TIW** **N = 943** **N %**
ALL subjects	1 0.2	3 0.5	2 0.2
Anaphylactic Reaction/Shock	1 0.2	1 0.2	2 0.2
Hypersensitivity	0	2 0.4	0

Table 50 Listing of Subjects with Immune Disorder SOC Pool 1

SUBJID	DOSE	PTT	AGE/SEX	SEVERITY	ACTION	OUTCOME	DAY ONSET	DURATION
9016-102507	GA 20 daily	Anaphylactic Rx Was in shock in ER	34 F	SEVERE			242	2
9016-321801	GA 40 daily	Hypersensitivity	43 F	MOD	D/C Later resumed	R	154	4
9016-500124	GA 40 daily	Hypersensitivity	22 F	SEVERE	D/C	R	92	1
9016-540914	GA 40 daily	Anaphylactic Shock- sounded atypical, not like shock	45 M	SEVERE	D/C	R	57	2

301-522718	GA 40 TIW	Anaphylactic Rx Sounds like shock	36 F	SEVERE	D/C	R	15	< Day
301-537312	GA 40 TIW	Anaphylactic Shock, not witnessed did not sound like shock, no BP measured	37 M	SEVERE	No Change	R	197	< Day

- 301-522718 A 37 year old overweight female who 12 days after her first injection of GA 40 mg TIW had an anaphylactic reaction with generalized rash, pruritus, flushing , vomiting, abdominal pain and drop in blood pressure to SBO = 70.She required treatment in an ICU and discontinued study medication. She fully recovered. *This appears related to Copaxone.*

- 301-537312 This 38 year old male was assigned to GA 40 mg TIW. He has a history of asthma. Since his first dose of study medication he has had mild intermittent injection site erythema. On day 197 he thought he injected the Copaxone IV rather than subcutaneous. He developed palpitations, dyspnea, weakness and a thrill. Symptoms resolved within minutes to hours. His symptoms were unwitnessed. No blood pressure was recorded but it was coded as anaphylactic shock. He remained in the trial on medication. *This probably is related to treatment. It is unclear why this is being called an anaphylactic reaction as it appears to be more consistent with IPIR.*

Pool 2
No subjects reported Immune Disorders as SAEs in the OL phase.

Reviewer's Comments
All cases with Immune Disorders appear related to Copaxone treatment. There did not appear to be an increase in SAEs due to anaphylaxis or hypersensitivity with the new formulation. In one of the narratives the term anaphylactic shock was used but the description was more characteristic of immediate post-injection reaction (IPIR). In another narrative the term anaphylactic reaction was used even though the patient was notably hypotensive. It was noted that the investigators used the terms hypersensitivity reactions, anaphylactic reactions and IPIR indiscriminatively at times. Although the investigators may have classified the adverse events incorrectly, it is important to note that all subjects recovered completely and their symptoms were relatively short-lived.

Eye Disorders
Pool 1
There was a single SAE for an eye condition, iridocyclitis in subject 301-592910, a 52 year old female with a history of recurrent iridocyclitis for at least three years prior to entering the trial. She was treated with GA 40 mg TIW in the trial. Nine months after enrollment, she was hospitalized with bilateral iridocyclitis. She was able to complete the protocol. *This is unlikely to be related given her past history*

Pool 2
The above mentioned subject, 301-592910, who was in the ES GA 40 mg TIW group, had further symptoms related to iridocyclitis.

Reviewer's Comment
The case of recurrent iridocyclitis is most likely related to the patient's underlying immune status, previous history and MS rather than treatment with Copaxone.

Metabolism and Nutritional Disorders
Pool 1
Metabolic and nutritional disorders accounted for few SAEs and those that occurred appeared to be unrelated to treatment. One on GA 40 mg/day had diabetes mellitus, one on GA 40 mg TIW had hypokalemia and another had an electrolyte imbalance as described in the narratives that follow.

- 301-537110 This 33 year old female was randomized to GA 40 mg TIW. She had a history of epilepsy treated with lamotrigine and had an abnormal label test 6 months after enrollment with a potassium of 2.9. She was not treated and a few days later became weak, vertiginous and had blurred vision. Sodium and potassium were both below normal limits and she was treated with IV dexamethasone as well as sodium and potassium supplementation both IV and oral. Symptoms resolved and she was able to continue in the study. *Most likely her hyponatremia is related to her lamotrigine.*

- 301-537306 This 26 year old female had numerous SAE reports including ovarian cyst, anxiety, palpitations, angioedema. She also had an episode with palpitations were she was seen in the ER and found to have a potassium of 3.62 and she was treated with IV electrolytes. *Cannot exclude relationship to study medication, but unlikely.*

- 9016-500907 This was a 22 year old male assigned to GA 40 mg/day that on day 63 was hospitalized and found to have symptoms of weight loss, weakness and dry mouth thought to be due to Type I diabetes mellitus. Insulin was started, he was stabilized and released and he continued to take Copaxone. *This is not felt to be related to Copaxone.*

Pool 2
There were no SAEs for Metabolic and Nutritional disorders in Pool 2.

Reviewer's Comment
SAEs for metabolic and nutritional disorders appear unlikely to be related to treatment with Copaxone.

Cardiac Disorders
Pool 1

The label for Copaxone cites several cardiac symptoms that occur with some frequency in the marketed product including palpitations in 9% of those on GA 20 mg/day and 4% on placebo. Chest pain is also frequently seen in those treated with Copaxone (13% of those on GA 20 mg/day and 6% of those on placebo). Cardiac symptoms are not thought to be due to ischemic heart disease, the etiology is unknown, and are often part of IPIR. They also are an infrequent cause of SAE as seen in Table 51. The narratives for those treated with Copaxone follow.

Table 51 Pool 1 Cardiac SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N =630 N	 %	GA 40 mg/day N = 615 N	 %	GA 40 mg TIW N = 943 N	 %	Placebo TIW N = 461 N	 %
ALL subjects	1	0.2	4	0.7	2	0.2	3	0.7
Angina Pectoris	0		0		0		1	0.2
Angina Unstable	0		0		1	0.2	0	
Cardiac Arrest	0		0		0		1	0.2
Cardiopulmonary Failure	0		0		0		1	0.2
Coronary Artery Stenosis	0		2	0.4	0		0	
Ischaemic Cardiomyopathy	0		0		1	0.1	0	
Myocardial Infarction	0		1	0.2	0		0	
Myocardial Ischaemia	0		0		1	0. 1	0	
Palpitations	1	0.2	1	0.2	2	0.2	0	
Supraventricular Tachycardia	0		1	0.2	0		0	
Tachycardia	0		1	0.2	0		0	

- 301-537306 This 26 year old female had 3 separate SAE over a short time course 6 months after starting GA 40 mg TIW. She had ovarian cyst surgery. While still hospitalized a week later she had an episode of angioedema after receiving a dose of Copaxone. This was treated successfully with IV hydrocortisone. As a result of this episode the subject developed moderately severe anxiety. Two months later she went to the ER with palpitations. She was noted to have hypokalemia with a K of 3.62 mmol/L. Symptoms resolved within a day. Eight days later she developed palpitations again and this time electrolytes and EKG were normal as well as a 24-hour Holter and stress test. The symptoms resolved. She was able to complete the DB phase of the trial but discontinued after 19 days in the OL label period due to ongoing anxiety. *Palpitations could be related to study medication but more likely related to anxiety.*

- 301-593114 This 39 year old male smoker had normal blood pressure and ECG at enrollment. He was treated with GA 40 mg TIW. On study day 113 he was hospitalized for a relapse. While hospitalized he developed angina and echocardiogram suggested ischemic cardiomyopathy. He was treated both for his cardiomyopathy as well as his MS. He continued in the study including the OL phase. *Cannot exclude that this episode is related to study medication.*

- 9006-1404 This 30 year old female on GA 40 mg/day developed injection site pruritus, burning, hemorrhage and urticaria about 4 months after starting treatment. She also developed shortness

of breath, palpitations, and anxiety and required hospitalization. She was diagnosed with IPIR and the subject was discontinued from the study. *This is likely related to Copaxone.*

- 9016-105602 This 54 year old male with a history of hyperlipidemia was on GA 40 mg/day. On day 78 of therapy he developed chest pain, nausea, and shortness of breath while swimming and sought care. An EKG was normal. He was admitted to the hospital for observation and found to have blood pressure elevation, troponin increase and arteriogram which revealed an LAD stenosis and a proximal large obtuse margin stenosis. A stent was placed and the episode resolved. He continued the study medication. *This degree of atherosclerosis is likely related to the subject's hyperlipidemia and not to Copaxone.*

- 9016-321801 This was a 43 year old female treated with GA 40 mg/day that shortly after drug injection on day 150 of the study had a myriad of symptoms suggestive of an allergic reaction that include tachycardia. Symptoms resolved within 2 hours. Four days later she developed a headache and joint pains. She had evidence of a viral syndrome in the hospital and also received a diagnosis of an allergic reaction. Copaxone was temporarily discontinued and later resumed. *Symptoms are probably related to Copaxone.*

- 9016-520301 This was a 43 year old female treated with GA 40 mg/day also on oxybutynin for urinary incontinence who developed a sudden episode of supraventricular tachycardia. Copaxone was discontinued. This occurred on day 3 of therapy. Previously she had had a normal ECG and cardiac exam on enrollment. After vagal stimulation and pharmacotherapy she was able to be discharged from the ER. *This episode is possibly related to Copaxone.*

- 9016-340907 A 33 year old female treated with GA 20 mg/day who on day 62 of protocol got hospitalized for severe headache with disorientation, palpitations and vomiting. Medication was withheld and workup was negative. All symptoms except palpitations resolved within 2 days and the palpitations resolved within 4 days.

Pool 2

A single subject 301-582612 had acute heart failure on ES GA 40 mg TIW and died in his sleep at age 40. This case is discussed in section 7.3.1.

Reviewer's Comment

Cardiac complaints were seen in all treatment arms including placebo. Palpitations, one of the most common AEs on Copaxone, were a relatively infrequent cause of SAE.

Vascular Disorders

Pool 1

There were a few subjects with vascular complaints on Copaxone and none were seen on placebo. None of the SAEs appeared related to treatment. Those seen included one with varicose veins and another with venous thrombosis with Factor V deficiency treated with GA 20 mg/day and one with hypertension treated with GA 40 mg TIW. The narratives are provided.

- 301 -536901 This was a 54 year old postmenopausal overweight female who had previously been a smoker with a history of hypertension, treated with captopril on an as needed basis. Her BP was normal at enrollment at 130/70 but she did have nonspecific T-wave changes in her ECG considered nonsignificant. At month 10 of the study the subject noted the acute onset of vertigo

and came to the clinic. BP was 150/80. She was hospitalized and treated with IM furosemide, oral enalapril, and oral indapamide. Symptoms resolved and oral agents continued. *This is unlikely to be related to the study medication*.

- 9016-311503 This was a 44 year old male on GA 20 mg/day who was admitted to the hospital for varicose vein stripping*. This is not related to treatment.*

- 9016-541109 This was a 31 year old male who had a deep right femoral and popliteal DVT on day 49 of therapy with GA 20 mg/day. He required anticoagulation. His workup revealed a mutated V factor Leiden syndrome. His Copaxone was continued. *This is unlikely to be related to Copaxone* .

Pool 2

Subject 9016 520304 had flushing, vomiting and headache 15 minutes after an injection. A diagnosis of vertebrobasilar TIA was made. Subject 9016-530709 was hospitalized for evaluation of her erratic BP after an injection. During the DB phase of the study she had been noted to have elevated BP readings intermittently, but was not treated until this episode. She was referred to an endocrinologist and hypertension clinic. She remained on Copaxone and was not felt to have related symptoms. Subject 301-537303 had an episode of IPIR accompanied by elevated BP that resolved in less than two hours.

Reviewer's Comment

A variety of unrelated SAEs occurred which appeared without clear relationship to Copaxone other than IPIR with associated blood pressure alterations.

Renal and Urinary Disorders

Pool 1

Renal symptoms were greatest in the placebo group. Nephrolithiasis occurred in both a subject on GA 20 mg/day, 9016-200406, as well as in a subject on placebo, 301-537905. Case 301-506404 had several SAEs that included both perinephritis as well as presumptively osseous TB.

Table 52 Pool 1 Renal and Urinary Disorders SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N = 461 N %
ALL subjects	1 0.2	1 0.1	2 0.4
Anuria	0	0	1 0.2
Calculus Ureteric	0	0	1 0.2
Hydronephrosis	0	0	1 0.2
Nephrolithiasis	1 0.2	0	2 0.4
Perinephritis	0	1 0.1	0

Renal Colic	0	0	1 0.2
Renal Failure	0	0	1 0.2

Pool 2
Two subjects had a reoccurrence of their chronic urinary incontinence, subjects 301-537024 and 301-537707.

Reviewer's Comment
SAEs in this SOC were most likely related to the underlying disease, MS or to other unrelated factors.

Pregnancy, Puerperium and Perinatal Conditions
Pool 1
A single spontaneous abortion was the cause for an SAE being filed for GA 40 mg/day and GA 40 mg TIW and two on placebo. There was also a threatened abortion for one on placebo.

Pool 2
There was a single subject 301-811106 whose partner had a spontaneous abortion.

Reviewer's Comment
SAEs due to abortions were more frequent on placebo than on active treatment. No subject was noted to have any mention of fetal malformation. It is unclear why only 4 SAEs were listed relating to abortion when there were 3 abortions noted on GA 20 mg/day, 2 abortions on GA 40 mg/day, 6 on GA 40 mg TIW and 3 on placebo in Pool 1. See section 7.6.2.

Reproductive System and Breast Disorders
Pool 1
There were few subjects with reproductive and benign breast complaints. The narratives were reviewed and included a case of atypical ductal hyperplasia in a patient on placebo (who was not captured in the Neoplasia SOC nor in the discussion in section 7.3.4 (subject 301-571206). There were also two subjects with ovarian cysts, one on GA 20 mg/day (9016-520208) and another on GA 30 mg TIW (301-537306) and finally a patient on placebo who had metrorrhagia.

Pool 2
There were few subjects with reproductive complaints in the OL phase as well. There was a case of endometrial hyperplasia on ES GA 40 mg TIW and two cases of menometrorrhagia on ES GA 40 mg/day.

Reviewer's Comment
There was no evidence to suggest that treatment with Copaxone was related to various reproductive system complaints.

Injury, Poisoning and Procedural Complications
Pool 1
The greatest number of SAEs in this SOC occurred in the subjects receiving placebo. All of the narratives were reviewed and none of the SAEs appeared related to treatment. The single subject on GA 40 mg TIW (301537013) was a 35 year old male who was ambulatory and two months into the study had an accidental fall with a triple bone fracture requiring surgery. Table 53 summarizes the SAEs.

Table 53 Pool 1 Injury, poisoning and procedural complications SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40 mg/day N = 615 N %	GA 40 mg TIW N = 943 N %	Placebo TIW N – 461 N %
ALL subjects	2 0.3	2 0.3	1 0.1	3 0.7
Ankle Fracture	0	0	1 0.1	0
Brain Contusion	0	0	0	1 0.2
Complicated Fracture	1 0.2	0	0	0
Contusion	3 0.6	0	0	3 0.6
Fall	0	1 0.2	1 0.1	0
Foot Fracture	0	0	0	1 0.2
Fractured Skull Depression	0	0	0	1 0.2
Laceration	0	0	0	1 0.2
Multiple Fractures	1 0.2	1 0.2	0	0
Multiple Injuries	0	1 0.2	0	1 0.2
Road Traffic Accident	0	0	0	1 0.2
Skull Fractured Base	1 0.2	0	0	0
Subdural Haematoma	2 0.4	0	0	0

Pool 2
All of the narratives described accidental injuries including a subject on DS GA 40 mg TIW who had a forearm fracture, a subject on ES GA 40 mg TIW who had a humerus fracture and a subject on ES GA 40 mg who had an ankle fracture.

Reviewer's Comment

The SAEs in this SOC appeared to be traumatically induced and did not appear related to Copaxone.

Respiratory, Thoracic, and Mediastinal Disorders
Pool 1
Most of the subjects with respiratory SAEs had them because of dyspnea which is described in the label of the marketed product (14% on GA 20 mg/day and 4% on placebo). In Pool 1 SAEs due to dyspnea were reported in none on GA 40 mg TIW, 0.8% of those on GA 40 mg/day. 0.2% of those on GA 20 mg/day and 0.2% of those on placebo. Review of the 7 narratives suggested that the dyspnea was part of a hypersensitivity reaction, IPIR or anaphylactic reaction rather than URI or a specific pulmonary disorder. The single patient on placebo in this group, 301-537017, was an exception. He had a pulmonary embolism and respiratory arrest as a complication of a motor vehicle accident that left him in a vegetative state with quadriplegia which was unrelated to Copaxone.

Table 54 Pool 1 Respiratory, Thoracic and Mediastinal disorders SOC by PT

System Organ Class Preferred Term	GA 20 mg/day N = 630 N %	GA 40mg/day N = 615 N %	Placebo TIW N = 462 N %
ALL subjects	1 0.2	5 0.8	1 0.2
Dyspnoea	1 0.2	5 0.8	0
Pulmonary Embolism	0	0	1 0.1
Respiratory Arrest	0	0	1 0.1

Pool 2
The four narratives are summarized below.

- 9016-501212 A 21 year old female patient who developed acute pancreatitis and bronchospasm was hospitalized during open-label treatment. The bronchospasm occurred within 1 minute of injection and was moderate, untreated and lasted for 40 minutes. In the hospital she was diagnosed with pancreatitis and treated for that, but did not need any treatment for bronchospasm. *This may be related to treatment with Copaxone.*

- 301-506406 A 52 year old female nonsmoker who two weeks into the open label period developed cough and a week later fever. She was diagnosed with bronchitis and respiratory insufficiency grade 0-1. She was placed on antibiotics. *This appears unrelated to treatment with Copaxone.*

- 301-537303 A 40 year old female with history of asthma who on her first dose in the open label period developed injection site erythema which continued during the open label period. Five months later she experience IPIR which included dyspnea just after an injection which resolved in less than two hours. She went to the ER where she was given steroids and the drug was temporarily discontinued. It was noted that a day before the adverse event she had started amoxicillin/clavulanic acid for a URI. Her drug was resumed and she continued in the study. *This appears related to treatment with Copaxone. This event was captured under IPIR.*

- 301-582905 A 40 year old female who on in the 16th month of treatment experienced dyspnea, pyrexia, rigor and asthenia following an injection of study medication. She was hospitalized and treated with steroids by emergency personnel. This was considered a moderately severe episode of hypersensitivity. The medication was not stopped. She had one further episode a day later under supervision but still continued the study medication for several more months before she withdrew consent without giving a reason. Apparently she had experienced insomnia and headache throughout the study and this resolved after she stopped Copaxone. *This appears related to treatment with Copaxone and was captured under hypersensitivity reactions.*

Reviewer's Comment
Respiratory disorders due to dyspnea appeared dose related to Copaxone and were the most common PT reported overall. Dyspnea is a nonspecific complaint which can be related to multiple SOCs. In both Pool 1 and 2 dyspnea most commonly was a component of hypersensitivity reactions, anaphylactic reactions and IPIR related to the use of Copaxone.

Investigations
SAEs due to investigations were well balanced among the treatment arms including placebo. They included a subject on GA 40 mg/day and GA 40 mg TIW who had blood pressure elevations, a subject with elevated troponin on GA 40 mg/day and a subject on placebo who had a cardiac catheterization. The narratives for those treated with Copaxone are provided.

- 301-583319 This 48 year old male was a nonsmoker with a history of untreated hypertension for several years treated in this study with GA 40 mg TIW. His blood pressure was not elevated at enrollment but rose 6 months into the study. He was treated with IM metoclopramide, IM furosemide and IV magnesium sulfate. The following day he came to the clinic and was examined for a possible stroke. He was hospitalized and his pressure was still high at 160/95. An MRI was performed and it was thought that he had a CVA based on clinical signs. His moderately severe BP remained unresolved with oral enalapril. His Copaxone was not stopped and he completed the study and entered the open label period. *Cannot rule out that this is related to study medication, but unlikely due to his preceding history.*

- 9016-105602 This 54 year old male with a history of hyperlipidemia was treated with GA 40 mg/day. On day 78 of therapy he developed chest pain, nausea, and shortness of breath while swimming and and sought care. An EKG was normal. He was admitted to the hospital for observation and found to have blood pressure elevation, troponin increase and arteriogram which revealed an LAD stenosis and a proximal large obtuse margin stenosis. A stent was placed and the episode resolved. He continued the study medication. *This degree of atherosclerosis is most likely related to the subject's chronic hyperlipidemia and unlikely to be related to the subject's use of Copaxone.*

Pool 2
The only investigation that took place for Pool 2 was a single patient, 301-582905, who was previously described under Respiratory disorders who had a fever workup as part of a hypersensitivity reaction.

Reviewer's Comment
The few cases in this SOC to have SAE appear related to the subjects' past history and unlikely to be related to treatment with Copaxone with the exception of one who had a fever workup as part of a hypersensitivity reaction.

Blood and Lymphatic Disorders
In Pool 1 there were no SAEs in this SOC. In Pool 2 there was a single subject 301-592604 on ES GA 40 mg TIW who had iron deficiency anemia probably unrelated to Copaxone.

Congenital and Familiar Disorders
In Pool 1 there were no SAES in this SOC. In Pool 2 subject 301-522803 on DS GA 40 mg TIW was hospitalized with a UTI. She had a history of a congenital ureteric anomaly.

7.3.3 Dropouts and/or Discontinuations

In Pool 1 the disposition of patients as reported by the sponsor is found in Table 55. There were fewer withdrawals on GA 40 mg TIW and placebo than on GA 20 mg/day or GA 40 mg/day. Withdrawal rate, particularly withdrawals due to adverse events appeared to be both dose related and frequency related. The GA 40 mg /day cohort reported the highest frequency of overall withdrawals (15.1%) compared to 11% for GA 20 mg/day and 8.9% for GA 40 mg TIW. The sponsor did not evaluate drop-outs due to lack of efficacy or relapse in their three studies, and their initial analysis did not include this category of drop-out as displayed in Table 55. They were asked to reanalyze their data to look for lack of treatment efficacy which they did as part of a post-hoc analysis as discussed in section 6.1 and that information is found in Table 9.

Table 55 Pool 1 Patient disposition

Disposition	GA 20 mg/day (N = 630) n %	GA 40 mg/day (N = 615) n %	Placebo TIW (N = 461) n %	GA 40 mg TIW (N = 943) n %
Completed study treatment	561 (89%)	522 (84.9%)	430 (93.3%)	859 (91.1%)
Did not complete study treatment	69 (11%)	93 (15.1%)	31 (6.7%)	84 (8.9%)
Reason:				
Adverse event	31 (4.9%)	57 (9.3%)	6 (1.3%)	29 (3.1%)
Poor compliance	2 (0.3%)	1 (0.2%)	*	2 (0.2%)
Lost to follow-up	7 (1.1%)	7 (1.1%)	1 (0.2%)	5 (0.5%)
Other	29 (4.6%)	27 (4.4%)	24 (5.2%)	48 (5.1%)

Percentages are calculated using the number of safety patients as the denominator.
adapted sponsor analysis Table 1 ISS

Adverse events leading to discontinuation in the DB pool are summarized by SOC in Table 56. For every SOC, those on GA 40 mg TIW had fewer dropouts than those on the marketed product. Events in the skin and subcutaneous tissue disorders and general disorders and administration site disorders accounted for the most withdrawals. These discontinuations were predominantly related to ISR and IPIR which are discussed in more detail in section 7.3.5, or angioedema and erythema, part of hypersensitivity reactions, which are discussed in section 7.3.4.

Table 56 Pool 1 Adverse events by SOC leading to treatment discontinuation

Primary System Organ Class	GA 20 mg/day N = 630 n (%)	GA 40 mg/day N = 615 n (%)	Placebo TIW N = 461 n (%)	GA 40 mg TIW N = 943 n (%)
Any class	31 (4.9%)	57 (9.3%)	6 (1.2%)	29 (3.1%)
Infections and infestations	3 (0.5%)	*	1 (0.2%)	*
Nervous system disorders	5 (0.8%)	10 (1.6%)	*	*
Gastrointestinal disorders	4 (0.6%)	8 (1.3%)	*	1 (0.1%)
Hepatobiliary disorders	1 (0.2%)	*	*	1 (0.2%)
Skin and subcutaneous tissue disorders	7 (1.1%)	14 (2.3%)	1 (0.2%)	6 (0.6%)
Musculoskeletal and connective tissue disorders	4 (0.6%)	2 (0.3%)	*	2 (0.2%)
Neoplasms benign, malignant and unspecified	*	*	1 (0.2%)	*
Psychiatric disorders	2 (0.3%)	3 (0.5%)	1 (0.2%)	1 (0.1%)
Ear and labyrinth disorders	*	1 (0.2%)	*	*
General disorders and administration site conditions	17 (2.7%)	33 (5.4%)	2 (0.4%)	15 (1.6%)
Surgical and medical procedures	1 (0.2%)	*	*	*
Immune System disorder	2 (0.3%)	5 (0.8%)	*	3 (0.3%)
Eye Disorders	*	1 (0.2%)	*	*
Metabolism and nutritional disorders	*	*	*	*
Cardiac disorders	4 (0.6 %)	5 (0.8%)	1 (0.2%)	1 (0.1%)
Vascular disorders	2 (0.3%)	5 (0.8%)	*	3 (0.3%)
Renal and urinary disorders	*	*	*	*
Pregnancy, puerperium and perinatal conditions	*	*	*	*
Reproductive system and breast disorders	1 (0.2%)	*	*	*
Injury, poisoning and procedural complications	1 (0.2%)	*	1 (0.2%)	*
Respiratory, thoracic and mediastinal disorders	7 (1.1%)	9 (1.5%)	*	1 (0.1%)
Investigations	1 (0.2%)	2 (0.3%)	*	*
Blood and Lymphatic System Disorders	1 (0.2%)	1 (0.2%)	*	1 (0.1%)

adapted from Post Text Table 44 ISS

The only individual AEs that led to early discontinuation in ≥ 1% of subjects were injection site erythema (1.8%, 0.5%, 0.3%), injection site pain (1.0%, 0.6%, 0.4%), and dyspnea (1.1%, 0.8%, 0.1%) in GA 40 mg/day, GA 20 mg/day, and GA 40 mg TIW respectively. Facial edema was reported by 0.8% of those on GA 40 mg/day, and 0.5% of those on GA 20 mg/day.

Pool 2
Discontinuations were relatively infrequent in this pool which included all subjects treated with GA for either an extended period (ES) with treatment over a year, or delayed start (DS) treatment where the first year were either on GA 20 mg/day or placebo. Discontinuation rates for those in Pool 2 can be found in Table 57. Just as in Pool 1, ISR and IPIR symptoms were the leading cause of discontinuation which are found in the skin and subcutaneous tissue disorders or general disorders and administration disorders SOC. Specifically injection site pain was the only AE which led to early discontinuation during this period in > 1% of subjects. There were 1.2% of subjects on DS GA 40 mg TIW who discontinued due to this AE.

Table 57 Pool 2 Adverse Events leading to Treatment discontinuation

Primary System Organ Class	DS GA 40 mg/day N = 523 n (%)	ES GA 40 mg/day N = 482 n (%)	DS GA 40 mg TIW N = 419 n (%)	ES GA 40 mg TIW N = 943 n (%)
Any class	14 (2.7%)	14 (2.9%)	14 (3.3%)	8 (1.0%)
Infections and infestations	3 (0.5%)	*	1 (0.2%)	*
Nervous system disorders	4 (0.8%)	3 (0.6%)	1 (0.2)	1 (0.1%)
Gastrointestinal disorders	2 (0.4%)	1 (0.2%)	2 (0.5%)	*
Hepatobiliary disorders	1 (0.2%)	*	*	1 (0.2%)
Skin and subcutaneous tissue disorders	7 (1.1%)	14 (2.3%)	1 (0.2%)	6 (0.6%)
Musculoskeletal and connective tissue disorders	4 (0.6%)	2 (0.3%)	*	2 (0.2%)
Neoplasms benign, malignant and unspecified	*	*	1 (0.2%)	*
Psychiatric disorders	1 (0.2%)	3 (0.6%)	1 (0.2%)	*
Ear and labyrinth disorders	*	1 (0.2%)	*	*
General disorders and administration site conditions	4 (0.8%)	6 (1.2%)	10 (2.4%)	4 (0.5%)
Surgical and medical procedures	1 (0.2%)	*	*	*
Immune System disorder	2 (0.3%)	5 (0.8%)	*	3 (0.3%)
Eye Disorders	*	1 (0.2%)	*	*
Metabolism and nutritional disorders	*	*	*	*
Cardiac disorders	2 (0.4%)	3 (0.6%)	1 (0.2%)	1 (0.1%)
Vascular disorders	2 (0.3%)	5 (0.8%)	*	3 (0.3%)
Renal and urinary disorders	1 (0.2%)	*	*	*

Pregnancy, puerperium and perinatal conditions	*	*	*	*
Reproductive system and breast disorders	1 (0.2%)	*	*	*
Injury, poisoning and procedural complications	1 (0.2%)	*	1 (0.2%)	*
Respiratory, thoracic and mediastinal disorders	7 (1.1%)	9 (1.5%)	*	1 (0.1%)
Investigations	1 (0.2%)	2 (0.3%)	*	*
Blood and Lymphatic System Disorders	1 (0.2%)	*	*	*

Source adapted from Post-Text Table 67 ISS

7.3.3.1 Discontinuations likely due to adverse events but not categorized as such in Study MS 301- GALA- DB phase

Narratives for subjects who prematurely discontinued were reviewed for Study MS-301-GALA, the pivotal trial. The subjects listed in Table 73 had ongoing adverse events at the time of discontinuation, although the sponsor's reason for terminating was typically "withdrew consent" or "failed to return for follow-up". A recalculation of those who withdrew due to AE was 7 subjects (1.7%) on placebo and 33 subjects on GA 40 mg TIW (3.5%).

Table 58 Subjects with Adverse Events in Pool 1 who were classified incorrectly as "failed to return for follow-up" or "withdrew consent"

Patient ID	Treatment	Sponsor termination reason	Narrative	Reclassify
129803	GA 40 mg TIW	Failed to return/lost to follow-up	Experienced mild injection site pain pruritus and then did not return	Due to AE
131002	GA 40 mg TIW	Failed to return /lost to follow-up	Experienced pain, pruritus, did not return	Due to AE
512904	Placebo TIW	Withdrew consent	Had AE of nausea, dizziness, vertigo, withdrew consent	Due to AE
522603	GA 40 mg TIW	Withdrew consent	Injection site nodule, pruritus withdrew consent	Due to AE
536908	GA 40 mg TIW	Withdrew consent	Shortly after developing arthralgias withdrew consent	Due to AE

Reviewer's Comment
Withdrawals due to AE were less on the new formulation GA 40 mg TIW when compared across trials to GA 20 mg/day. They were somewhat higher than on placebo, but still were relatively infrequent. The major cause of withdrawal relates to injection site reactions, so it would be anticipated that the less frequent dosing will afford a significant benefit to patients who wish to avoid injection related AEs.

7.3.4 Significant Adverse Events Adverse Events of Special Interest (AESI)

The DNP and the Applicant agreed on a list of AESI that would be evaluated. These included breast cancer, embolic and thrombotic events, hepatitis and liver injury, lipoatrophy, hypersensitivity/anaphylaxis, and thrombocytopenia. These were largely chosen based on adverse events noted in the post-marketing literature. The definition (search terms) for the AESI are presented in each section. Since many of the categories of AE are in several SOC the preferred terms (PT) are also shown.

Breast Cancer

AERS reports of patients on Copaxone who develop breast cancer have been frequent over the pasts few years. This reviewer used Empirica Signal to evaluate this informally and there appeared to be a potential association of Copaxone and breast cancer with an EGBM of 4.76 and an EB05 of 3.86. The current label does not include a warning about breast cancer or any other type of malignancy nor does the preclinical section of the label suggest that the drug is carcinogenic or mutagenic. This NDA was an opportunity to evaluate this AE in controlled trials. Previously, the original NDA safety review[9] did not describe any cases of breast cancer among its subjects, nor did the two additional trials that are described in the label.[10, 11]

In this submission the sponsor conducted the following query to search for the occurrence of breast cancer which was verified by this reviewer. The preferred terms associated with breast cancer include breast cancer, breast dysplasia, breast lump removal, malignant breast lump removal and mastectomy. In addition to the cases that the sponsor identified one further case of breast atypical hyperplasia was found on a subject on placebo by this reviewer.

Pool 1

All three cases of breast cancer in Pool 1 were treated in the GA 9016 trial. Two of the subjects (0.03%) were on GA 20 mg/day (#321406, #322204) and one subject (0.01%) was on GA 40 mg/day (#341201). All three cases withdrew from the study. One subject in study MS-301 on GA 40 mg TIW reported atypical ductal hyperplasia. A summary of the cases follows.

- **GA-9016- 321406 invasive ductal adenocarcinoma**
  GA 20 mg/day dose day 47 of treatment - abnormal mammogram
  A 52 years old female was diagnosed with left breast cancer and lymph node metastases during the double blind phase of the study. The subject underwent a routine screening mammography on day 47 of the double blind phase, which revealed a 17mm suspected focus in the left breast. A

9 NDA 20622 Safety Review John Dikran Ballan, 1996.
10 NDA 20622 Clinical Review of Study 9006 Gerald Tremblay 2002.
11 NDA 202 Clinical Review of PreCISe trial Jody Green 2008.

breast sonogram was done the same day, revealing a 14 mm round lesion. A punch biopsy was done on day 54 of the double blind phase. Pathology report of the biopsy revealed invasive duct adenocarcinoma of the breast. The subject underwent lumpectomy on day 83 under general anesthesia and resection of lymph node metastasis on day 95. Patient discontinued the study drug on day 118 of the DB phase of the study and was treated with chemotherapy.

- **GA 9016- 322204 T1c breast carcinoma with extensive DCIS**
  GA 20 mg/day dose day 52 of treatment - lump detected
  This was a 51 year old female who had been on GA 20 mg/day when a solid nodule of her right breast discovered by her gynecologist on day 52 of the double-blind period of the study was noted. Wide excision and sentinel lymph node dissection was performed on day 64 (b) (6) (b) (6) of the double blind phase, and pathological report revealed a T1c tumor and extensive DCIS. All sentinel lymph nodes were free of tumor. The patient was estrogen receptor positive, HER2 negative. Metastatic work-up including chest x-ray, bone scan and abdominal ultrasound, was negative for metastasis. Because of extensive DCIS in the specimen, the subject underwent a completion mastectomy. She discontinued the study drug on day 94 of the DB phase of the study due to AE of breast cancer and began chemotherapy.

- **GA- 9016/341201 infiltrating ductal carcinoma**
  GA 40 mg/day approximately day 170 days of treatment - abnormal mammogram
  This was a 48 year old female diagnosed with right breast cancer approximately 6 months into the double blind phase of the study. Mammogram and ultrasound suggested the diagnosis. Core biopsy revealed NST grade 2 infiltrating duct carcinoma. The subject was hospitalized and underwent right mastectomy with axillary dissection on day 199 of the double blind phase of the study. She discontinued the study drug on day 274 of the DB phase of the study and began chemotherapy.

- **GA-301-571206 atypical ductal hyperplasia**
  Placebo TIW This was a 50 year old premenopausal overweight female who did not take oral contraceptives. Eight months before enrollment she was noted to have a right breast mass and an ultrasound exam revealed fibrosis of glandular tissue, widened ducts and a mass. Ten months later and about ten weeks into the study the right breast mass appeared enlarged on ultrasound. A month later she underwent an elective sectoral resection of the right breast which confirmed atypical ductal hyperplasia. This case was found in the SAE narratives but was not provided by the sponsor as part of this analysis.

Pool 2

A total of three subjects developed breast cancer and one developed breast dysplasia during this period. The three with breast cancer were considered SAE (0.4% of the GA 40 mg/day group, and 0.2% of the GA 40 mg TIW group). They were all withdrawn from the study. The fourth had breast dysplasia only and did not withdrawal. All four had been on continuous Copaxone for both the DB and OL periods and none had been on placebo for the first 12 month period.

- **GA-9016/102201 invasive lobar breast carcinoma**
  40 mg/day dose day 473 of treatment - cancer diagnosis
  A 49 year old female patient with a history of adenoma of breast since 2003, hypothyroidism who was enrolled into the GA9016 study on the 40 mg arm and she continued to the open label phase with GA 40 mg . She did not take oral contraception or other hormonal therapy. The study investigator reported that the subject experienced discomfort and pain in left breast and

ultrasound showed masses and a 3.5 cm tumor. A needle biopsy was performed and on study day 473 invasive lobular breast cancer was diagnosed. Of note, one year earlier the subject had a mammogram and ultrasound assessed as negative. Early termination took place and the patient started chemotherapy.

- **GA-301/129703 invasive ductal carcinoma**
  40 mg TIW dose 378 days of treatment at time of biopsy
  This was a 52 year old premenopausal female nonsmoker with a history including lumpectomy for benign breast neoplasm (1976) and no relevant concomitant medications that was enrolled into the GALA study on GA 40 mg TIW and continued to the open label phase. She did not take oral contraception or other hormonal therapy. Three weeks into the open label phase the subject had a mammogram that was reported as abnormal and a needle biopsy was performed. The subject was diagnosed with invasive ductal carcinoma of breast, stage I, grade I (tumor 2 mm, non aggressive). The AE was assessed as severe. The subject underwent two surgeries (b) (6) - (b) (6) Surgical pathology report from (b) (6) reported superior anterior margin negative for malignancy, estrogen and progesterone receptors positive. She was treated with tamoxifen and radiation therapy. The study drug was taken as per protocol throughout this episode, but patient dropped out of the study after this AE was noted due to "refused to sign the consent".

- **GA-9016/541108 invasive ductal carcinoma**
  40 mg/day diagnosis day 447 on drug
  A 49 years old female completed 364 days of the double blind phase of the study. She was diagnosed with left breast ductal carcinoma on day 83 of the open label phase.
  The subject underwent regular screening mammography on day 81 of the open label phase. Retroareolar fibrosis of the left breast was detected. Breast ultrasound on the same day revealed 12 x 11 mm tumor. A biopsy was taken 2 days later, confirming invasive ductal carcinoma and surgery was planned. This subject dropped out because of "sponsor's decision" and not because of AE, but this AE preceded drop-out.

- **GA-301/522201 breast dysplasia**
  40 mg TIW dose day 450 of treatment -diagnosed
  No narrative provided but sponsor did respond to an information request on September 11, 2013 which confirms the subject's benign breast disease with bilateral breast dysplasia. In the most recent 120 day follow-up it stated that there was no change to the bilateral breast dysplasia with a borderline lump in breast.

120 Day Safety Update

The sponsor continues to follow 2 subjects GA-301-129703 and GA-301-52220. No new cases were reported.

Table 59 Summary of cases with breast cancer related AEs (DB and OL phases)

Patient ID #	Diagnosis	Treatment	Time on Treatment when diagnosed
9016-321406	Breast cancer	GA 20 mg/day	Day 47
9016-322204	Breast cancer	GA 20 mg/day	Day 52
9016-341201	Breast cancer	GA 40 mg/day	Day 170
9016-102201	Breast cancer	GA 40 mg/day	Day 473
301-129703	Breast cancer	GA 40 mg TIW	Day 378
9016-541108	Breast cancer	GA 40 mg/day	Day 447
301-522201	Breast dysplasia	GA 40 mg TIW	Day 450

301-571206	Breast atypical hyperplasia	placebo	Approximately Day 100

In their most recent PSUR Teva calculated an overall breast cancer reporting rate of 18.24 cases per 100,000 PY. They compared this rate to that of females above and below the age of 65 and found no increased risk of breast cancer associated with the use of Copaxone.

Based on the findings in the ISS as well as what has been identified in the post-marketing literature Dr. Gerald Boehm, safety reviewer was asked to evaluate Teva's breast cancer estimates and determine if there was a signal for Copaxone. He was able to obtain from Teva the female exposure to Copaxone in Pool 1 so that he could more accurately make this assessment. He then compared the risk of breast cancer with Copaxone to that of other MS treatments. He provided the analysis found in Table 60 which suggested that breast cancer is increased in MS patients in general and is not specific to MS treatment. Dr. Boehm also reviewed the literature and found supportive evidence that breast cancer is increased in those with MS in a Danish Cancer registry[12] as well as in a retrospective cohort study in Norway[13,] although not all the literature he reviewed supported this assertion. In summary, Dr. Boehm found that even though the Copaxone sNDA breast cancer rate was higher than the estimate for the general population (SEER data) it was similar to that of other development programs for MS treatment and unlikely to be a risk truly associated with the drug rather than the disease. No regulatory actions were recommended based on his review.

Table 60 Breast cancer incidence for recently reviewed MS treatments

Drug	# breast cancer cases	Person years (female)	Rate of breast cancer	95% CI
Copaxone	6	2382	2.5/1000 PYs	1.0, 5.4
Dalframpridine	3	1000	3/1000 PYs	0.8, 8.2
PEGylated β-1a	2	1694	1.2/1000 PYs	0.2, 3.9
Fingolimod	5	2472	2/1000 PYs	0.7, 4.5
Teriflunomide	2	3038	0.7/1000 PYs	0.1, 2.2
Dimethyl fumarate	3	3022	1/1000 PYs	0.3, 2.7

Provided by Gerald Boehm, MD, PhD based on recent NDAs/BLAs

Embolic and Thrombotic events

A broad MedDRA query was done by the sponsor to look for embolic and thrombotic events as seen in Table 61 and was confirmed by the reviewer.

[12] Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M, Hjalgrim H. Cancer risk among patients with Multiple Sclerosis: A population based register study. Int. J. Cancer 2006: 118, 979-984.

[13] Midgard R, Glattre E, Riise T, Edland A, Nyland H. Multiple Sclerosis and cancer in Norway. A retrospective cohort study. Acta Neurol Scand. 1996 Jun;93(6):411-5.

Table 61 MedDRA query for Embolic and Thrombotic events

Embolic and Thrombotic	Arterial thrombosis limb
	Coronary Arterial Stent Insertion
	Hemiparesis
	Ischemic Stroke
	Monoparesis
	Myocardial Infarction
	Paresis
	Pulmonary embolism
	Superficial thrombophlebitis
	Thrombosis
	Thrombosis in Device
	Transient Ischemic Attack
	Venous Thrombosis Limb

Pool 1

Embolic and thrombotic events were investigated because they appeared to be found in a number of post-marketing reports, although not described in the label. Empirica Signal did not reveal evidence for a signal. In Pool 1 thrombotic and embolic events occurred with treatment with all formulations of GA and were rare with placebo. Such events were found in 4 subjects on GA 20 mg/day (0.6%), 3 subjects on GA 40 mg/day (0.5%), and 3 subjects on GA 40 mg TIW (0.3%), and 1 subject on placebo TIW (0.2%) according to the sponsor's analysis. None of these patients discontinued because of this AE, although four were considered severe. Because the frequency of such events appeared higher on GA than on placebo, the sponsor was sent an information request to supplement their narratives so that causality could be better assessed.

Table 62 Pool 1 Narratives for those with Thrombotic or Embolic Events

Study	Treatment	Narrative
GA 9006-2518	GA 40 mg/day	This was a 29 year old female who experienced superficial thrombophlebitis day 55 of treatment lasting 73 days. She was on birth control pills. *BCP is a risk factor for thromboembolic events.*
GA 9016-105602	GA 40 mg/day	54 year old male with history of hyperlipidemia, bradycardia, and glaucoma had an SAE. On initial screening BP was mildly elevated at 142/64, pulse of 46. On day 78 of treatment with GA 40 mg had nausea and shortness of breath while swimming. He was admitted to the hospital and found to have a mild myocardial infarction and after stenosis of the LAD was found a stent was placed. He remained in the study until the study was ended on day 544. *Case confounded by several cardiovascular risk factors.*
GA9016- 311105	GA 20 mg/day	A 48 year old female with a history of hyperglycemia treated with GA 20 mg/day was found one month into the study to have a right leg paresis which resolved the next day. *History of hyperglycemia*

		is a likely risk factor for this event which may have been a TIA.
GA9016-321202	GA 40 mg/day	A 40 year old female with negative PMH treated with GA 40 mg/day. Nine months into the study she experienced a right leg paresis as well as restlessness and insomnia. The monoparesis remained severe as was a speech disturbance. *Cannot be certain if this is CVA or MS exacerbation. Cannot exclude the possible relationship to Copaxone, too little information available.*
GA 9016-322411	GA 20 mg/day	This 42 year old female was treated with GA 20 mg/day. Two months into the study she experienced a severe hemiparesis on the right side. She was evaluated for relapse and the event was not felt to be a relapse. The hemiparesis resolved within 6 weeks. *.Cannot be certain if this is CVA or MS exacerbation. Cannot exclude the possible relationship to Copaxone, too little information available.*
GA9016-541109	GA 20 mg/day	This 31 year old male without relevant history was assigned to GA 20 mg/day. He was noted to have an elevated cholesterol level. Seven weeks into the study he experienced symptoms of a right femoral and popliteal deep vein thrombosis. He was treated with IV heparin and then warfarin. He was found to have a Factor V deficiency. *Thrombosis due to Factor V deficiency.*
GA 9016 -321902	GA 20 mg/day	This 18 year old female with negative past medical history experienced left hand paresis on study day 5. At time of assessment this was thought to be related to a relapse which was treated with iv steroids. *Very unlikely to be causative given short latency and likelihood of relapse.*
GA 301-326501	GA 40 mg TIW	This was a 28 year old female former smoker and current oral contraceptive user with a history of a venous thrombosis and activated protein C resistance test positive who was assigned to GA 40 mg/day. Thrombosis of right leg day occurred on 301 of treatment and she was given heparin and later rivaroxaban. *Has risk factors for thromboembolic disease.*
GA 301-537017	Placebo TIW	Pulmonary embolism (PE) on day 321 of treatment considered severe SAE in a 48 year old male after being on placebo for 323 days as a complication of a MVA with multi-organ injury. He remained hospitalized in a vegetative state with quadriplegia and was terminated from the study. *PE is most likely related to immobility related to being in a vegetative state.*
GA 301-537906	GA 40 mg TIW	A 39 year old female with negative history who was assigned to 40 mg /day of GA. Eleven months into the study she experienced a right hand paresis which resolved in less than a day. The investigator attributed this to overheating in the sun. *Too little information available.*
GA 301-583319	GA 40 mg TIW	Ischemic Stroke, severe, SAE, recovered 48 year old male with a history of untreated blood pressure, and obesity who had a severe ischemic stroke approximately 6 months after initiating treatment with the study medication. At enrollment his blood pressure was not noticed to be elevated, but 6 months into study he was noted to have hypertension which was treated, but the following day he was hospitalized with a stroke. His hypertension was treated during his hospitalization and he remained in the study. *Had other risk factors.*

Pool 2
There were 5 more possible cases of thromboembolic disease on Copaxone during the OL phase, and none on placebo that are summarized here.

Table 63 Pool 2 Thrombotic or Embolic Events

Study	Treatment	Narrative
9016-101902	GA 40 mg/day	A 39 year old male who on day 278 of the OL period experienced a moderately severe hemiparesis lasting for 8 days. He was obese and had elevated cholesterol. He also experienced moderately severe dizziness. There was no further information about stroke workup available but there were no remarks suggesting that this was a relapse. *Too little information available. Appears likely to be related to cardiovascular risk factors.*
9016-103701	GA20 mg/ GA 40 mg/day	A 42 year old overweight male with elevated cholesterol and sleep apnea treated with nasal CPAP. .He had several SAE prior to his superficial venous thrombosis of his left arm which included, Chron's Disease exacerbation, GERD, pancreatitis, chest pain due to the pancreatitis, mild hypertension which developed during the first month of the OL period. Eight months later he developed the superficial thrombophlebitis in his left arm. His event was not felt by the sponsor to be related to the drug treatment. *Too little information available to determine causality.*
9016-520304	20 mg/40 mg/day	A 47 year old overweight female who had a history of elevated cholesterol and type 2 diabetes treated by diet. Six months into the OL period 15 minutes after administering study drug the patient had flushing, vomiting, and headache and at the hospital this was called a transient ischemic attack despite the lack of focal deficits. ECG, EEG and CT of brain were negative. *Diagnosis uncertain as too little history is available.*
301-592303	Placebo/40 mg	A 48 year old female with a history of superficial thrombophlebitis of the left leg experienced a second episode during the open label period. *Too little information available may have a risk factor for thromboembolic disease, but further history not available.*
301-593401	Placebo/40 mg	A 50 year old overweight female with history of hypertension. Five months into the OL period she developed a thrombosis of the left posterior tibial artery. The event was considered unrelated and the treatment continued and she recovered, Ultimately she was discontinued from the study after experiencing an episode of anaphylactic shock. *Too little information available, but probably related to her cardiovascular risk factor of hypertension.*

120 Day Safety Report
No additional cases were reported.

Reviewer's Comment's
The thromboembolic events described in the narratives occurred on all doses of Copaxone and were less frequent on placebo. Many of those with events had histories so limited that it was unclear if they actually had a thromboembolic event; some sounded more like relapses. Many had confounding factors such as use of BCP, history of hypertension, hypercoagulability syndromes. Many of the narratives were inadequate to evaluate thromboembolic events as risk factors such as tobacco abuse were not mentioned; workup for hypercoaguability syndromes is not reported. As a result, no clear evidence of a relationship between treatment with Copaxone and thromboembolic events can be determined at this time.

Hepatitis/liver injury
Hepatitis and liver injury is a topic of concern for those who treat multiple sclerosis patients. Many of the immunomodulators have this as an associated AE. Previously an Empirica Signal query was performed and no signal was detected in postmarketing reports, but this application was an opportunity to evaluate this potential problem in controlled clinical trials. The sponsor conducted a broad MedDRA query to investigate hepatitis and liver injury as seen in Table 64 and the query was confirmed by this reviewer.

Table 64 MedDRA query for Hepatitis and Liver Injury

Hepatitis /Liver Injury	Alanine Aminotransferase Abnormal	Bilirubin Conjugated Increased	Hyperbilirubinemia
	Alanine Aminotransferase Increased	Gamma-Glutamyltransferase Increased	Hypertransaminasemia
	Aspartate Aminotransferase Abnormal	Hepatic Enzymes Increased	Liver Function Test Abnormal
	Aspartate Aminotransferase Increased	Hepatic Steatosis	Liver Tenderness
	Blood Bilirubin Increased	Hepatitis Toxic	Drug-Induced Liver Injury
	Blood Bilirubin Unconjugated Increased	Hepatomegaly	Transaminase Increased

Pool 1
In general, the AEs related to hepatitis and liver injury were of similar incidence in all treatment groups in the DB phase. If one excludes those who had abnormal liver functions at baseline, the incidence of AEs related to hepatitis and liver injury was 2.69% (11 subjects) on placebo, 2.33% (14 subjects) on GA 20 mg/day, 2.44% (15 subjects) on GA 40 mg/day, and 2.33% (22 subjects) on GA 40 mg TIW. Those AEs noted on drug were more severe and caused more withdrawal than those on placebo.

Sixty six subjects reported an AE related to hepatitis and liver injury in Pool 1. Two were regarded as severe by the sponsor. Both severe cases had been treated with GA 40 mg/day (subjects #101605 and #511013) but due to pregnancy-related issues were withdrawn from study medication at the time of transaminase elevations. Two subjects on GA 40 mg TIW were reported as having SAE, #592408 and 506012 due to hepatitis or liver injury. Select cases will be described (those deemed more serious).

- 9016-101605 This was a 24 year old randomized to GA 40 mg/day that was terminated early from the study because of pregnancy. In order to terminate the pregnancy she took a dose of mifepristone abortion pill. Her liver functions had been previously normal. Severe elevation of liver functions was observed sometime after that, one month after stopping Copaxone.

  The sponsor was asked for more information about this case. The subject had a negative past medical history but used naproxen and paracetamol for menstrual cramps and a multivitamin. At enrollment (2/13/07) ALT was slightly elevated at 49 IU/L (normal range 0-48). A month after starting 40 mg/day (3/14/07) her liver functions revealed ALT 118 IU/L (2.5 x ULN), AST 55 IU/L (1.3 x ULN) and ALP and bilirubin were normal. Two days later she informed investigator that she was pregnant and the study drug was terminated. (b) (6) later she underwent an elective abortion and took one dose of mifepristone abortion pill. At early termination visit a month later (4/11/07) her ALT was 217 IU/L (4.5 x ULN) and AST 74 IU/L (1.8 x ULN). Even though she was no longer on the study drug she remained in follow-up. She began monthly treatment with IV methylprednisolone 1000 mg and then began GA 20 mg/day outside the study. At follow-up a month later liver functions were normal and the adverse event was resolved. At month 6 (8/7/07) she returned for laboratory testing and the liver functions were elevated with ALT 186 IU/L (3.9 x ULN) and AST 90 IU/L (2.1 x ULN). Abdominal ultrasound was normal. History of misuse of alcohol, chemical agents, other drugs, herbs and dietary supplements and serologies for infectious and autoimmune hepatitis were all unavailable. Enzymes remained elevated and two months later peaked on 10/30/07 at ALT 484 IU/L (10.1 x ULN), AST 244 IU/L (5.8 x ULN) and Copaxone was stopped. The labs continued to be checked until they normalize on 1/15/08. On 2/15/08 Copaxone 20 mg/day was restarted by her physician and liver functions remained normal until the last follow-up on 8/12/08. *Copaxone is unlikely to be related to the transaminase elevation. The patient was rechallenged twice with Copaxone. Although transaminase levels rose the first time, she had also been treated with the steroids. The second time she was rechallenged the transaminase levels did not rise and this strongly suggests that Copaxone was not the cause.*

- 9016-101605 This was a 24 year old treated with GA 40 mg/day that was terminated from the study because of pregnancy after approximately 1 month of treatment. In order to terminate the pregnancy she took a dose of mifepristone abortion pill. Her liver functions had been previously normal. Severe elevations of transaminase levels were observed one month after stopping Copaxone and after the mifepristone. *Transaminase elevations unlikely to be related.*

- 9016-511013 This 28 year old female was treated with GA 40 mg/day. She withdrew consent on day 88 in order to get pregnant. A week after terminating study drug she was noted to have severely elevated transaminase levels. It appeared that she previously had an AE of herpes infection in the month preceding the elevation. *This may be related to Copaxone or may be related to the herpetic infection. More information was requested.*

  At screening this subject had significant transaminase elevations with ALT 387 IU/L (8.1 xULN) and AST 167 IU/L (4x ULN) and normal ALP and bilirubin. At enrollment ALT was 62 IU/L and AST was normal and at one month her labs were also normal. Her last study drug was on

07/01/07 and her labs at the early termination visit 07/06/07 (day 88) were ALT 247 IU/L (5.1 ULN) and AST 114 IU/L (2.7 xULN). It was noted that preceding this she had added treatment with alprazolam and amantadine. These were discontinued and her labs normalized at her last follow-up visit 8/27/07. *The transaminase elevations are unlikely to be related to Copaxone. She used concomitant medication that could cause liver dysfunction, she had a herpetic infection, and she had abnormal liver functions before she started Copaxone.*

- 9016-500204 This patient was treated with 20 mg/day and did not discontinue after having liver injury of moderate severity that was deemed non-serious. *The sponsor was asked to provide more information about this case.*

  This was a 23 year old underweight female who was treated for her chronic pyelonephritis four weeks before enrollment with oral akritoin started 03/29/07. She uses no alcohol or other drugs. At enrollment on 4/16/07 she had transaminase elevations with ALT 187 IU/L (3.9 x ULN) AST 97 IU/L (2.3 x ULN). ALP and bilirubin were normal. Follow-up testing on 4/24/07 showed a further increase with ALT 290 IU/L (6 x ULN), AST 152 IU/L (3.6 x ULN). These increases were attributed by the sponsor to the drug. No information was available about environmental or chemical agents or serology for infectious or autoimmune hepatitis. The investigator was concerned that the akritoin was playing a role and this was discontinued on 4/24/07 and the transaminase elevations resolved. On the same day that the liver functions were normal the investigator filed a report for "chronic toxic allergic hepatitis", a moderately severe AE possibly related to study drug. Liver and pancreas ultrasound were normal. Liver functions remained normal but study drug treatment was interrupted for a week from 06/07/07 to 06/14/07 and then resumed and subjected completed the DB phase of the study and entered the OL phase without further events. *This case is confounded by abnormal liver functions at enrollment compounded by the akritoin therapy. This is unlikely due to the study medication as she did well when she was rechallenged with Copaxone.*

The following two SAEs were already described in section 7.3.2 and are briefly summarized again here.

- 301-592408 A 46 year old male was treated with 40 mg TIW. He was hospitalized with symptoms of jaundice including yellow sclera and dark urine after a month on Copaxone. His symptoms probably started 10 days earlier. He was noted to have liver function elevations including an AST of 347 IU/L, ALT 577 IU/L, and total bilirubin 168.9 mmol/L. It is unclear if this is a case that meets Hy's Law criteria as the reference range of the hospital where these labs were obtained was unknown. After Copaxone was stopped his ALT and AST returned to close to normal within two weeks, but bilirubin was still elevated at 41 umol/L (1.9 x ULN). The sponsor felt that his rapid recovery, tender liver, and mildly elevated monocyte count made viral hepatitis more likely, even though the serologies obtained were negative. *A rapid recovery and tender liver can be seen with DILI and not exclusively with viral hepatitis and the lab tests are suggestive that he met Hy's Law criteria. No re-challenge was performed.*

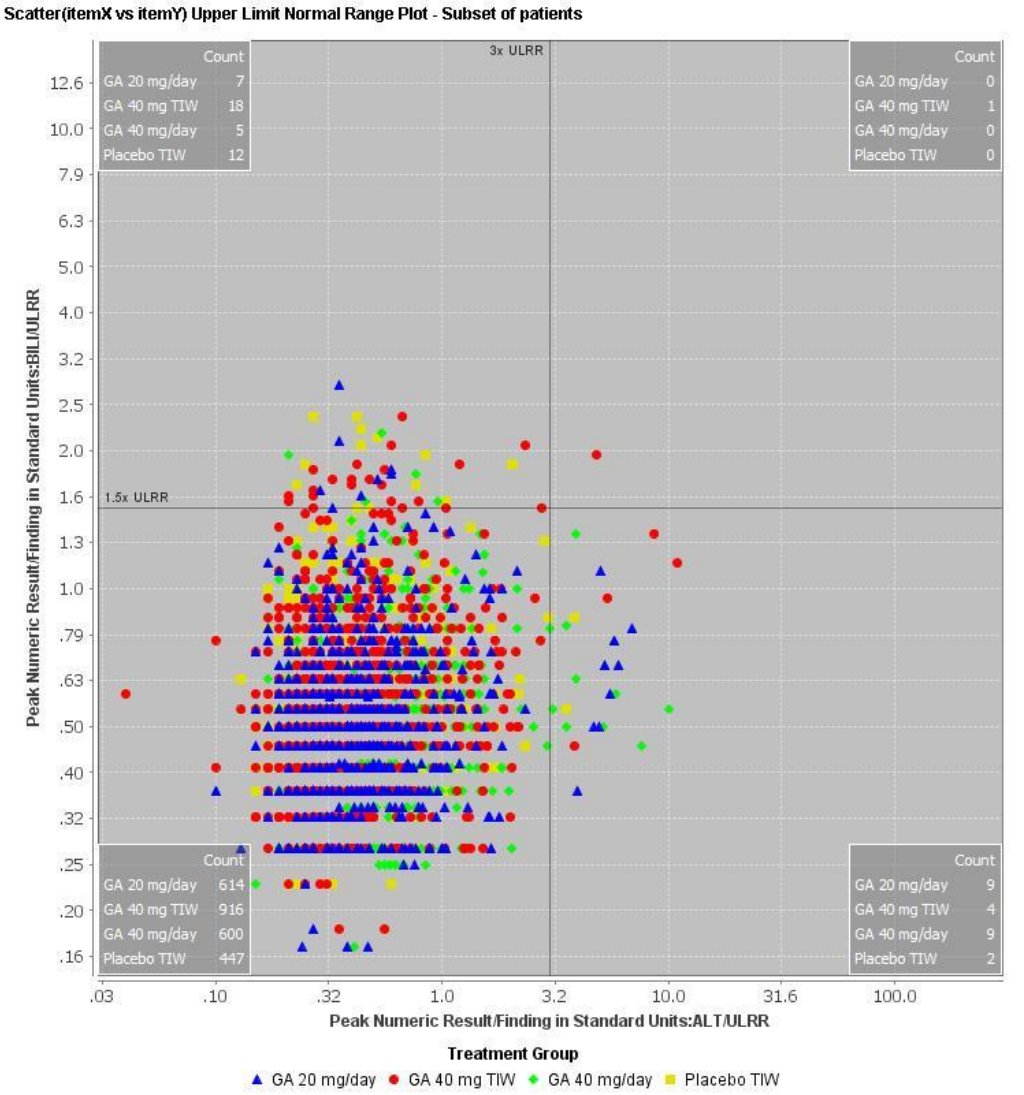
- 301-506012 A 34 year old female was treated with 40 mg TIW. She was treated with BCP marvelon chronically. She had a relapse one month into the study and was treated with IV steroids for five days and then oral steroids. Treatment with steroids was for over a month (a protocol violation). Several weeks later her liver functions rose to ALT 528 IU/l (11x ULN), AST 324 IU/l (7.7 x ULN), ALP 160 IU/l (1.3 x ULN), total bilirubin 25 umol/L (1.1 x ULN) and direct bilirubin 9 umol/L (1.5 x ULN). Despite these changes she remained on study medication. One week later liver functions rose further to AST 542.4 (17 x ULN), ALT 494 (15.9 x ULN). Serology for infectious hepatitis was negative and information regarding alcohol, herbs, dietary supplements, autoimmune hepatitis was unknown. Jaundice was evident and abdominal ultrasound showed hepatomegaly, chronic cholecystitis, and diffuse changes suggestive of

> chronic hepatitis. The gastroenterologist thought that this represented a case of drug induced liver dysfunction and drug was permanently discontinued on day 129. Liver functions returned to normal. Several months later the patient had another relapse and received steroid treatment again. She was noted to have mild elevation in transaminase levels with an ALT of 113 U/l and AST 55 U/l. *This case of moderately severe DILI is confounded by her concomitant medications including BCP, steroids, but effect of study medication cannot be excluded.*

Pool 1 transaminase and bilirubin levels were then analyzed using a scatter plot to screen for cases that may have been missed (Figure 4). Bilirubin values ≥ 1.5 were charted against AST levels using the Patient Selection criteria of JReview. In the analysis performed only subjects on drug in the DB PC period were included, not those not receiving medication or who had failed screening. The analysis did not include lab values from outside labs.

Only a single subject, a 35 year old male, met these criteria, subject 301-901806, and his labs were reviewed. He had been treated with GA 40 mg TIW. At screening his ALT was 62 U/L, AST 34 U/L, Bili 19 umol/L and ALP 76 U/L, within a month of treatment his ALT was 51 U/L, his AST was 24 U/L, bilirubin 39 umol/L, and ALP 75 U/L. At approximately three months labs included ALT 231 U/L (5 x ULN), AST 84 U/L (2x ULN), Bilirubin 17 umol/L, and Alk Phos 102 U/L. Copaxone treatment was interrupted. A week later his ALT was 155 U/L, AST was 58 U/L, bilirubin 23umol/L, and ALP 83 U/L, and the following week ALT was 91 U/L, AST 36 U/L, bilirubin peaked at 43 umol/L (2x ULN), and ALP 83 U/L. When his Copaxone was resumed, he tolerated the rechallenge well and was able to complete treatment and enter the OL phase. No cause for his elevated liver functions was ever found.

Figure 4 Pool 1 Scatter plot of Bilirubin ≥ 1.5 vs. AST



Pool 2

No hepatitis and liver injury AEs that occurred during the OL period lead to SAEs nor were they reported as severe or causing discontinuation. Hepatitis and liver injury were reported by 1.5% of subjects in the ES GA 40 mg/day group, 0.6% of those in the DS group, 0.5% of those in the ES GA 40 mg TIW group and 0.5% of those in the DS GA 40 mg TIW group.

120-Day Safety Report
All cases reported were mild and nonserious and none led to discontinuation. Hepatitis and liver injury were reported by 1.0% (4 subjects) in the DS group and 0.5% (4 subjects) in the ES group.

Reviewer's Comments
Although drug-induced liver injury (DILI) is well known to occur with the beta interferons, and has been reported with Tysabri, it is not reported in the clinical trial section of the label for GA although it has been reported rarely in the literature.[14]It has also been pointed out that before indicting liver toxicity to a disease-modifying therapy a thorough workup should take place to evaluate for viral infection, serological markers of autoimmunity, alcohol intake, bile duct obstruction, and other drug use such as non-steroidals, acetaminophen and other pain medication. [15]Liver function abnormality, liver damage, hepatitis are mentioned in the post marketing section of the Copaxone label which may or may not have a causal relationship to the drug. Careful examination of the cases presented here suggests that almost all were confounded by various factors such as concomitant medications, liver function abnormalities preceding enrollment or following discontinuation, other conditions. Several other cases that had no definitive etiology, tolerated a rechallenge with Copaxone without any further liver function abnormalities. Only subject 301-592408 may have met the conditions of Hy's Law, as there is no definitive evidence for a viral hepatitis such as positive serology, but the reference range of the laboratory where his labs were sent is unknown and so a determination cannot be made. He also was never rechallenged with Copaxone. Given the uncertainty about this case, and the fact that overall liver function abnormalities on Copaxone occurred at the same frequency as placebo, this does not need to be added to the clinical trial section of the label.

Hypersensitivity/anaphylaxis
This topic was explored because the immunogenicity of the GA 40 mg TIW dose is unknown. It is a concern that a more concentrated formulation of Copaxone might be more immunogenic. A prior Empirica Signal search of postmarketing reports suggested that there might be an increased risk for hypersensitivity, but not anaphylaxis, as demonstrated in Table 65. The drug label already acknowledges the risk for hypersensitivity. Outcomes that the sponsor selected for this analysis covered SAEs such as death, disability, hospitalization, life-threatening conditions requiring intervention to prevent permanent damage.

14 Subramanian, K, Pavli P, Llewellyn, H, S Chitturi Glatiramer acetate induced hepatotoxicity Current Drug Safety 2012 Apr, 7 (2): 186-8.

15 Hotermans C, Belachew S, Goonen G and J Delwaide Letter to the Editor Severe Liver Dysfunction in a patient with MS: the Guilty party is not always the disease-modifying therapy Multiple Sclerosis 15 (11) 1378-1379

Table 65 Empirica signal search for hypersensitivity association with Copaxone

PT	*Outcome*	*N*	*EBGM*	*EB05*	EB95	INTSS	*RR*	*E*
Drug hypersensitivity	*Hospitalized*	*33*	*3.88*	*2.90*	*5.11*	*0.827*	*4.03*	*8.20*
Drug hypersensitivity	*Other*	*45*	*3.54*	*2.76*	*4.49*	*0.787*	*3.62*	*12.4*
Hypersensitivity	*Hospitalized*	*67*	*3.49*	*2.85*	*4.24*	*1.11*	*3.57*	*18.8*

According to the sponsor's analysis the search terms for the category hypersensitivity and anaphylaxis included anaphylactic reaction, anaphylactic shock, hypersensitivity, and drug hypersensitivity. In the sponsor's analysis hypersensitivity and anaphylaxis overall were reported in less than 1% of subjects in the double-blind pool, 0.4% on those on placebo TIW (2 subjects), 0.6% in those on GA 20 mg/day (4 subjects), 1.6% on those on GA 40 mg/day (10 subjects), and 0.7% on those on GA 40 mg TIW (7 subjects). Many of those that were reported were attributed to medications other than Copaxone because of the close proximity to administration of other drugs and not to their Copaxone injection. All who reported this AE had their symptoms resolve according to the sponsor. Those that were reported as severe were reviewed. An analysis was then done by this reviewer and the narratives are listed in Table 66.

Table 66 Narratives for anaphylaxis and hypersensitivity reactions

Patient identifier	Dose	Narrative
GA 9016 102507	20 mg/day	35 year old female hospitalized because of anaphylactic reaction with diffuse erythema, facial flushing, chest pressure, In ER found to be in shock, resulting in drug discontinuation day 242 reported as an SAE, but not serious.
GA 9016 104906	40 mg/day	Considered a severe event, but not serious.
GA 9016 322002	40 mg/day Open label phase	27 year old female completed 364 days of the DB phase and entered the OL phase. She discontinued the drug on day 150 of the OL study after developing a panic attack after a recurring IPIR. The symptoms of IPIR included tachycardia, dyspnea. This was considered a severe event and an SAE. *This does not sound consistent with either anaphylaxis or hypersensitivity.*
GA 9016 500124	40 mg/day	22 year old female with a severe life threatening allergic reaction on day 92 of the DB phase resulting in drug discontinuation. Symptoms included a swollen face, rash on neck, fever, dyspnea. *This sounds consistent with an anaphylactic reaction.*
GA 9016 540914	40 mg/day	45 year old male who developed acute symptoms a few seconds after injection on day 57 of the DB phase. He experienced palpitations, vertigo, visual impairment, dysphagia, conjunctival erythema, diarrhea, palpitations, dyspnea. The study drug was discontinued and this was event was considered severe and an SAE. *This event sounds*

		more consistent with IPIR.
GA 9016 541112	40 mg/day	46 year old male who experienced facial flushing, paraesthesias, tremor on day 187 of the DB phase of the study. The symptoms were considered severe and study drug was discontinued. Lab work showed a low phosphorus level of uncertain significance. *This sounds consistent with an allergic reaction.*
GA 9016 321801	40 mg/day	43 year old female seen in an ER on day 150 of the DB phase for SAE of shortness of breath, chills, diarrhea, vomiting, back pain and inability to speak event which resolved in 2 hours. Four days later she was hospitalized with diffuse pain in the hands, arms, hips, knees, feet and slight headache considered an allergic reaction. This event was considered moderate and she did not need to discontinue drug. *This event sounds consistent with drug hypersensitivity.*
GA 301 522718	40 mg TIW	37 year old female who experienced moderate rash which resolved, then three days later ten minutes after injection experienced rash, pruritus, flushing vomiting, abdominal pain and a drop in blood pressure requiring medical treatment. This resulted in discontinuation on day 17 of the DB phase. The event was considered severe event, SAE. *This sounds consistent with anaphylactic shock.*
GA 301 537312	40 mg TIW	38 year old male with history of asthma who experienced mild intermittent injection site erythema and on day 197 of the DB phase of the study he developed acute weakness, dyspnea, palpitations and "thrills". The event was unwitnessed except for the patient who thought he injected himself intravenously rather than subcutaneously. This event was considered severe and SAE. *This sounds consistent with IPIR.*
GA 301 537503	40 mg TIW	Considered severe but not serious
GA 301 537702	40 mg TIW	55 year old male who in the DB phase of the study he experienced swelling at the site of the study drug injection. Two days later on study day 10 he developed chest pain, palpitations, dyspnea, chills, diaphoresis, nausea, hypotonus and facial swelling. Symptoms were considered severe but of moderate intensity and led to permanent discontinuation of the study drug on day 13. *This sounds consistent with anaphylactic reaction.*
GA 301 902105	40 mg TIW	33 year old female with intermittent drug hypersensitivity reaction leading to treatment discontinuation on day 23 of the DB period. Symptoms not listed but considered severe but not serious.

Reviewer's Comments

There does not appear to be a significant concern for increased risk of hypersensitivity or anaphylaxis with the GA 40 mg TIW product compared with the marketed product, GA 20 mg/day. Both are associated with infrequent hypersensitivity and anaphylaxis, in the current studies affecting less than 1%. Those treated with GA 40 mg/day had the greatest frequency of such reactions, but this is not a dose for which approval is sought. The narratives suggested that investigators might use terms like hypersensitivity and immediate post injection reaction (IPIR) indiscriminately as several of the events coded to hypersensitivity sounded more like

IPIR. True drug hypersensitivity reactions typically are accompanies by rash, fever, prolonged clinical symptoms and laboratory abnormalities or evidence of internal organ involvement. An independent search of the AE tables for cases with rash + urticarial or hypotension did not turn up any additional cases.

Lipoatrophy
This is discussed in section 7.3.4.1 under ISR.

Thrombocytopenia
The search term for thrombocytopenia included the PTs of platelet count decreased and thrombocytopenia. Only 0.2% (1 subject) in the GA 20 mg/day and 0.1% (1 subject) in the GA 40 mg TIW group reported this AE and both were considered mild and required no intervention. The subject on 20 mg/day began with normal platelet function which decreased below normal level at one month and then to a potentially clinically significant PCS level at month 3, but resolved by month 6 without any treatment or withdrawal. The subject on GA 40 mg TIW had a normal platelet level at screening, it was reduced at baseline and then normalized and subsequently dropped again at the termination visit at 12 months.

Chest Pain
The following preferred terms were used to evaluate the AE of chest pain: chest pain, chest pressure, musculoskeletal chest pain and non-cardiac chest pain. Chest pain was evaluated as it is a component of the Warnings and Precautions section of the label and according to the sponsor the incidence of chest pain is much less on the new formulation. They reported previously that 13% of patients exposed to marketed GA 20 mg/1mL, and 6% exposed to placebo in the 5 placebo-controlled trials reported in the label experienced chest pain. On the new formulation the sponsor reported that 2% of patients exposed to GA 40 mg TIW, and 1% exposed to placebo experienced chest pain. Independent analysis confirmed that less chest pain was experienced in the recent trial as demonstrated in Table 67. In the present studies 8.8% of those on GA 20 mg/day had chest pain, less than previously reported in the label and no increase was observed with the higher dose of GA 40 mg/day.

Table 67 Pool 1 Incidence of Chest Pain as AE

Symptom	**GA 9006 and GA 9016**						**MS- GA 301- GALA**					
	GA 20/day N = 630			GA 40 mg N = 615			Placebo TIW N = 461			GA 40 mg TIW N = 943		
	# report	# sub	% sub	# report	# sub	% sub	# report	# sub	% sub	# report	# sub	% sub
Chest pain	23	16	2.5	20	17	2.8	3	3	0.7	10	8	0.8
Chest pressure	51	36	5.7	36	31	5	1	1	0.2	5	5	0.5
Musculoskeletal chest pain	2	2	0.3	3	1	0.2	*	*	*	4	4	0.4
Non-cardiac	2	2	0.3	*	*	*	*	*	*	*	*	*

chest pain												
Totals	78	56	8.8	59	49	8.0	4	4	0.9	19	17	1.7

Reviewer's analysis

Those cases that were treated with GA 40 mg TIW in the GALA study were examined in more detail. Few narratives were available as their symptoms were considered mild to moderate and not severe and did not typically lead to SAEs or discontinuations. As the label suggests, many episodes of chest pain were in the context of IPIR and others were not. Most subjects had chest pain that lasted less than a day, although a few outliers had pain up to 17 days. Specifically the time of onset of the chest pain was between 15 to 332 days after starting treatment with a mean of 145 days. As the label suggests, some patients with chest pain experienced more than one episode. The few narratives reviewed suggested that there were no unresolved sequelae.

In Pool 2 chest pain was less frequent on GA 40 mg TIW regardless of duration of treatment than on GA 40 mg/day either delayed start or early start as seen in Table 68.

Table 68 Pool 2 Incidence of Chest Pain as AE

GA9016 and MS-GA-301 - OL phase	GA9016						MS-GA-301					
	Delayed Start GA 40 mg/day (N=523)			Early Start GA 40 mg/day (N=482)			Delayed Start GA 40 mg TIW (N=419)			Early Start GA 40 mg TIW (N=834)		
	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects
Chest Pain	29	19	3.6	17	11	2.3	5	5	1.2	6	3	0.4

Sponsor provided analysis p9 Amendment July 30, 2013

Reviewer's Comments

Those who reported chest pain in the recent trials were less than previously reported in the label at all doses both on the new formulation as well as on the old formulation. As the label suggests, the chest pain appears to be short lived, without sequelae, rarely leading to discontinuation and often part of IPIR, but not exclusively.

7.3.5 Submission Specific Primary Safety Concerns

Injection Site Reactions

The most frequent AE reported in prior controlled trials was injection site reaction (ISR). Table 69 displays the PTs classified as ISR in the current label for the GA 20 mg/day dose. As one can see, injection site erythema and injection site pain are the most commonly reported PTs and injection site atrophy and injection site fibrosis are the least commonly reported PTs. Injection site necrosis was not reported in past controlled trials, but has been noted infrequently in the post-marketing period.

Table 69 Injection site reactions as reported in the label for the approved product GA 20 mg/day as seen in prior controlled trials

Preferred Term (PT)	GA 20 mg N = 563	Placebo N = 564
Injection site erythema	43%	10%
Injection site pain	40%	20%
Injection site pruritis	27%	4%
Injection site mass	26%	6%
Injection site edema	19%	4%
Injection site inflammation	9%	1%
Edema	8%	2%
Injection site reaction	8%	1%
Injection site hypersensitivity	4%	0%
Local reaction	3%	1%
Injection site fibrosis	2%	1%
Injection site atrophy	2%	0%

Current Drug Label GA

Table 70 Injection Site Reactions Preferred Term and assigned category

Category Term	Preferred Term
Injection Site Abscess	Injection Site Abscess
Injection Site Atrophy	Injection Site Atrophy
	Lipoatrophy
	Lipodystrophy Acquired
Injection Site Discolouration	Injection Site Discolouration
Injection Site Erythema	Injection Site Erythema
	Injection Site Rash
Injection Site Haemorrhage	Injection Site Haematoma
	Injection Site Haemorrhage
Injection Site Hypersensitivity	Injection Site Hypersensitivity
	Injection Site Urticaria
Injection Site Infection	Injection Site Infection
Injection Site Inflammation	Injection Site Eczema
	Injection Site Inflammation
	Injection Site Irritation
	Injection Site Warmth
Injection Site Mass	Injection Site Induration
	Injection Site Mass
	Injection Site Nodule
	Injection Site Papule
	Injection Site Hypertrophy
Injection Site Oedema	Injection Site Oedema
	Injection Site Swelling
Injection Site Pain	Injection Site Discomfort
	Injection Site Pain
Injection Site Pruritus	Injection Site Pruritus
Injection Site Reaction	Injection Site Reaction
Injection Site Sensory Abnormalities	Injection Site Anaesthesia
	Injection Site Paraesthesia
	Injection Site Dysaesthesia
Injection Site Vesicles	Injection Site Vesicles

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Sponsor Post –Text Table 4 ISS, p 11.

For the ISS, under the SOC of "administration site disorders" the PTs were grouped into categories by the sponsor including those listed in Table 70. In addition some PTs found in the SOCs of "skin and subcutaneous tissue" were relevant. The list of PTs thought to be associated with ISR were gathered under categories and were used to assess subjects in Pool 1 and Pool 2.

Pool 1

ISRs were reported on all formulations, 57.3% of those on GA 20 mg/day, 59.0% of those on GA 40 mg/day, 35.2% of those on GA 40 mg TIW, and 5% of those on placebo as see in Table 71.

The most common symptom of ISR was "injection site erythema". In Pool 1 33.7% of those on GA 20 mg/day, 35.9% of those on GA 40 mg/day, 21.7% of those on GA 40 mg TIW, and 2% on placebo had this symptom.

Table 71 Pool 1: Frequency and Incidence of Injection Site Reactions by Category

GA9006 GA9016 and MS-GA-301 - DB phase	GA9006 and GA9016						MS-GA-301					
	GA 20 mg/day (N=630)			GA 40 mg/day (N=615)			Placebo TIW (N=461)			GA 40 mg TIW (N=943)		
	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects
Category Term												
-ALL	882	361	57.3	934	363	59.0	32	23	5.0	683	332	35.2
Injection Site Abscess	1	1	0.2	.	.	.	.	.	.	1	1	0.1
Injection Site Atrophy	7	7	1.1	14	14	2.3	.	.	.	5	5	0.5
Injection Site Discolouration	1	1	0.2	1	1	0.2	.	.	.	1	1	0.1
Injection Site Erythema	229	212	33.7	260	221	35.9	11	9	2.0	292	205	21.7
Injection Site Haemorrhage	63	53	8.4	47	43	7.0	3	3	0.7	10	9	1.0
Injection Site Hypersensitivity	11	11	1.7	21	21	3.4	.	.	.	.	.	.
Injection Site Infection	1	1	0.2	1	1	0.2	.	.	.	.	.	.
Injection Site Inflammation	19	17	2.7	13	12	2.0	1	1	0.2	25	22	2.3
Injection Site Mass	134	123	19.5	169	149	24.2	1	1	0.2	64	57	6.0
Injection Site Oedema	84	78	12.4	93	88	14.3	4	2	0.4	80	55	5.8
Injection Site Pain	199	170	27.0	181	153	24.9	9	9	2.0	111	98	10.4
Injection Site Pruritus	114	108	17.1	120	113	18.4	.	.	.	71	56	5.9
Injection Site Reaction	13	13	2.1	7	7	1.1	1	1	0.2	15	14	1.5
Injection Site Sensory Abnormalities	6	5	0.8	5	5	0.8	2	2	0.4	8	6	0.6
Injection Site Vesicles	.	.	.	2	2	0.3	.	.	.	.	.	.

Sponsor Table 7 ISS

The next most common category experienced after erythema was “injection site pain” and this occurred in 27.0% of those on GA 20 mg/day, 24.9% of those on GA 40 mg/day, 10.4% of those on GA 40 mg TIW, and 2% of those on placebo. Injection site abscess and injection site vesicles rarely ever occurred on any formulation.

The two most concerning categories of ISR, injection site necrosis and injection site atrophy, may lead to long-term sequelae where the affected tissue remains permanently damaged or scarred. Both are listed under Warnings and Precautions. They were evaluated as an AESI. It is thought that injection site atrophy and injection site necrosis can be avoided by rotating the injection site. These AEs were reported infrequently.

Injection site necrosis did not occur in the DB phase of the trial, but atrophy did occur. The search terms for lipoatrophy included the PTs of injection site atrophy, lipoatrophy acquired and lipoatrophy. All cases of lipoatrophy occurred on those on GA and none occurred among placebo patients. In the DB phase a total of 1.1% (7 subjects) developed lipoatrophy on GA 20 mg/day, 2.3 % (14 subjects) in those on GA 40 mg/day and 0.5% (5 subjects) in those on GA 40 mg TIW. All cases were deemed mild to moderate and none severe. As seen in Table 72 only two subjects on GA 40 mg/day stopped the medication due to lipoatrophy in the DB period. Several subjects were reported to have more than one such lesion in AE reports. Lipoatrophy rarely occurred immediately after initiating therapy and usually occurred after treatment of at least 6 months as demonstrated in Table 72.

Table 72 Lipoatrophy Category in the Pool 1

Study	Dose	Site	Time of Onset (days)	Severity	Serious	ACTION
9016-102207	GA 20 mg	Not noted	174	MILD	N	NONE
9016-105409	GA 20 mg	Not noted	Not noted	MILD	N	NONE
9016-105410	GA 20 mg	Bilateral thighs	146	MILD	N	NONE
9016-380609	GA 20 mg	Abdominal area	Not noted	MILD	N	NONE
9016-500903	GA 20 mg	Hips and Abdomen	189	MILD	N	NONE
9016-340912	GA 20 mg	Not noted	Not noted	MODERATE	N	NONE
9016-301702	GA 20 mg	Not noted	184	MILD	N	NONE
9016-102305	GA 40 mg	Bilateral thighs and right hip	247	MILD	N	NONE
9016-104605	GA 40 mg	Not noted	5	MILD	N	NONE
9016-104705	GA 40 mg	Not noted	259	MILD	N	NONE
9016-105102	GA 40 mg	Not noted	364	MILD	N	NONE
9016-105907	GA 40 mg	Not noted	190	MILD	N	NONE
9016-111702	GA 40 mg	Bilateral legs	234	MILD	N	NONE
9016-311106	GA 40 mg	Not noted	357	MILD	N	NONE
9016-321505	GA 40 mg	Not noted	34	MODERATE	N	STOP
9016-321603	GA 40 mg	Right thigh	Not noted	MILD	N	NONE
9016-321801	GA 40 mg	Not noted	201	MODERATE	N	NONE
9016-322306	GA 40 mg	Thighs	222	MILD	N	NONE
9016351101	GA 40 mg	Not noted	363	MILD	N	STOP
9016-520210	GA 40 mg	Not noted	361	MILD	N	NONE
9016-530117	GA 40 mg	Left and right arms	351	MILD	N	NONE
301-5055231	GA 40 mg TIW	Not noted	Not noted	MILD	N	NONE
301-583118	GA 40 mg TIW	Not noted	Not noted	MILD	N	NONE
301-592205	GA 40 mg TIW	Left extremity	Not noted	MILD	N	NONE
301-592210	GA 40 mg TIW	Lower extremities	Not noted	MILD	N	NONE
301-592211	GA 40 mg TIW	Not noted	Not noted	MILD	N	NONE

ISRs were not a cause for SAEs in Pool 1, although they were the most common cause of discontinuing early. Early discontinuations due to ISR were seen in 1.6% of those on GA 20 mg/day, 4.2% of those on GA 40 mg/day, 1% of those on GA 40 mg TIW, and not seen on placebo. Pertaining to the seriousness of the complaints, most of the complaints were mild to moderate. For those with serious complaints this represented 1.7% of those on the approved product, 2.4% of those on GA 40 mg/day, and only 0.1% of those on GA 40 mg TIW.

Pool 2

Table 73 Pool 2 Frequency and Incidence of ISRs by Category Term

GA/9016 and MS-GA-301 - OL phase	GA/9016						MS-GA-301					
	Delayed Start GA 40 mg/day (N=523)			Early Start GA 40 mg/day (N=482)			Delayed Start GA 40 mg TIW (N=419)			Early Start GA 40 mg TIW (N=834)		
	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects
Category Term												
-ALL	100	70	13.4	61	48	10.0	272	147	35.1	150	97	11.6
Injection Site Atrophy	6	6	1.1	11	11	2.3	1	1	0.2	5	5	0.6
Injection Site Discolouration	1	1	0.2	.	.	.	.	.	.	.	.	.
Injection Site Erythema	27	27	5.2	11	11	2.3	104	101	24.1	78	66	7.9
Injection Site Haemorrhage	6	6	1.1	5	5	1.0	3	3	0.7	1	1	0.1
Injection Site Hypersensitivity	1	1	0.2	2	2	0.4	.	.	.	.	.	.
Injection Site Mass	19	19	3.6	8	8	1.7	32	32	7.6	9	8	1.0
Injection Site Oedema	9	9	1.7	10	10	2.1	29	29	6.9	21	13	1.6
Injection Site Pain	25	24	4.6	12	12	2.5	50	49	11.7	22	19	2.3
Injection Site Pruritus	6	6	1.1	1	1	0.2	21	20	4.8	8	7	0.8
Injection Site Inflammation	.	.	.	1	1	0.2	12	12	2.9	3	3	0.4
Injection Site Reaction	.	.	.	.	.	.	17	6	1.4	3	3	0.4
Injection Site Sensory Abnormalities	.	.	.	.	.	.	3	3	0.7	.	.	.

NDA 20622 ISS page 34 Table 8

As seen in the preceding table, those on continuous therapy with GA 40 mg TIW, the ES group, had an ISR rate of 11.6% whereas those who had DS treatment had a rate of 35.1%. For those treated with GA 40 mg/day ES they had a 10.0% incidence of ISR, and those who had DS had a 13.4% incidence. It must be noted that the two DS groups cannot be meaningfully compared, as those on GA 40 mg TIW were being treated de novo with Copaxone, whereas those treated with GA 40 mg/day had prior exposure to Copaxone 20 mg/day for the preceding year.

Just as for Pool 1, those subjects in Pool 2 had erythema as their most frequent category of ISR. Skin necrosis was not reported in any subject and atrophy was uncommon, 2.3% in the ES GA 40 mg cohort, 0.6% in the ES GA 40 mg TIW cohort, 1.1% in the DS GA 40 mg, and 0.2% in the DS GA 40 mg TIW cohort. The majority of ISRs seen in subjects in Pool 2 were of mild to moderate severity and none were reported as SAEs.

120 Day Safety Update

No new findings were seen in the 120 day safety update where the most common ISRs were erythema, pain, mass, edema and pruritus. As before, ISR were more frequent in those in the DS 40 mg TIW cohort rather than in the ES 40 mg TIW cohort (37.0% vs. 12.6%). Discontinuations remain low from ISR a total of 2 (1.9%) of those in the DS cohort and 1 (0.4%) of those in the ES cohort. There were 2 cases of atrophy reported (0.5%) in the DS group and 6 cases in the ES group (0.7%).

Reviewer's Comments

Subjects continued to have frequent local reactions at the injection site on all doses of Copaxone; erythema was the most common reaction. The percentage distribution of the

categories of ISR with the new product was similar to what had been seen previously. In general, ISRs are less on GA 40 mg TIW than on the approved product. This included the most worrisome PTs such as lipoatrophy and necrosis as well as those with serious complaints or discontinuation. GA 40 mg/day compared unfavorably with the approved product. Pool 1 data suggests that both dose as well as frequency of administration is correlated with frequency of ISR. Pool 2 data suggests that regardless of dose, over time the frequency of such reactions lessen, with the exception of lipoatrophy.

Immediate Post-Injection Reaction (IPIR)

IPIR is a syndrome known to be associated with subcutaneous injections of GA that is described in the label under warnings and precautions. The syndrome is defined differently in the US and in Europe. In the European Union IPIR is defined as a reaction associated with one or more symptoms including: vasodilatation, chest pain, dyspnea, palpitation or tachycardia. For the purposes of this review and the label the syndrome will be defined as it is in the USA and includes at least two of the following symptoms: flushing (vasodilatation), chest pain, palpitations, anxiety, dyspnea, constriction of the throat (throat tightness), and urticaria. Only 16% of subjects on GA 20 mg/day and 4% of those on placebo had IPIR in the 5 PC trials described in the label.

The AEs that comprise this syndrome typically come from several different SOCs including cardiac, general and administration site conditions, musculoskeletal and connective tissue, psychiatric disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders and vascular disorders. Since some of the AEs may be reported in more than one SOC they are grouped together into categories using PTs listed in Table 74.

Table 74 Immediate Post-Injection Reaction (IPIR)

Category	Preferred Term
Anxiety	Anxiety
	Nervousness
	Stress
Chest Pain	Chest Discomfort
	Chest Pain
	Musculoskeletal Chest Pain
	Non-Cardiac Chest Pain
Dyspnoea	Dyspnoea
Palpitations	Palpitations
Throat Tightness	Throat tightness
	Pseudoangina
Urticaria	Urticaria
Vasodilatation (Flushing)	Feeling Hot
	Flushing
	Hot Flush
	Hyperaemia
	vasodilatation

Sponsor Post-Text Table 4 US/Canada Label Definition ISS

Pool 1

The label states that in the 5 DB, PB- controlled trials for marketed GA 20 mg/day approximately 16% of patients experienced IPIR, whereas 4% of those on placebo did. In the more recently conducted studies there were no IPIR in those on placebo, they were only present in those on Copaxone as seen in Table 75. The frequency appeared related to both the dose and frequency of injection with the least experienced in the GA 40 mg TIW group.

Table 75 Incidence of Immediate Post Injection Reactions using US category terms for the Pool 1

DB Cohort IPIR	GA 9006 and GA 9016				MS-GA-301	
	GA 20 mg/day N = 630		GA 40 mg/day N = 615		GA 40 mg TIW N = 943	
	# subjects	% subjects	# subjects	% subjects	# subjects	% subjects
	41	6.5%	52	8.5%	14	1.5%

Those cases with IPIR were examined in more detail for the GA 40 mg TIW dose. IPIR occurred in 14 such subjects and only one such subject, #522108, discontinued because of IPIR. The cases are reviewed in Table 76.

Table 76 Pool 1 IPIR GALA study (GA 40 mg TIW)

Subject #	Days since start GA	Time after injection	Severity	Narrative
Double-blind cohort				
130304 130304	Day 50 Day 211	1 minute 1 minute	mild moderate	43 year old female who had 2 episodes of IPIR. The first was accompanied by flushing, palpitations, and the second by feeling hot and dyspnea; both episodes were less than a day, dose not changed
130605	Day 23		mild	34 year old female who had chest tightness, dyspnea, flushing, episode less than a day, dose not changed
308401	Day 75	1 minute	severe	31 year old female who had dyspnea and feeling hot, episode less than a day, dose not changed
326401	Unknown	12 seconds	mild	31 year old female with dyspnea, feeling hot, flushing lasting 2 minutes, dose not changed
326403	Day 60	unknown	mild	34 year old female with dyspnea and flushing, lasting 10 minutes, dose not changed
343802	Day 10	10 days	mild	27 year old female with musculoskeletal pain, dyspnea lasting 10 days, not thought to be related, dose not changed
344002	Day 99	unknown	mild	39 year old female with chest tightness and dyspnea lasting 15 days, dose not changed
505301	Day 292	unknown	mild	20 year old male with chest discomfort, palpitations lasting less than a day, dose not changed
522108	Day 71	5 minutes	moderate	49 year old female with 2 episodes. The first was

522108	Day 74	10 minutes	moderate	experienced as flushing, mild dyspnea, flushing lasting less than a day, dose not changed Second episode with dyspnea lasting less than a day, **drug was withdraw**
537004	Day 92	2 minutes	moderate	32 year old female with dyspnea, flushing, dose not changed
537329 537329	Day 165 Day 347	1 minute 1 minute	severe moderate	50 year old female with 2 episodes including anxiety, dyspnea, drug interrupted Second episode with anxiety, feeling hot, urticarial, dose not changed
583609	Day 67	1 minute	moderate	38 year old female with dyspnea, feeling hot, dose not changed
592902 592902	Day 138 Day 147	1 minute 5 minutes	mild mild	43 year old female with chest pain, dyspnea, and a second episode with chest pain and dyspnea, dose not changed
601034	Day 71	5 minutes	mild	24 year old female with flushing and palpitations, dose not changed

Three subjects had a second episode. Almost all episodes experienced were extremely brief, lasting for minutes. Only two had episodes lasting for days and these were predominantly characterized by chest tightness, which may have had another etiology. The episodes occurred between days 10 to 347 days; for an average time of 93 days after the first injection.

An analysis was then performed to look at those subjects that had severe AEs that were components of IPIR symptoms as seen in Table 77. No subject on placebo had any AEs that were associated with IPIR that were severe; severe events were low for all doses but in a dose dependent fashion with the lower incidence in those who received GA 40 mg TIW.

Table 77 Pool 1 Incidence Severe symptoms that compose IPIR

		GA 20 mg/day N= 630	GA 40 mg/day N = 615	GA 40 mg TIW N = 943	All Subjects N = 2649
Category Term of IPIR US	**Preferred Term**	**Severe IPIR**	**Severe IPIR**	**Severe IPIR**	**Severe IPIR**
Anxiety	Anxiety	0 (0.00%)	1 (0.04%)	2 (0.08%)	3 (0.11%)
Chest Pain	Chest Discomfort	6 (0.23%)	2 (0.08%)	0 (0.00%)	8 (0.30%)
	Chest Pain	2 (0.08%)	3 (0.11%)	0 (0.00%)	5 (0.19%)
	Non-Cardiac Chest Pain	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.04%)
Dyspnea	Dyspnea	11 (0.42%)	6 (0.23%)	3 (0.11%)	20 (0.76%)
Palpitations	Palpitations	3 (0.11%)	2 (0.08%)	0 (0.00%)	5 (0.19%)
Throat Tightness	Throat Tightness	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.04%)
Vasodilatation	Feeling Hot	2 (0.08%)	1 (0.04%)	1 (0.04%)	4 (0.15%)

	Flushing	5 (0.19%)	8 (0.30%)	0 (0.00%)	13 (0.49%)
	Hot Flush	1 (0.04%)	1 (0.04%)	0 (0.00%)	2 (0.08%)
Total	**Subjects**	**61 (2.30%)**	**82 (3.10%)**	**39 (1.47%)**	**(100.00%)**

Pool 2
The incidence of IPIR during the OL phase was infrequent in all categories as seen in Table 78.

Table 78 Pool 2 Incidence of IPIR

OL Cohort IPIR	GA 9016				MS-GA-301			
	Delayed Start GA 40 mg/day N = 523		Early Start GA 40 mg/day N = 482		Delayed Start GA 40 mg TIW N = 419		Early Start GA 40 mg TIW N = 834	
	# subjects	% subjects	# subjects	% subjects	# subjects	% subjects	# subjects	% subjects
	13	2.5 %	9	1.9 %	4	1.0 %	4	0.5 %

The GA 40 mg TIW dose was associated with less IPIR than the 40 mg/day dose, regardless of whether or not the drug was used for more or less than a year.

120-Day Safety Summary
In the 120-Day Safety Summary four additional subjects in the ES GA 40 mg TIW cohort had IPIR. All were mild to moderate. One on GA 40 mg TIW DS was reported as a SAE including dyspnea and urticaria, but did not discontinue.

Table 79 120 Day Safety Summary IPIR

OL Cohort IPIR	GA 9016				MS-GA-301			
	Delayed Start GA 40 mg/day N = 523		Early Start GA 40 mg/day N = 482		Delayed Start GA 40 mg TIW N = 419		Early Start GA 40 mg TIW N = 834	
	# subjects	% subjects	# subjects	% subjects	# subjects	% subjects	# subjects	% subjects
	13	2.5 %	9	1.9 %	4	1.0 %	8	1.0 %

Reviewer's Comment
Recent clinical trials have a lower incidence of IPIR than that reported previously in the label. The reason for this is unknown, but may have to do with the lower AE reporting in Eastern European subjects. Despite this observation, if one looks across clinical trials at the DB cohort, it appears that the incidence of this event is dose related. GA 40 mg TIW has the lowest incidence of IPIR compared with both the approved dose as well as the GA 40 mg/day. When one looks at the OL phase this pattern persists. In general episodes were short-lived, generally lasting for minutes, and often occurred about three months after the first injection. It was

rare for episodes to reoccur, and the data suggests that they decline in frequency over time. Exploring the relationship of IPIR to cytokine levels, immunoglobulin levels, relapse rate, might further our understanding of this phenomenon.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Since the label will only describe the AE with an incidence ≥ 2% of patients on GA 40 mg TIW than with placebo, this will be reviewed first. Once treatment commenced after baseline visit in this trial there were a total of 4306 AE overall, 3468 on DB treatment and 838 on OL treatment. The AE that had the highest incidence were mostly related to ISR and included injection site erythema, pain, pruritus, edema. These are listed in Table 80. Table 81 lists the AEs cited in the label for Copaxone 20 mg/day.

Table 80 AE during PB phase, GALA trial, with an incidence ≥ 2% of patients on GA 40 mg/1mLTIW and greater than placebo

SOC	PT	GA 40 mg/1 mL (N=943)	Placebo (N=461)
General Disorders And Administration Site Conditions	Injection Site Erythema	22%	2%
	Injection Site Pain	10%	2%
	Injection Site Mass	6%	0%
	Injection Site Pruritus	6%	0%
	Injection Site Edema	6%	0%
	Pyrexia	3%	2%
	Influenza Like Illness	3%	2%
	Injection Site Inflammation	2%	0%
	Chills	2%	0%
	Chest Pain	2%	1%
Infections And Infestations	Nasopharyngitis	12%	9%
	Respiratory Tract Infection Viral	3%	2%

SOC	PT	GA 40 mg/1 mL (N=943)	Placebo (N=461)
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	3%	0%
Vascular Disorders	Vasodilatation	3%	0%
Gastrointestinal Disorders	Nausea	2%	1%
Skin And Subcutaneous Tissue Disorders	Erythema	2%	0%
	Rash	2%	1%

Copaxone proposed label

Table 81 AE in PB-controlled trials with incidence ≥ 2% of patients and more frequent with GA 20 mg/day than placebo as described in current label

SOC	PT	GA 20 mg/1 mL (N=563)	Placebo (N=564)
Blood And Lymphatic System Disorders	Lymphadenopathy	7%	3%
Cardiac Disorders	Palpitations	9%	4%
	Tachycardia	5%	2%
Eye Disorders	Eye Disorder	3%	1%
	Diplopia	3%	2%
Gastrointestinal Disorders	Nausea	15%	11%
	Vomiting	7%	4%
	Dysphagia	2%	1%
General Disorders And Administration Site Conditions	Injection Site Erythema	43%	10%
	Injection Site Pain	40%	20%
	Injection Site Pruritus	27%	4%
	Injection Site Mass	26%	6%
	Asthenia	22%	21%
	Pain	20%	17%
	Injection Site Edema	19%	4%
	Chest Pain	13%	6%
	Injection Site Inflammation	9%	1%
	Edema	8%	2%
	Injection Site Reaction	8%	1%
	Pyrexia	6%	5%
	Injection Site Hypersensitivity	4%	0%
	Local Reaction	3%	1%
	Chills	3%	1%
	Face Edema	3%	1%
	Edema Peripheral	3%	2%
	Injection Site Fibrosis	2%	1%
	Injection Site Atrophy*	2%	0%
Immune System Disorders	Hypersensitivity	3%	2%

SOC	PT	GA 20 mg/1 mL (N=563)	Placebo (N=564)
Infections And Infestations	Infection	30%	28%
	Influenza	14%	13%
	Rhinitis	7%	5%
	Bronchitis	6%	5%
	Gastroenteritis	6%	4%
	Vaginal Candidiasis	4%	2%
Metabolism And Nutrition Disorders	Weight Increased	3%	1%
Musculoskeletal And Connective Tissue Disorders	Back Pain	12%	10%
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Neoplasm of Skin	2%	1%
Nervous System Disorders	Tremor	4%	2%
	Migraine	4%	2%
	Syncope	3%	2%
	Speech Disorder	2%	1%
Psychiatric Disorders	Anxiety	13%	10%
	Nervousness	2%	1%
Renal And Urinary Disorders	Micturition Urgency	5%	4%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	14%	4%
	Cough	6%	5%
	Laryngospasm	2%	1%
Skin And Subcutaneous Tissue Disorders	Rash	19%	11%
	Hyperhidrosis	7%	5%
	Pruritus	5%	4%
	Urticaria	3%	1%
	Skin Disorder	3%	1%
Vascular Disorders	Vasodilatation	20%	5%

Reviewer's Comment
All of the AEs cited in the GALA trial were already seen in prior clinical trials with the exception of nasopharyngitis and respiratory tract infection viral. (See Table 81). Both of these may be incidental symptoms rather than represent any previously recognized untoward AE. It is noted that in trials GA 9006 and GA 9016 nasopharyngitis and rash were both seen on the GA 20 mg dose as seen in the Table 82, so it is unlikely that the findings on the GA 40 mg TIW dose are really something new.

Table 82 AE on the GA 20 mg/day dose seen in recent controlled trials not previously reported in prior controlled trials

GA 9006 and GA 9016 (N= 630 GA 20 mg/day)	# of Reports	# of Subjects	% of Subjects
Nasopharyngitis	109	84	13.3
Respiratory Tract infection viral	9	9	1.4
Rash	21	18	2.7

Pool 1

In Pool 1 treatment emergent adverse events (TEAE) were lower for the GA 40 mg TIW dosing than for the GA 20 mg/day and GA 40 mg/day dosing (72.1% on GA 40 mg TIW, 86.2% on GA 20 mg/day, 87.2% on GA 40 mg/day and 61.6% on placebo). The most common PTs were associated with ISR and IPIR and ISR was the HLT with the highest incidence for subjects on all doses of Copaxone. Treatment emergent AE were primarily mild or moderate in severity. AEs leading to termination were primary because of ISR and IPIR. SAEs were comparable in all groups, in 4.1% of subjects on GA 20 mg/day. 4.2% of subjects on GA 40 mg/day, 4.6% of subjects on placebo, and 4.5% of subjects on GA 40 mg TIW.

As Infections and Infestations led to an increased number of SAE including tuberculosis and herpetic infections this SOC was further explored to see if there were any previously unidentified infections common to immunocompromised hosts and the results can be found in the following table. No other cases of tuberculosis were reported but there were a number of cases of herpetic infections that were not SAE.

Table 83 Pool 1 AE Herpetic Infections

	(GA 20 mg/day) N = 630		(GA 40 mg TIW) N = 615		(GA 40 mg/day) N = 943		(Placebo TIW) N = 416	
Preferred Term	N	%	N	%	N	%	N	%
Genital Herpes	4	0.6	2	0.3	1	0.1	1	0.2
Herpes Simplex	1	0.3	3	0.5	0	*	0	*
Herpes Simplex Ophthalmic	0	*	0	*	1	0.1	0	*
Herpes Zoster	7	1.0	4	0.7	6	0.6	1	0.2
Herpes Zoster Ophthalmic	0	*	2	0.3	0	*	0	*
Total	12	1.9	11	1.8	8	0.8	2	0.5

Pool 2

In the 120 day safety update the total number of AEs were higher in the DS GA 40 mg TIW group (61.6%) compared with the ES GA 40 mg TIW group (56.1%). The DS group received placebo for the first year. The most common SOC represented general disorders and administration site conditions which represented 39.4% of the subjects with the DS GA 40 mg TIW and 16.5% of the subjects with the ES GA 40 mg TIW. Injection site reactions (ISR) were the HLT of highest incidence in this SOC for a total of 37.0% in those in the DS group and 12.5% in those in the ES group. Erythema due to injection site reaction was the more common symptom in those in the DS group (25.8% vs. 8.8%) as well. SAEs were reported by 2.9% of those on DS GA 40 mg TIW and 2.4% on ES GA 40 mg TIW as well as 2.5% of those on ES GA 40 mg/day and 1.3% of

those on DS GA 40 mg/day. Treatment emergent AE in Pool 2 were primarily mild or moderate in severity. ISR and IPIR accounted for almost all the discontinuations. The incidence of discontinuations due to AE was 3.3% on DS GA 40 mg TIW, 1.0% on ES GA 40 mg TIW, 2.9% on ES GA 40 mg/day and 2.7% on DS GA 40 mg/day.

Reviewer's Comment
For all doses of Copaxone PTs associated with ISR and IPIR are the most prevalent experienced, and the least are noted on GA 40 mg/day compared with GA 40 mg/day and the marketed product. The higher prevalence of ISR in those in the delayed start group who had less exposure to GA suggests that ISR diminishes over time and are more common in the first year of use. Although there is an increased incidence of herpetic infections, greater on Copaxone than on placebo, it is less than 2% and no greater than approved product. The slight increase in herpetic infections is already mentioned in the label.

7.4.2 Laboratory Findings

Laboratory measures were presented in SI units and were defined for each study by a central laboratory with pre-defined potentially clinically significant limits (PCS). Each lab was classified as within limits or below or above the normal range. Two types of analyses were then performed on laboratory data.

1. For selected parameters for which PCS limits were pre-defined, shifts from values within normal or abnormal range at baseline to either PCS high or PCS low any time during the study were identified.
2. An analysis based on the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 was used to perform shift analysis for selected parameters.

Shift analyses from baseline grade to worse post-baseline grade at any time during the study were generated for selected parameters. The selected parameters included blood counts, K, Na, P, creatinine, Alkaline Phosphatase, AST, ALT, bilirubin, albumin, and proteinuria. Blood sugar was not included as the labs were not fasted and calcium was not included as the technique to assess calcium as presented in the CTCAE assessment was not observed.

Laboratory testing included hematology, chemistries and urinalysis for the three studies. Blood testing was performed at screening, baseline, months 1,3,6,9, in all three studies and also included month 12 for the FORTE and GALA studies. Unscheduled visits also occurred where blood tests were drawn. Blood tests that occurred during the time of the study, but not at the study lab were not included in this analysis, but could be included in the AE reporting.

Results
Summary

There were no grade 5 (deaths) for any laboratory parameter for either Pool 1 or Pool 2. The sponsor's ISS reported no clinically significant laboratory test results related to serious AEs for any dose (see Table 97), although it must be noted that there were serious AEs filed for labs done outside of the study previously described in this review for subject 301-592408. This was a 46 year old male treated with Copaxone 40 mg TIW who was hospitalized with jaundice, yellow clear and dark urine one month after starting treatment. His liver functions were AST 347 IU/L, ALT 577 IU/L, and total bilirubin 168.9 mmol/L at the hospital. He was taken off Copaxone permanently and his labs returned to normal within a few weeks. He was not considered to have his treatment withdrawn due to a laboratory finding in the study because his labs were drawn at an outside facility. Two subjects on GA 40 mg/day dose did have their medication withdrawn due to abnormal labs within the study as can be seen in Table 84. In general there were a lot of isolated abnormalities. The most notable findings were an isolated case of hemoglobin decreased to grade 4 thought to be spurious, transaminase levels rising to grade 3 in all doses, one of which was an SAE on GA 40 mg TIW, a case of an elevated creatinine most likely related to dehydration, several cases of isolated hyperkalemia and hypophosphatemia on the GA 20 mg/day and GA 40 mg/day but not on the GA 40 mg TIW dose

Table 84 Pool 1 Laboratory Investigation as AE in the ISS

Drug	**GA 20 mg/daily 630 subjects**	**GA 40 mg/daily 615 subjects**	**GA 40 mg TIW 943 subjects**	**Placebo 461 subjects**	**All**
	Number of Adverse Events on each treatment in DB phase				
N unique subjects	32	31	25	14	
N AE	49	48	42	28	167
AE Severity					
Missing	0	4	0	3	7
Mild	39	29	39	21	128
Moderate	10	9	3	7*	29
Severe	0	6	0	0	6
AE Serious					
Missing	0	4	0	3	7
Y	0	0	0	0	0
N	49	44	42	25	160
AE Action					
Not changed	47	43	41	28	159
Interrupted	2	3	1	0	6
Withdrawn	0	2	0	0	2
AE Drug Related					
Possible	9	12	11	8	40
Unlikely	40	37	27	17	121
Unknown			4	3	7

Laboratory Shifts <grade 5

Hematology
Overall there were few shifts that occurred at any dose. The shifts from baseline according to CTCAE are described and the shifts from normal baseline parameters are only mentioned if they were highly significant or discrepant with the prior findings. The narratives for these shifts were reviewed and did not reveal any remarkable findings.

Neutrophils
Shifts from CTCAE
In Pool 1 there were two shifts that occurred for the GA 40 mg TIW dose from grade 0 to 4 for neutrophils, eight shifts in the 40 mg TIW, one shift in the GA 40 mg/day, three in the placebo TIW from grade 0 to 3. Almost all of these appeared to be laboratory findings and were not accompanied by AE reports with the exception of one subject on GA 40 mg TIW #682904 who had neutropenia and leukopenia associated with mild nasophyaryngitis.

Lymphocytes
In the Pool 1 there were several subjects who had changes in lymphocytes reported as AEs. There were three subjects that had shifts from grade 0 to grade 3; one on a subject on GA 20 mg/day and two in subjects on GA 40 mg/day, but none were on GA 40 mg TIW. All of those found subsequently normalized. In the OL phase a single subject on GA 40 mg had a grade 3 shift. This patient terminated and did not follow-up and an AE was not file.

Hemoglobin
In Pool 1 there was an isolated shift from 0 to grade 4 in a single subject on GA 40 mg TIW (#538104). The narrative was reviewed and the subject had changes consistent with pancytopenia at their month 3 collection which all normalized a week later. It was felt by the investigator that the results were spurious due to either lab error or poor handling. Two additional shifts were from grade 2 to grade 3, one in a placebo TIW subject and one in a GA 40 mg/day subject.

Platelets
In Pool 1 there were two subjects who had a shift from grade 0 to grade 4; one was a placebo TIW subject and one was a GA 40 mg TIW subject, the subject with pancytopenia described above.

Chemistries
Few shifts were noted according to CTCAE grading and none were higher on the GA 40 mg TIW dose.

Transaminases – In Pool 1 there were two shifts in CTCAE grade to grade 3 in ALT for the GA 40 mg TIW dose and both of these were reported as SAEs and previously discussed in section 7.3.2 7.3.4. There were six shifts noted in the GA 20 mg/day dose and two in the GA 40 mg/day dose. There was a single grade 3 shift for AST noted in a subject on GA 20 mg/day. All shifts were captured as AEs, save one.

In Pool 1 shifts from normal to high PCS levels at any time during the study for ALT, and AST were highest in the GA 20 mg/day group, but when bilirubin was included with the ALT, AST, the greatest amount of shifts occurred in the GA 40 mg TIW group and placebo group than in the GA 40 mg/day group. This is displayed in the Table that follows.

Table 85 Pool 1 Shift analysis of Transaminase > 3 ULN and Bilirubin > 1.5 ULN anytime during the study

GA9006 GA9016 and MS-GA-301 - DB phase		GA9006 and GA9016						MS-GA-301					
		GA 20 mg/day (N=630)			GA 40 mg/day (N=615)			Placebo TIW (N=461)			GA 40 mg TIW (N=943)		
		All*	PCS	%	All*	PCS	%	All*	PCS	%	All*	PCS	%
Hepatobiliary	AST (U/L) > 3 ULN	12	4	33.3	14	1	7.1	6	0	0.0	23	0	0.0
	ALT (U/L) > 3 ULN	18	4	22.2	34	7	20.6	11	1	9.1	39	0	0.0
	Bilirubin (umol/L)> 1.5ULN	19	7	36.8	18	4	22.2	25	12	48.0	39	17	43.6

Alkaline phosphatase, bilirubin, albumin – In Pool 1 no grade 3 shifts noted.

Creatinine – In Pool 1 a single subject on placebo and one on GA 40 mg/day had a grade 3 shift which resolved.

Hypernatremia – In Pool 1 a single shift to grade 3 was noted on a subject on GA 20 mg/day that resolved. In Pool 2 one subject had a shift to grade 3 after 12 month in the OL period on ES GA 40 mg TIW.

Hyperkalemia - In Pool 2 one subject on DS GA 40 mg TIW had grade 4 hyperkalemia at the 12 month visit and it was not reported as an AE.

Hypophosphatemia- There were two subjects in Pool 1 on GA 40 mg TIW and four subjects on GA 20 mg/day and five subjects on GA 40 mg/day who had a shift to grade 3, but it is noted that six of these had grade 2 shifts at baseline. In Pool 2 three subjects on DS GA 40 mg/day shifted to grade 3 and all were withdrawn without being reported as AEs.

Hyperkalemia – There was one subject in Pool 1 on GA 20 mg that had multiple shifts from normal to grade 3 during the study, but baseline and the terminal visit were normal and no etiology could be found for these changes. There were eleven other subjects on all doses of drug and placebo that had shifts of grade 3 or 4, but all were isolated, and returned to normal. In Pool 2 a single subject on DS GA 40 mg TIW shifted to grade 4 at the 12 month visit and it was not reported as an AE.

Hypokalemia – A single subject in Pool 1 on GA 40 mg TIW had a grade 3 shift associated with limb weakness and imbalance, and this required hospitalization and resolved with treatment.

Urinalysis –Ten subjects in Pool 1 including two on GA 20 mg/day, two on GA 40 mg/day, three on GA 40 mg TIW, and three on placebo had grade 3 shifts that were isolated occurrences. Two grade 2 shifts were also observed on Copaxone. In Pool 2 one subject on ES GA 40 mg TIW had urine protein +3 after 12 months in the OL phase not reported as an AE.

Reviewer's Comment
There were no changes in laboratory values of apparent significance other than the changes in liver functions previously discussed.

7.4.3 Vital Signs

Although tachycardia is an AE associated with the use of Copaxone, other alterations in vital signs are not known to be related to the product. No restrictions for the use of this product exist with respect to vital signs. As vital signs were reported at different time intervals in the studies that comprise the ISS, they were not analyzed collectively, but were analyzed separately.

MS- GA-301 GALA Study
In this study vital signs were obtained on screening and baseline visit, months 1,3,6,9 and 12 during the DB phase and then at months 15, 18, 21, 24 and subsequently every 6 months during the OL phase as well as unscheduled visits. A total of 17923 pulse and BP measurements were obtained in the DB period. The mean and minimum SBP, DBP and pulse were comparable at baseline and throughout treatment for both those on placebo and Copaxone (Table 86). The maximum heart rates SBP, and DBP were higher on Copaxone, but shifts to clinically significant values were minimal in both groups (Table 87).

Table 86 GALA trial DB phase SBP, DBP, Pulse (with min, max)

Visit #	VS	Copaxone 40 mg TIW			Placebo		
		n	min	max	n	min	max
Baseline pre-dose	SBP	118	75	175	118	80	165
	DBP	76	40	120	76	50	105
	P	74	47	130	73	50	101
1	SBP	118	85	170	119	90	160
	DBP	75	50	120	76	50	100
	P	74	52	108	73	50	100
2	SBP	119	90	168	118	85	160
	DBP	76	48	110	75	50	105
	P	74	50	130	74	50	109
3	SBP	119	85	170	118	90	150
	DBP	76	40	115	75	50	112
	P	74	49	115	73	50	102
4	SBP	118	90	170	118	80	160
	DBP	76	50	110	76	50	100
	P	74	50	135	74	51	112
5	SBP	119	90	180	118	88	160
	DBP	76	55	110	75	50	100
	P	74	46	109	73	50	100

Table 87 Vital Sign Shifts within Non-PCS and Above Upper PCS Limit at "Anytime during Study"

GALA (MS-GA-301)		Placebo (N=461, Subject Years=442.5)		GA 40 mg (N=943, Subject Years=884.4)	
		N	%	N	%
Systolic Blood Pressure (mmHg)	All	461	100.0	939	100.0
	<=90	30	6.5	55	5.9
	>90 and <180	461	100.0	939	100.0
	>=180	.	.	1	0.1
Diastolic Blood Pressure (mmHg)	All	461	100.0	939	100.0
	<=50	5	1.1	4	0.4
	>50 and <100	461	100.0	939	100.0
	>=100	17	3.7	33	3.5
Pulse Rate (bpm)	All	461	100.0	939	100.0
	>45 and <120	461	100.0	939	100.0
	>=120	.	.	1	0.1

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Table 15.10.2.8 CSR GALA

There was a single discontinuation due to a severe AE with alterations in VS. Subject 301-583510 treated with GA 40 mg TIW was a 30 year old male smoker with a history of untreated hypertension who had a normal EKG at enrollment, but an elevated BP of 140/93. One hour after injection his BP was 160/95 and Vasoretic was started. Five days into the study just after another injection he developed headache, nausea, palpitations and hyperthermia with a temperature of 40C. He was noted to have a BP of 170/100. This was considered a severe AE and he was permanently discontinued. After treatment ceased the BP returned to 143/89 but ECG now showed a first degree AV block.

There was a single subject with an SAE related to VS; subject 301-536901 treated with GA 40 mg TIW. She was a 54 year old obese female with history of hypertension treated with captopril that on enrollment had a BP of 130/70 and an ECG with nonspecific T wave abnormality. At month 10 of treatment she got hospitalized for vertigo and hypertension with a BP of 150/80. Her elevated SBP was treated successfully with further medication. Symptom was felt to be mild but serious.

Reviewer's Comments
There was a single case of mild hypertensive changes that led to an SAE on GA 40 mg TIW and another case of severe AE leading to drug discontinuation, also on GA 40 mg TIW. Both took place in patients with preceding history of hypertension and were not noted de novo. The first case had blood pressure alterations with close proximity to injections, suggesting IPIR. The second case was associated with an ECG change and may have been unrelated. One had untreated hypertension at the time of entry into the study and the second was already on an antihypertensive and required a dose adjustment. Even though the maximal heart rates, SBPs and DBPs were slightly higher on Copaxone than on placebo, clinically significant changes were rare. For those whom narratives were provided, many were related to IPIR and transient.

GA/9016 FORTE
In this study vital signs were obtained at screening, baseline, months 1,2,3,6,9,12 15, 18 21, 24 as well as unscheduled visits. In this study there was no placebo comparison. According to the sponsor there were potentially clinically significant changes in VS on both GA 20 mg/day and GA 40 mg/day primarily tachycardia related to IPIR. There were a few AEs due to hypertension and most were in patients with prior history.

GA 9006
In this study vital signs were obtained at screening, baseline, months 1,3,6,7,8,9 and unscheduled visits. In this study there was no placebo comparison. According to the sponsor no potentially clinically significant change in VS was seen in either the GA 20 mg/day or the GA 40 mg/day.

7.4.4 Electrocardiograms (ECGs)

ECG changes have not been described with Copaxone, but it is noted that a dedicated QT study has never been performed for this product nor has any study explored ECG changes associated with IPIR, a syndrome characterized by chest pain and palpitations. ECGs were performed at different times intervals in the various studies and were evaluated separately and not as part of the ISS.

MS- GA-301 GALA
There were a total of 6380 ECGs performed on subjects assigned to Copaxone 40 mg TIW, both the DB and OL portion of the study. Of these 552 had an ECG that was interpreted as abnormal (368 on placebo and 184 on Copaxone 40 mg TIW), but most were nonsymptomatic requiring no change in management. The sponsor reports 19.7% of those on placebo and 20.5% of those on GA 40 mg TIW had abnormal ECG readings at baseline. Two of those in the GA 40 mg TIW cohort had baseline abnormalities that continued throughout the study. Subject #505306 had sinus bradycardia and subject #504708 had sinus bradycardia with post-infarction septal changes. There was a single subject on GA 40 mg TIW with shift from normal values at baseline to clinically significant values at the last observed measurement. This subject, #583510 developed first degree AV block at time of early discontinuation for hypertensive crisis and hyperthermia. This is the same case that was described in the section on vital sign alterations, subject 301-583510. This 30 year old male was treated with Copaxone 40 mg TIW. He entered the study with a normal ECG at screening and baseline. His enrollment BP was 140/93 and one hour after the study medication it was 160/95. He was begun on antihypertensive medication. Five days into the study he developed a hypertensive crisis after his second injection with the study medication and he developed a bad headache, nausea and BP elevation of 170/100. He was additionally hyperthermic with a temperature of 40 C. His drug was discontinued. An ECG was done at termination and revealed a first degree atrioventricular heart block. He did not come back for further follow-up visit.

GA/9016 FORTE trial
Two subjects on GA 40 mg/day had a change at baseline in QTcF > 60 msec, but which did not reach a level of QTcF > 480. With treatment in the DB phase one subject on GA 20 mg/day and six subjects on GA 40 mg/day had a change from baseline in QTcB greater than 60 msec and none were symptomatic. The ECG changes did not persist in anyone other than a single subject. None of the QTcF exceeded 500 msec.

GA/9006
There were no alterations of potential clinical significance in ECG according to the sponsor for GA 40 mg/day.

Copaxone is not known to have any specific effect on ECG despite the fact that chest pain and palpitations are frequent adverse events after injection as part of IPIR. In order

to explore this further and compare Copaxone 40 mg TIW to the approved product, all AEs were sorted by the SOC of Investigations for a total of 355 AEs, and then sorted by cardiac and vascular investigations for a total of 42 subjects. Of those, there were only two with AE due to abnormal ECG and neither was deemed serious or a cause of discontinuation. One took place on a subject on 20 mg/day in a 19 year old female and the second took place in a 29 year old male on 40 mg/day. None took place on subjects on the GA 40 mg TIW dose. Both episodes resolved. There were also eight subjects that had tachycardia while the ECG was being performed and none had interventions or were thought to be anything other than mild and non-serious. Of those eight, five were on a dose of GA 20 mg/day and three were on a dose of GA 40 mg TIW.

The AE database was then examined again and found to have 12.426 entries. It was then sorted by the SOC Cardiac which had 205 entries. Those entries that could be related to ECG findings are summarized in the table below.

Table 88 Summary of PT related to ECG findings under Cardiac SOC in Pool 1

Preferred Term	GA 20 mg/day N = 630	GA 40 mg/day N = 615	GA 40 mg TIW N = 943	Placebo N = 416	Total
Bradycardia	2	2	3	1	8
Tachycardia	33	37	13	1	84
Palpitations	31	39	11	1	82
PVCs	1	2	0	0	3
SVT	0	1	0	0	1
L Anterior Hemiblock	0	2	0	0	2
1st Degree Heart Block	1	1	1	0	3
Right BBB	0	1	0	0	1
Arrhythmia	0	0	0	1	1
Total	68	85	28	4	185

Reviewer's Comments
Although there were ECG changes noted on Copaxone, they were less on GA 40 mg TIW than on GA 20 mg/day. Events were most frequent on the GA 40 mg/day dose, but this does is not intended for marketing.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Immunogenicity was assessed by the sponsor by measuring anti-GA antibodies as an ancillary part of the GALA study in a subset of 400 subjects. Samples were collected at months 0, 1, 3, 6, 9, 12, 18, and 24. Immunogenicity results for the GA 40 mg/mL TIW were not part of the submission, nor was there a justification for why immunogenicity data was not necessary for approval of this new dose. When questioned, the sponsor stated that these results would be provided in a future submission. This topic was not addressed in the ISE or ISS, but an immunogenicity study report for study GA-9006 was noted to be part of this submission.

Dr. Xinning Yang, Ph.D. evaluated the clinical study report containing the immunogenicity data from Study GA-9006 which showed a signal for the presence of an anti-GA IgE antibody in a small number of patients. The GA 40 mg/day group had less IgE antibodies detected in fewer patients than the GA 20 mg/day group. For the 20 mg group, the IgE antibodies appeared between months 1-6 and then declined toward baseline by month 9. The assay used to measure the IgE antibody was optimized but not validated. IgG antibodies were detected in most of the samples with a similar time-profile for both doses but a slightly higher peak for the GA 40 mg/day dose. Because of the small size of the sample from the GA 9006 study, the lack of validation of the IgE assay, and the lack of data on the GA 40 mg/mL TIW dose, no conclusions could be made about the immunogenicity of the GA 40 mg/mL TIW dose. Since there did not appear to be clinical evidence for a signal of increased hypersensitivity or anaphylaxis in the GALA study, it was felt that immunogenicity data for the GA 40 mg/mL TIW dose was not needed prior to approval.

At the time of this review the sponsor was advised that for the GALA study analysis they would need to develop a validated assay to measure the anti-IgE antibodies. They were also asked to provide the validation report for the IgG assay used to analyze results in study 9006.

7.5 Other Safety Explorations

None

7.5.1 Dose Dependency for Adverse Events

The ISS afforded a good opportunity to compare doses across clinical trials as no single trial compared all the doses. The DB ISS database was composed of 575 years of patient exposure on GA 20 mg/day, 539.6 years of exposure on GA 40 mg/day and 875 years of exposure on GA 40 mg TIW. Discontinuations due to adverse events were 9.3% on GA 40 mg/day, 4.9% on GA 20 mg/day, and 1.2% on GA 40 mg TIW

suggesting that there was a dose response. Specifically IPIR, ISR, lipoatrophy one of the more noxious components of ISR, hypersensitivity reactions, and dyspnea were all greatest on the GA 40 mg/day dose and lowest on the GA 40 mg TIW dose. Although breast cancer was rare and seen in less than 1% of subjects in the ISS, the incidence was also greatest on the GA 40 mg/day dose.

7.5.2 Time Dependency for Adverse Events

This topic was not addressed by the sponsor, presumably because the DB trials reported in this submission ranged between 9 to 12 months not affording much opportunity to investigate time dependency. The OL data is difficult to interpret because it is not controlled and the cohorts are not comparable. Those on Delayed Start GA 40 mg TIW had been on placebo in the first 12 months and those on Delayed Start GA 40 mg/day were not naïve to Copaxone but had been on GA 20 mg/day in the preceding 12 months.

7.5.3 Drug-Demographic Interactions

Comparable to other MS studies, female subjects predominated, with 1566 females and 692 males for a ratio of approximately 2.3:1. There did not appear to be any clinically meaningful male/female differences in AE, although overall female subjects were noted to have slightly more injection site erythema.

A meaningful drug-demographic analysis for race and ethnicity could not be performed as the population was predominantly Caucasian and from Eastern Europe. Because the pivotal GALA trial had few US subjects and mostly Eastern European subjects a limited analysis was performed to get a sense of how Eastern Europeans (EE) compare to the rest of the world (ROW) in the frequency of AE reporting. The sponsor was sent an information request to provide an analysis of all adverse events by country and by region. They responded with a detailed analysis that summarized all AEs, as well as summaries of those resulting in death, withdrawal, SAE reports, AE by severity, AE with sequelae, and AE events thought to be related to treatment.

All countries reported AEs, and in general in Eastern Europe there were less AEs, less SAEs reported, and less discontinuations, but variability was noted between countries. In general AE were reported more frequently in subjects from ROW (89.6% on placebo, 90.9% on drug) than from Eastern Europe (58.4% on placebo, 69.3% on GA). The number of SAEs was greater in ROW (6.3% on placebo, 5% on GA) compared with EE (4.4% on placebo, 4.4% on GA). Drug discontinuations due to AE were greater in ROW (4.2% on placebo, 4.1% on GA) compared with EE (1.0% on placebo, 2.9% on GA). AEs were considered severe in ROW, (10.4% on placebo, 7.4% on GA), in EE, (2.7% on placebo and 3.6% on GA), moderate in ROW, (43.8 % on placebo, 42.1% on GA), in EE (19.4% on placebo, 27.4% on GA), and mild in ROW, (77% on placebo, 82.6% on

GA), and in EE, (50.8% on placebo and 59.7% on GA). It cannot be determine what effect these discrepancies might have on individual AEs. Although subjects in EE underreported their AEs compared with the ROW, this was the case for those on placebo as well as those on drug. There is no evidence to suggest that particular types of AEs were unreported, and in fact, the AE reporting in the studies described in this submission were similar in nature to what had been reported in the original trials described in the label.

7.5.4 Drug-Disease Interactions

Copaxone has not been specifically studied for those with renal impairment. There is no evidence to suggest that any particular group of subjects is at risk of using Copaxone and there are no restrictions to its use with regard to known disease status.

7.5.5 Drug-Drug Interactions

According to the sponsor drug-drug interactions have not been fully evaluated for Copaxone, but the PK profile of Copaxone suggests that interactions are unlikely. The drug, which is injected subcutaneously, is rapidly degraded on site and then is metabolized as amino acids. Earlier in vitro studies found that Iodine^{125}-GA did not significantly affect the binding of carbamazepine or phenytoin to plasma proteins, nor did these drugs affect the binding of Copaxone to human serum proteins.

The label states that GA 20 mg/1mL has not been shown to have any significant interactions with corticosteroids used for up to 28 days in prior clinical studies. In the GALA trial that was part of this supplement, corticosteroids were used concomitantly in 36% of placebo subjects and 24% of GA 40 mg TIW subjects.

Concomitant use of beta interferon has been studied by the sponsor along with Biogen in a joint Industry and NIH supported study, the CombiRx trial[16]. That three year double-blind trial with an OL extension did not show that combined therapy of GA and Interferon caused any new safety issues.

16 Lublin, F., Cofield, S., et. al. Randomized Study Combining Interferon and Glatiramer Acetate in Multiple Sclerosis Annuals of Neurology 2013; 73:327-340.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

According to the drug label Copaxone is not advised in pregnancy unless clinically necessary as there are no adequate or well-controlled studies in pregnant women to determine the effect of GA on the unborn. In addition, information regarding the excretion of GA and its metabolites or antibodies into human milk is also unknown. Animal studies are inadequate to determine the effect on pregnancy, embryonic and fetal development, parturition and postnatal development in humans.

In the studies described here a total of 22 pregnancies took place in Pool 1 and 10 in Pool 2. Of these, a total of 5 were treated with GA 20mg/day, 8 were treated with GA 40 mg/day, 14 were treated with GA 40 mg TIW, and 5 were treated with placebo. Narratives when provided were reviewed. No developmental abnormalities were reported in any of the live births. Table 89 displays pregnancy outcomes. Follow-up information was not available for three women who became pregnant while on study drug.

Table 89 Pregnancy Outcomes in DB and OL phases

Outcomes	GA 20 mg/day N = 5	GA 40 mg/day N = 8	GA 40 mg TIW N = 14	Placebo N = 5
Spontaneous abortion	1	1	1	1
Elective abortion	2	1	5	2
Live birth	2	2	5	1
Live birth C section	*	3	1	1
Unknown	*	1	2	*

7.6.3 Pediatrics and Assessment of Effects on Growth

[redacted] (b) (4) [redacted]. The number of pediatric patients is small and geographically dispersed. The prevalence for pediatric MS, a rare disorder, is estimated to be 0-22 cases per 100,000 in Europe, which corresponds to the 0.05% threshold defined for an orphan indication, which is no more than 50 cases per 100,000.

Previously it was thought that worldwide no more than 250-500 subjects with pediatric MS would be available for a clinical trial within each 2-3 year period of time, and recruitment of sufficient subjects would be a nearly insurmountable goal. In addition, the sponsor commented that PREA allows for extrapolation from adequate and well controlled studies in adults if the disease and the effects of the drug are thought to be sufficiently similar in adults and the pediatric population. Most of the new oral medications for MS when approved, namely, Aubagio, Gilenya, and Tecfidera have been granted a waiver for those ages 0-10 and a deferral for those ages 10 to age 18.

(b) (4). The committee agreed to a waiver for those ages 0-10 and recommended for those ages 10-17 a randomized, well-controlled, parallel group superiority trial to evaluate the safety and efficacy of the product in this age group. A juvenile animal toxicology study in rats to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development was also recommended as this type of study has not been performed in the past.

Reviewer's Comment
Copaxone has been a popular off label choice in the pediatric population. More information about its safety and efficacy in a carefully controlled pediatric study would be desirable.

7.7 Additional Submissions / Safety Issues

Sequence # 0085 April 23, 2013
On April 23, 2013 the sponsor submitted a request for a (b) (4). In addition the Sponsor submitted some additional datasets that were requested that were inadvertently omitted from the original submission. These datasets contained information needed to plan site inspection.

Sequence #0086 May 10, 2013
On May 10, 2013 the sponsor responded to two requests dated May 3 and May 8, 2013 for clarification regarding their databases. The first request from the May 3rd letter was for an explanation of why there did not appear to be a reviewer's guides for the ISS/ISE, but there did appear to be two reviewer's guides labeled MS-GA-301, in addition to one for GA-9006 and one for GA-9016. The two reviewer's guides with the same title appeared to have different content and describe different data. The sponsor was asked to submit modified datasets, if possible, that contained an EPOCH variable for the AE, CM, VS, and LB files for the MS-301-GALA trial and the GA-9016 trial which they did. An additional request was for the addition of a treatment emergent flag for the ADAE and ADLB datasets so that the data could easily be reanalyzed for events on and off therapy and this was also provided. Step-by-step algorithms for all the ISS datasets used to populate the tables in the ISS were provided.

The sponsor next addressed the requests from the May 8th email for an explanation of the various datasets submitted since multiple datasets have the same name and variables names but contain different data. All three individual trials appeared to have three sets of data rather than just an SDTM and ADAM dataset. The sponsor provided an explanation for the naming of the datasets and the cut-off dates for each.

Sequence #0087 June 25, 2013
In response to an Agency request for a Proprietary Name Amendment to change the product name from (b) (4) to GA (b) (4), the sponsor sent in documentation for a name change.

Sequence #0088 June 26, 2013
This submission was in response to a request made by the Agency on May 23, 2013 for several labeling format issues. The sponsor sent in a new draft of labeling.

Sequence #0090 July 17, 2013
This submission provided, as requested, answers to various CMC requests which included the incubation conditions for the biological indicators use for the (b) (4) (b) (4) as well as a description of the type of indicator used. Other questions about the media fill program were answered as well as data to support the adequacy (b) (4) to detect potential microbial contamination and related issues.

Sequence #0091 July 26, 2013
This contained the 4-Month Safety Update.

Sequence #0092 July 30, 2013
This was a response to a request for information regarding an analysis of dropouts due to lack of efficacy for the ISS DB and OL cohorts, an analysis of stratification by country and region, an analysis of chest pain, more narratives for those with embolism and thrombosis, and an explanation of SMQ analysis.

Sequence # 0094 August 7, 2013
This contained the revised carton, blister, and syringe label with the accepted proprietary name, GA.

Sequence # 0095 August 12, 2013
This was a response to a request for information regarding several patient profiles that had transaminase elevations.

Sequence # 0096 August 15, 2013
This contained the artwork for the revised 20 mg/mL product label, box and blister.

Sequence # 0098 September 11, 2013
This was a response to further information regarding a subject with breast cancer and exposure table for the drug in women.

Sequence # 0102 November 7, 2013
This was a response to an information request regarding submitting the DSMB minutes for clinical studies.

8 Postmarket Experience

According to the Company Core Safety Information No 751/01/11/12 dated November 22, 2012 there have been approximately (b) (4) doses of daily GA sold during the monitoring period for a total of (b) (4) patient-years of exposure. The cumulative world-wide exposure to GA is (b) (4) patients-years ending in November, 30, 2012. Clinical trials have enrolled 8524 subjects for a total of 16,779 patient-years of exposure. From the clinical trials there have been a total of 4976 case reports of AE from all the countries where GA is registered; of these 1238 were medically confirmed reports deemed serious AE and non-serious unlisted AE, 745 cases were medically confirmed describing non-serious listed reactions, and the remaining 2993 cases were reported by non-healthcare professionals.

According to the latest PSUR from November, 2012 no new safety issues were identified. The following topics were discussed; thrombocytopenia, cardiotoxicity including myocardial infarction, cardiac arrest, cardiomyopathy, heart failure, and angina pectoris. Additionally pancreatitis, hepatic disorders, pneumonia, breast cancer, leukemia, lymphoma, nervous disorders such as CVA, hypoaethesia/paresthesia, renal disorders, pulmonary embolism/DVT, alopecia and pruritus were discussed. Based on this report no new changes were made to the current Company Core Safety Information.

During the period of monitoring a total of 32 cases of liver function abnormalities were detected and hepatomegaly as well as elevated liver enzyme levels as listed in the Copaxone CCSI with no evidence of clinically significant sequelae. The sponsor also monitored AEs of hepatitis and jaundice and did a separate analysis of non-infectious hepatitis and hepatic failure to look for possible signals.
Preferred Terms included in the analysis:

- drug induced liver injury
- hepatotoxicity
- hepatitis
- hepatic failure
- autoimmune hepatitis
- hepatitis chronic active
- hepatitis toxic

- hepatocellular injury
- hepatic necrosis
- hepatitis acute
- ischemic hepatitis
- acute hepatic failure
- hepatitis alcoholic
- hepatitis fulminant
- liver disorder
- liver injury
- jaundice

During this marketing period there were 22 such cases for a cumulative number of 121 events. This represented a rate of 6.89 per 100,000 patient-years, which did not represent a change for the drug from the past. The sponsor feels that there is no signal based on the past two years' worth of data.

During the last PSUR a total of 32 new cases of breast cancer were received. In Teva's analysis of these cases they found an age adjusted rate of 18.24/100,000 female patient-years which was unchanged from the past two PSURs. Their rates were compared to SEER age-adjusted incidence rates of females below the age of 65 and Teva's current rates were below what would be predicted from the SEER age-adjusted incidence rates.

9 Appendices

9.1 Literature Review/References

Citations are noted within the text with footnotes at the bottom of the relevant pages.

9.2 Labeling Recommendations

The label was not complete at the time of this review. Please see the label for recommendations.

9.3 Advisory Committee Meeting

No advisory committee meeting was scheduled as safety and efficacy of Copaxone 40 mg three times a week was felt to be sufficiently similar to the approved product not to warrant such a meeting.

9.4 Additional Information not Presented in the Body of the Review

Appendix 1 Schedules of the Trials

Schedule of the DB, PC portion of Trial MS- 301

Visit	V-1 Screening	V BL	V1	V2	V3	V4[i]	V5 Termination/ Early discontinuation (PC)	Un-scheduled Visit[a]
Month	**-1**	**0**	**1**	**3**	**6**	**9**	**12**	
Informed Consent	X							
Eligibility Criteria	X	X						
Medical History	X							
MS History	X							
Historical and Concomitant medication	X	X	X	X	X	X	X	X
First Dose at Site		X						
Physical Examination	X	X			X		X	X
Vital Signs[b]	X	X[c]	X	X	X	X	X	X
ECG	X	X					X	X
Chest X-ray[d]	X							X
Safety Laboratory Evaluation (CBC, Chemistry, Urinalysis)	X	X	X	X	X		X	X
Serum βHCG[e]	X	X					X	X
MRI (T1,T2)		X[f]			X		X	
Evaluation of Relapse[g]	X	X	X	X	X	X	X	X
Serum for anti GA antibodies		X	X	X	X	X	X	
Blood for PBL Proliferation (ancillary study)		X	X	X	X		X	
PGx Testing[h]		X						
Neurological examination (EDSS/FS/AI)	X	X		X	X	X	X	X
EuroQoL (EQ5D)		X					X	
WPAI		X		X	X	X	X	
Drug Compliance & Dispensing		X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X

CSR MS-301 page 44 Visits are at months -1, 0, 1, 3, 6, 9, 12 and unscheduled.

Schedule OL Extension Phase Trial MS- 301

Visit	Baseline OL extension Phase[a]	V1E	V2E	V3E	V4E	Every 6 months (in OL extension phase)	Every 12 months (in OL extension phase)	Termination/ET OL extension Phase	Un-scheduled Visit[b]
Month	**12**	**15**	**18**	**21**	**24**				
Informed Consent	X								
Eligibility Criteria	X								
Concomitant medication	X	X	X	X	X	X		X	X
First Dose at Site	X								
Physical Examination	X		X		X	X		X	X
Vital Signs[c]	X[d]	X	X	X	X	X		X	X
ECG	X				X		X	X	X
Safety Laboratory Evaluation (CBC, Chemistry, Urinalysis)	X				X		X	X	X
Serum β–HCG[e]	X				X		X	X	X
Evaluation of Relapse[f]	X	X	X	X	X	X		X	X
Serum for anti GA antibodies	X		X[g]		X				
Neurological examination[i]	X		X		X	X		X	X
Drug Compliance & Dispensing	X	X	X	X	X	X		X[h]	X
Adverse Events	X	X	X	X	X	X		X	X

Protocol MS-301- GALA page 33

Schedule Study 9006

Procedure	Screening	Baseline	Visit Months						Unsched. Visit
Months*	-1	0	1	3	6	7	8	9 /ET	
Informed Consent	X								
Eligibility Criteria	X	X[1]							
Medical History	X								
Historical and Concomitant Medication	X	X[1]	X	X	X	X	X	X	
Physical Examination	X							X	
Vital Signs	X	X[3]	X	X	X	X	X	X	X**
ECG	X	X	X	X	X			X	
Chest X-ray	X								
Neurological Exam & Timed 25-ft. Walk	X	X		X	X			X	X**
Evaluation of relapse	X[1]	X[1]	X	X	X	X	X	X	X**
Laboratory Evaluation	X	X	X	X	X			X	X**
Serum βHCG	X[4]	X[4]							
MRI	X			X		X	X	X***	
Drug Dispensing		X[2]		X	X				X**
Adverse Experiences		X[2]	X	X	X	X	X	X	X**

Protocol Study 9006

Schedule for efficacy and safety measurements Trial 9016 FORTE

Procedure/Visit Number	Screening V -1	Baseline V0	V1	V2	V3	V4	V5	V6 End of DB Phase	V7	V8	V9	Termination V10/(early discontinuation)	Unscheduled Visit[b]
Month*	(up to) -1	0	1	2	3	6	9	12	15	18	21	24	
		Double-Blind Phase							Open Label Phase				
Informed Consent	X												
Eligibility Criteria	X	X											
Past & Current Medical Condition	X												
MS History	X												
Previous/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X			X		X		X		X	X
Chest X-ray[c]	X												
Neurological Examination	X	X			X	X	X	X		X		X	X
Evaluation of Relapse[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory Tests	X	X	X		X	X	X	X		X		X	X
Serum β-hCG[e]	X	X						X				X	X
Serum for anti GA antibodies (ancillary study)		X	X		X	X	X	X		X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
MRI (T_1, T2)		X[f]						X					X
Frequent MRI (sub group)			X	X	X	X	X					X	
Vital Signs[g]	X	X[h]	X	X	X	X	X	X[d]	X	X	X	X	X
Physical Examination	X							X				X	X
First IMP/study drug administration at site		X						X					
MSFC	X[i]	X						X				X	
Pharmacogenetic parameters (ancillary study)		X[j]											
MT/MRS (sub group)		X[k]						X					
IMP/study drug Dispensing & Accountability		X	X	X	X	X	X	X	X	X	X	X[l]	X
Subject Compliance			X	X	X	X	X	X	X	X	X	X	X
Termination Documentation & Notification of Early Termination												X	

CSR Study 9016 , page 45

Appendix 2 Summary of prior studies described in the label

Two trials led to the approval of GA 20 mg/day in 1996. The first trial, study 1, BR-1, was a small study performed at a single clinical center with 50 subjects randomized in a 1:1 fashion on Copaxone or placebo. Subjects with RRMS were examined every three months for two years. The primary outcome measure was the proportion of patients that remained relapse-free at two years. Secondary outcome measures included the change in the EDSS score from baseline, the proportion of progression-free patients and the time to progression. Entrance into the study required at least two exacerbations in the preceding two years, a diagnosis of RRMS, an EDSS of 6 or below. A relapse was defined as lasting at least 48 hours. Other measurements obtained were the frequency of attacks and the change in the number of attacks compared to the 2 years prior to study entry. In this study 7 patients withdrew from the trial over 2 years for a total of 88% of those assigned to Copaxone and 84% of those assigned to placebo remaining in the study. A total of 56% of those treated with Copaxone remained relapse-free at two years whereas 28% of those on placebo remained relapse-free ($p = 0.085$). The mean relapse frequency on Copaxone was 0.6 relapses/2 years, and 2.4 relapses/2years on placebo ($p = 0.005$). A total of 20/25 subjects (80%) were progression-free on Copaxone and 13/25 were progression-free (52%) on placebo ($p = 0.07$) at two years with a relative risk (RR) of having a relapse of 0.25. The statistical model for analysis took into account a regression model with drug and center as factors and 2-year relapse rate and baseline Kurtzke scores as covariates.

The second trial supporting efficacy was study 2, study 01-9001, a multicenter trial done in the US with 251 subjects, also randomized in a 1:1 fashion with similar entrance criteria and similar design to study 1. The primary endpoint was the mean two year relapse rate. There were a total of 251 subjects with RRMS enrolled in a 1:1 ratio of drug to placebo. The primary outcome measure was the mean 2-year relapse rate. Secondary outcome measures included the change in EDSS from baseline, the proportion of progression-free patients, and time to progression.

In study 2, 36 of the patients withdrew from the trial over 2 years for a total of 85% of those assigned to GA and 87% of those assigned to placebo completing treatment at 24 months. The mean number of relapses at 2 years was 1.19 on Copaxone and 1.68 on placebo, for a reduction of 29% on drug ($p = 0.055$) or a RR of 0.71. A total of 34% were relapse-free on Copaxone and 27% were relapse-free on placebo, ($p = 0.25$). Few patients in either arm had confirmed disease progression and 98/125 were progression –free on Copaxone (78%) and 95/126 were progression-free on placebo (75%), ($p = 0.48$).

Based on these two studies Copaxone was given an approval for reduction in the frequency of relapses, but not for the delay of disability progression.

Efficacy Study 1 (BR-1)

	GA (N=25)	Placebo (N=25)	P-Value
% Relapse-Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Prestudy	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

From Copaxone Label

Efficacy Study 2 (01-9001)

	GA (N=125)	Placebo (N=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68 /2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

From Copaxone Label

After drug approval, two further clinical trials mentioned in the label described the MRI endpoints associated with Copaxone and described the effectiveness of the medication in those with an isolated demyelinating episode who had lesions typical of MS on MRI. The 9 month MRI study, study 4, evaluated the median cumulative number of T1 Gd-enhancing lesions based on 9 scans. The score was 11 on GA 20 mg and 17 on placebo for a p value of 0.003. The median cumulative number of T1 Gd-enhancing lesions was reduced by 35%.

In study 3, those with an isolated demyelinating episode were randomized to receive either GA 20 mg/day (n =243) or placebo (n = 238). Patients were followed for up to three years and the primary outcome measure achieved was time to second exacerbation. Disability progression was not assessed. Time to development of a second exacerbation was significantly delayed in patients treated with Copaxone compared to placebo (Hazard Ratio = 0.55). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the Copaxone group.

Based on the studies previously described in the label, Copaxone is indicated to decrease relapses in those with RRMS and those with a first clinical episode and MRI evidence of MS. The prior studies provide grounds to broaden the indication of Copaxone to the relapsing forms of multiple sclerosis similar to the other immunomodulators.

Appendix 3 Clinical Laboratory Tests Performed GALA trial

Serum Biochemistry	Hematology	Urinalysis	β-HCG
Sodium (mmol/L) Potassium (mmol/L) Calcium (mmol/L) Phosphate (mmol/L) Glucose (mmol/L) Blood Urea Nitrogen (mmol/L) Creatinine (umol/L) Alkaline Phosphatase (U/L) Aspartate Transaminase (U/L) Alanine Transaminase (U/L) Bilirubin (umol/L) Protein (kg/m^3) Albumin (kg/m^3)	Leukocytes (GI/L) Neutrophils (GI/L) Neutrophils/Leukocytes (%) Lymphocytes (GI/L) Monocytes/Leukocytes (%) Eosinophils (GI/L) Basophils (GI/L) Neutrophils Segmented/Leukocytes (%) Lymphocytes (%) Monocytes (GI/L) Eosinophils (%) Basophils (%) Hemoglobin (kg/m3) Hematocrit (1) Erythrocytes (TI/L) Platelets (GI/L)	pH Glucose Ketones Erythrocytes Leukocytes Protein	Choriogonadotropin-beta

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Appendix 4 Normal Range of Laboratory findings

Normal range laboratories and Pre-defined PCS Limits used for analysis in study MS-301 GALA and GA 9016

Parameter	Normal Range	Lower Clinically Significant range	Upper Clinically significant range
Hematology			
Leukocytes	3.8-10.8 GI/L	2.,5	21
Neutrophils	1.8-8 GI/L	1.49	*
Lymphocytes	0.85-4.1 GI/L	*	*
Hemoglobin F	120-156 kg/m3	100	185
Hemoglobin M	0.35-5.2 TI/L	115	200
Platelets	130-400 GI/L	100	600
Biochemistry			
Sodium	135-146 mmol/L	130	150
Potassium	3.5-5.3 mmol/L	3	6
Calcium	2.12-2.56 mmol/L	1.87	2.75
Phosphate	0.8-1.45 mmol/L	0.65	1.61
Glucose F ages18-50	3.9-6.4 mmol/L	2.78	13.88
Glucose F ages 50-58	3.9-6.9 mmol/L	2.78	13.88
Glucose M ages 18-50	3.9-6.4 mmol/L	2.78	13.88
Glucose M ages 50-57	3.9-6.9 mmol/L	2.78	13.88
BUN	2.5-9 mmol/L	*	14.3
Creatinine F ages 18-20	42.4-94,6 umol/L	*	133.95
Creatinine F ages 20-30	50.4-91.1 umol/L	*	136.65
Creatinine F ages 30-40	51.3-93.7 umol/L	*	140.55
Creatinine F ages 40-50	52.2-94.6 umol/L	*	141.9
Creatinine F ages 50-58	53-97.2 umol/L	*	
Creatinine M ages 18-20	59.2-111.4 umol/L	*	
Creatinine M ages 20-30	70.7-114.9 umol/L	*	
Creatinine M ages 30-40	69.8-117.6 umol/L	*	
Creatinine M ages 40-50	69-118.5 umol/L	*	
Creatinine M ages 50-57	67.2-129.1	*	186
Creatinine all study 9016	44-124		
Alk. Phosphatase F 18-20	30-165 U/L	*	412.5
Alk. Phosphatase F 20-58	20-125 U/L		312.5
Alk. Phosphatase M 18-20	30-225 U/L		562.5
Alk. Phosphatase M 20-57	20-125 U/L		312.5
ALT/SGPT	0-48 U/L	*	144
AST/SGOT	0-42 U/L	*	126
Bilirubin	0-22 umol/L	*	33
Albumin	32-50 kg/m3	25	*

Source: reference lab values in the patient profiles
*Number not established

Normal range laboratories and Pre-defined PCS Limits used for analysis in GA 9006 study

Parameter	Normal Range	Lower Clinically Significant Range	Upper Clinically Significant Range
Hematology			
Leukocytes	3.8-10.7 GI/L	2.5	21
Neutrophils	1.96-7.23 GI/L	1.49	*
Lymphocytes	0.91-4.28 GI/L	*	*
Hemoglobin F	116-164 kg/m3	100	185
Hemoglobin M	127-181 kg/m3	115	200
Platelets	140-400 GI/L	100	600
Biochemistry			
ALT/SGPT F	6-34 U/L	*	102
ALT/SGPT M	6-43 U/L	*	129
AST/SGOT F	9-34 U/L	*	102
AST/SGOT M	11-36 U/L	*	108
Sodium	132-147 mmol/L	130	150
Potassium	3.4-5.4 mmol/L	3	6
Calcium	2.075-2.65 mmol/L	1.87	2.75
Phosphate	0.7106-1.6473 mmol/L	0.65	1.61
Glucose	3.885-6.3825 mmol/L	2.78	13.88
BUN	1.428-8.568 mmol/L	*	14.3
Creatinine M 26-50	44.2-106.08 umol/L	*	159.12
Creatinine M 51-52	44.2 – 114.92	*	172.38
Creatinine F	35.36-97.24 umol/L	*	145.86
Bilirubin	3.42-20.52 umol/L	*	30.78
Alk. Phosphatase F 23-49	31-106 U/L	*	265
Alk. Phosphatase F 51	35-123 U/L	*	307.5
Alk. Phosphatase M 26-50	31-129 U/L	*	322.5
Alk. Phosphatase M	35-131	*	327.5
Albumin	33-49 kg/m3	25	*

Source: reference lab values in the patient profiles
*Number not established

Mapping of Laboratory Measurement to CTCAE v 4.0 in all three studies

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L	Hgb < 6.5 g/dL; <4.0 mmol/L; < 65 g/L	Death
Blood and lymphatic system disorders	Leukocytosis	-	-	>100,000/mm3	-	Death
Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Investigations	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Investigations	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Investigations	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Investigations	Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Investigations	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Investigations	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Investigations	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L;	>7.0 mmol/L	Death
Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L	Death
Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L		Death
Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L	Death
Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L	Death
Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L;	Death
Renal and urinary disorders	Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-

Post-Text Table 3 p 10 ISS

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/s/

JODY E GREEN
01/27/2014

JOHN R MARLER
01/27/2014

Safety Review

sNDA number	020622 s089
Application holder	Teva
US product trade name(s)	Copaxone
Product established name	Glatiramer acetate
Date of first US approval	1996
US approved indications	Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.
Issue	Breast Cancer
sNDA submission	3/29/13
Medical reviewer and Office/Division	Gerard Boehm, MD, MPH ODE 1/DNP

Background

On 3/29/13, Teva submitted a supplemental NDA (sNDA) for a new formulation of Copaxone. The currently approved Copaxone formulation is a 20mg dose of glatirimer acetate in a prefilled syringe and is administered daily. The sNDA is for a new 40mg dose and is to be administered 3 times a week (TIW) (clinical overview, p.5).

The current Copaxone labeling does not include a Warnings and Precautions statement about breast cancer or any other type of malignancy. Section 13.1 of Copaxone labeling includes the following information:

> In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m^2 basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.
>
> In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in neoplasms was observed.
>
> Glatiramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two

separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

In the pre-submission meeting for the sNDA, the Division asked Teva to include breast cancer as an event of special interest in their presentation of safety data. This request was based on a data mining result that suggested increased reporting for breast cancer in Copaxone patients (EGBM 4.76, EB05 3.86).

In a preliminary evaluation of the data submitted by Teva in the sNDA, Dr. Jody Green considered 7 potential Copaxone breast cancer cases and 1990 total person years to calculate a breast cancer rate of 402/100,000PYs. She compared this rate to SEER background rate for women <65 (82.8/100,000), suggesting an increased breast cancer risk among Copaxone subjects.

The Clinical review team requested that the Safety group review the breast cancer related data in the sNDA submission.

3/29/13 sNDA Submission

Included Trials

This sNDA submission included three trials, MS-GA-301, GA/9006, and GA9016. I provide summaries for those trials below.

MS-GA-301, a Phase III placebo-controlled (PC) double blind (DB) trial, designed to assess the efficacy, safety and tolerability of GA 40 mg/ml administered 3 times a week (GA 40 mg TIW) versus placebo in subjects with RRMS (duration 12 months). The PC phase was completed and the OL phase is ongoing. All subjects who completed the DB phase were provided the opportunity to continue treatment with GA 40 mg TIW regardless of randomization during the PC phase, until the GA 40 mg TIW dose strength is commercially available for the treatment of RRMS, or until the sponsor stops development of this dose regimen.

GA/9006, a completed Phase II double-blind trial conducted in the USA, compared GA 40 mg/day versus GA 20 mg/day (Copaxone®) in subjects with RRMS, for a treatment duration of 9 months.

GA/9016, a completed multinational, multicenter, randomized, Phase III DB trial, compared GA 40 mg/day versus GA 20 mg/day (Copaxone®) administered once daily in subjects with RRMS for a treatment duration of 12 months. This trial was terminated early by the Sponsor during the open-label (OL) extension phase, after analysis of the DB phase did not show GA 40 mg/day to present an efficacy advantage over the marketed dose, GA 20 mg/day. (SCS, p.15).

Exposure

Because breast cancer is a disease primarily experienced by women, I am focusing on female exposure during clinical trials.

For purposes of analysis, Teva pooled safety data from trial GA9006 with safety data collected during the placebo controlled phase of trials GA9016 and MS-GA 301. Teva called this the Double blind phase cohort. In their sNDA, Teva reported exposure data for the Double blind phase cohort, but did not provide such information for females only. FDA requested a table that summarized female exposure in the Double blind phase cohort. I summarize that information below.

Female Exposure, Copaxone sNDA Double Blind Phase Cohort

	Trial GA9006 and GA9016		Trial MS GA 301	
	20mg/day	40mg/day	40mg TIW	Placebo
Number of female subjects	452	444	641	313
Female Person years exposure	410	391	594	298

From Table 2, Submission dated 9/10/13

Teva separately pooled the data from the open label extension of trials GA/9016 and MS GA 301. Teva called this the open label phase cohort. In their sNDA, Teva reported exposure data for the open label phase cohort, but did not provide such information for females only. FDA requested a table that summarized female exposure in the open label phase cohort. I summarize that information below.

Female Exposure, Copaxone sNDA Open Label Phase Cohort

	Trial GA9016		Trial MS GA 301	
	Delayed start 40mg/day	Early start 40mg/day	Delayed start 40mg TIW	Early start 40mg TIW
Number of	371	348	288	559

subjects				
Person years exposure	209	198	192	387

Early start refers to those patients who received GA in the double blind phase prior to OL phase, Delayed start refers to those patients who receive placebo in the double blind phase prior to OL phase

From Table 3, Submission dated 9/10/13

Teva summed exposure by dose and reported that the overall female exposure for these trials was: Placebo 298PY, 20mg/day 410 PY, 40mg/day 797 PY and 40mg TIW 1,175 PY. Therefore, the total female person time exposure to Copaxone was 2,382 PYs.

Breast Cancer Cases

Teva explained that they identified potential cases of breast cancer using the following search terms:

> Breast cancer, breast dysplasia, breast lump removal, malignant breast lump removal, and mastectomy.

In their Summary of Clinical Safety, Teva reported the following regarding breast cancer cases:

Double blind phase cohort
Potential breast cancer AEs were reported in 3 subjects (all in Study GA/9016); 2 subjects (#321406 and #322204) in the GA 20 mg/day group and one subject (#341201) in the GA 40 mg/day group. No AEs of breast cancer were reported in the TIW groups. All AEs were reported as SAEs. Study drug was withdrawn for one subject (#322204) who had AEs of malignant breast removal and mastectomy. The other two were withdrawn from the study per the Sponsor's request to terminate the study. I provide information from Teva's narratives for these events below.

GA-9016- 321406 A 52 year old female treated with Copaxone 20mg/day was diagnosed with left breast cancer and lymph node metastases during the double blind phase of the study. The subject underwent a routine screening mammography on day 47 of the double blind phase, which revealed a 17mm suspected focus in the left breast. A breast sonogram was done the same day, revealing a 14 mm round lesion. A punch biopsy was done on day 54 of the double blind phase under local anesthesia with SC lidocaine 5ml. Pathology report of the biopsy revealed invasive ductal adenocarcinoma of the breast. The subject underwent lumpectomy on day 83 under general anesthesia.

Resection of lymph node metastasis was performed on day 95 of the double blind phase. The subject recovered well from both procedures. Postoperatively, the subject received adjuvant radiation therapy and PO tamoxifen 20mg QD from day 114. Because of the chemotherapy treatment and per sponsor's decision, the subject discontinued the study drug on day 118 of the double blind phase of the study.

GA 9016- 322204This 51 year old female had been treated with Copaxone 20 mg/day when a solid nodule of her right breast discovered by her gynecologist on day 52 of the double-blind period of the study was noted. Wide excision and sentinel lymph node dissection was performed on day 64 (b) (6) of the double blind phase, and pathological report revealed a T1c tumor and extensive ductal carcinoma in situ (DCIS). All sentinel lymph nodes were free of tumor. The tumor was estrogen receptor positive, and HER2 negative. Metastatic work-up including chest x-ray, bone scan and abdominal ultrasound, was negative for metastasis. Because of extensive DCIS in the specimen, the subject underwent a completion mastectomy on day 70 ((b) (6) of the double blind phase with immediate reconstruction by an expander. She discontinued the study drug on day 94 of the double blind phase of the study in relation to the breast cancer. She began chemotherapy courses including cyclophosphamide, epirubicin and 5-flurouracil on day 99 of the double blind phase and is planned for later radiation and antiestrogen therapy.

GA- 9016/341201 This 48 year old female had been treated with Copaxone 40mg/day and was diagnosed with right breast cancer approximately 6 months into the double blind phase of the study. Mammogram and ultrasound suggested the diagnosis. Core biopsy revealed NST grade 2 infiltrating duct carcinoma. The subject was hospitalized and underwent right mastectomy with axillary clearance on day 199 of the double blind phase of the study. On day 258 of the double blind phase of the study the subject commenced chemotherapy courses including IV dexamethasone 4mg QID, IV epirubicin 190mg QD, IV fluorouracil 900mg QD and IV cyclophosphamide 950mg QD, resulting in the sponsor's decision to discontinue the study drug on day 274 of the double blind phase of the study.

Open label phase cohort
Potential breast cancer AEs were reported in 0.4% (2 subjects) in the ES GA 40 mg/day group and 0.2% (2 subjects) in the ES GA 40 mg TIW group.

The AE term for one potential breast cancer event was "breast dysplasia" and Teva included limited information about this case in the sNDA. The Division requested follow up information for this case. Teva reported that this patient underwent a breast biopsy and was diagnosed with benign breast disease and the AE was considered closed. I provide details about the remaining cases below.

GA-9016/102201 This 49 year old female with a history of adenoma of breast (2003) was enrolled into the GA 40 mg arm in the double blind phase of the GA9016 study on 17-APR-2007 and continued to the open label phase with first dose of GA 40 mg on 11-

APR-2008. She did not take oral contraception or other hormonal therapy. The study investigator reported that the subject experienced discomfort and pain in left breast and ultrasound showed masses and a 3.5 cm tumor. On 11-JUL-2008, a needle biopsy was performed and on study day 473 (01-AUG-2008), invasive lobular breast cancer was diagnosed. Of note, one year earlier the subject had a mammogram and ultrasound assessed as negative. Breast cancer diagnosis led to the temporary interruption in the study drug that day (01-AUG-2008) and on 05-AUG-2008 the subject started chemotherapy (protocol unknown). Temporary interruption of the study became a permanent discontinuation and early termination took place on 08-OCT-2008.

GA-301/129703 This 52 year old premenopausal normal weight female nonsmoker with a history including lumpectomy for benign breast neoplasm (1976) and no relevant concomitant medications was enrolled into the GA 40 mg arm in the double blind phase of the GALA study on 15-MAR-2011, and continued to the open label phase with first dose of GA 40 mg on 08-MAR-2012. She did not take oral contraception or other hormonal therapy. Three weeks into the open label (28-MAR-2012), the subject had a mammogram that was reported as abnormal and a needle biopsy was performed on 11-APR-2012. The subject was diagnosed with invasive ductal carcinoma of breast, stage I, grade I (tumor 2 mm, non-aggressive). The AE was assessed as severe. The subject underwent two surgeries (b) (6) Surgical pathology report from (b) (6) reported superior anterior margin negative for malignancy, estrogen and progesterone receptors positive. M1B1 proliferation rate was favorable and Oncotype DX recurrence score was low and chemotherapy was not required. Two weeks after the second surgery, the subject started treatment with tamoxifen and on 18-JUN-2012 she started a six and a half week course of radiation therapy. The study drug was taken as per protocol throughout this episode. The adverse event is under treatment and the subject is continuing in the open label study.

GA-9016/541108 A 49 years old female completed 364 days of the double blind phase of the study. She was diagnosed with left breast ductal carcinoma on day 83 of the open label phase. The subject underwent regular screening mammography on day 81 of the open label phase. Retroareolar fibrosis of the left breast was detected. Breast ultrasound on the same day revealed 12 x 11 mm tumor. A biopsy was taken 2 days later, confirming invasive ductal carcinoma. The subject is planned for surgery on day 95 of the open label phase.

Copaxone sNDA trial breast cancer rate
One of 7 potential breast cancer cases was subsequently diagnosed as benign breast disease and will not be considered in the following rate calculations for breast cancer.

Of the 6 included cases of breast cancer identified by Teva, 3 are from double blind phase cohort and 3 are from open label cohort. The three cases from the DB phase cohort occurred after 47 days (20mg), 52 days (20mg) and 170 days (40mg) of exposure to Copaxone. The three cases from the open label cohort occurred after 378 days (40mgTIW), 450 days (40mg), and 447 days (40mg) of Copaxone.

Considering all breast cancer cases and all exposure, the breast cancer rate in the submitted trials was 251/100,000PY (6/2382PYs).

PSUR (1/30/13)
In the most recent PSUR for Copaxone, Teva provided an analysis of Post Marketing spontaneous reports of breast cancer. I summarize that information below.

For their analysis of breast cancer, Teva included all confirmed cases, regardless of whether the event was considered related or non-related to Copaxone treatment. During the current PSUR period Teva identified 32 new reports of breast cancer. Of these reports one was of unknown sex and will be considered as if it was of female patient. Thus 32 female patients reported breast cancer to provide a cumulative number of 266 reports since the launch of Copaxone. In addition, during the period covered by the PSUR, the data open to the public were issued from the British authority pharmacovigilance databases, included 11 cases of breast cancer attributed to Copaxone which were reported in the past to this local authority. Since Teva routinely receives cases from this authority they assumed that the cases were already reported to Teva and entered into their database. Therefore these 11 reports were not considered as new cases and were not added to the cumulative number. Teva is checking to ensure that all cases are indeed in their data-base.

Teva calculated female person years of exposure using the sex distribution information retrieved from their database, which yielded 83% to 17% female to male ratio. Based on this information, Teva estimated exposure of 1,458,343 female PY and 298,696 male PY. Using the total number of breast cancer reports and the female exposure, Teva calculated an overall breast cancer reporting rate of 18.24 per 100,000 female PY.

Teva compared the reporting rate for breast cancer to the SEER age-adjusted incidence rates of females below and above the age of 65 years. Of the 266 confirmed cases of breast cancer, 228 occurred in females under the age of 65, and 12 occurred in females 65 years or older. The remaining 26 cases occurred in females of unknown age. Since the majority of the breast cancer population in their database is comprised of patients under the age of 65, Teva included these 26 cases in the "<65y" calculation. Those results are shown in the table below, where the Copaxone cohort number of expected events is based on the reference rate and the estimated exposure in females. The standardized incidence ratio is based on the Copaxone observed events compared to the Copaxone expected events

All Copaxone-to-SEER ratios were below 1 with the upper 95% confidence intervals below 1.

Comparison of Copaxone breast cancer reporting rates to SEER Breast Cancer Rates

	Copaxone cohort number of observed events	Reference rate[6] (per 100,000 PY)	Copaxone cohort number of expected events	Standardized Incidence Ratio (SIR) (95% CI)
All ages	266	124.3	1812.7	0.147 (0.130,0.165)
< 65y	254	82.8	1159.2	0.219 (0.193,0.248)
≥ 65y	12	411.3	239.9	0.05 (0.026,0.087)

Based on consistent rates of breast cancer across PSUR periods, and the above comparisons that resulted in reference ratios well below the value of 1, Teva concluded that there is no increased risk of breast cancer in association with the use of Copaxone.

SEER Breast Cancer Data
I reviewed breast cancer data on the SEER website and found it to agree with the data presented by Teva. SEER reports that there are 125 new cases of breast cancer per 100,000 females per year (age adjusted, 1975-2010). In their standard analysis presentation, SEER reported an incidence of 43/100,000/yr for females <50 years old, and 341/100,000/yr for females >50 years old. I was unable to locate the specific age stratified rates (<65, >=65) that Teva presented in their PSUR analyses.

Other recently approved MS treatments
I compared the breast cancer risk in the Copaxone sNDA to that seen with other recently reviewed MS treatments. In the following table, I summarize the breast cancer rates for these MS treatments. The table includes a number of treatments with differing pharmacology, chemical structures, and presumably mechanisms of action. Most of these treatments are considered immunomodulators, except for dalfampridine (potassium channel blocker, approved for improved walking speed).

Breast cancer incidence for recently reviewed MS treatments

Drug	# breast cancer cases	Person years (female)	Rate of breast cancer	95% CI
Copaxone*	6	2382	2.5/1000PYs	1.0, 5.4
Dalfampridine	3	1000	3/1000PYs	0.8, 8.2

PEGylated interferon B-1a	2	1694	1.2/1000PYs	0.2, 3.9
Fingolimod	5	2472	2/1000PYs	0.7, 4.5
Teriflunomide	2	3038	0.7/1000PYs	0.1, 2.2
Dimethy fumarate	3	3022	1/1000PYs	0.3, 2.7

*sNDA data only
Data provided by the Safety Reviewers for these applications, see Appendix to this review

Literature Review
I provide information from published medical literature regarding breast cancer risk in females with MS.

Breast cancer and MS
Among the limited number of published studies of cancer risk with MS, some, but not all, suggest an increased breast cancer risk.

Midgard et al conducted a population based retrospective cohort study in Norway to examine cancer risk in 1271 MS patients. The authors found an increased risk of breast cancer (SIR 1.7, 1.05-2.60) and a decreased incidence of GI related cancers (0.51, 0.24-0.93).[1]

Nielsen et al examined a Danish Cancer registry and a MS registry to assess cancer risk (follow up period 1968-1995). The overall incidence of cancer was not increased, but the authors found a 1.6 fold increased risk of breast cancer in females with MS that persisted after adjustment for age at parity and age at first child delivery. The authors also found that compared to women without MS, women with MS had larger breast tumors at the time of diagnosis[2].

Sun et al found an increased risk of overall cancer (hazard ratio [HR] 1.85, 1.26-2.74) and breast cancer 2.23 (1.11-4.46) in Taiwanese patients with MS.[3]

In a retrospective cohort study that used a population based clinical database, Kingwell et al found no increased risk of breast cancer among females with MS (SIR 0.94, 0.77-1.13).[4]

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[1] Midgard R, Glattre E, Riise T, Edland A, Nyland H. Multiple Sclerosis and cancer in Norway. A retrospective cohort study. Acta Neurol Scand. 1996 Jun;93(6):411-5.

[2] Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M, Hjalgrim H. Cancer risk among patients with Multiple Sclerosis: A population based register study. Int. J. Cancer 2006: 118, 979-984.

[3] Sun LM, Lin CL, Chung CJ, Liang JA, Sung FC, Kao CH. Increased breast cancer risk for patients with multiple sclerosis: a nationwide population-based cohort. Eur J Neurol. 2013 Sep 19 (ePub).

Achiron et al examined cancer incidence and immunomodulatory treatments in MS patients. Their study included a cohort of 1338 MS patients. The authors felt that "female patients treated with glatirimer acetate showed an elevated rate of breast cancer …" but this statement was based on limited data. The cohort included only 4 MS patients diagnosed with breast cancer after initiation of immunomodulatory treatment (number with Copaxone not provided). The reported measure of association was a HR of 3.01 with a 95% CI 0.86-11.1.[5]

Discussion

This memo summarizes the Division's evaluation of whether 6 cases of breast cancer in the Copaxone sNDA represent a safety signal of concern. These clinical trial data are not ideal for assessing cancer risks for several reasons. The relatively small size of the MS clinical trials populations does not allow for robust estimates of relatively infrequent event rates. In addition, these clinical trials were not designed specifically to capture incident malignancies. Investigators were not required to screen to exclude tumors at baseline. In the Copaxone sNDA there were 3 breast cancers that were detected after only 6 months exposure, raising the question about whether these malignancies pre-dated exposure to Copaxone. The MS clinical trials brief exposure times and observation periods limit assessment of malignancy risk for those events which require prolonged exposure and induction periods prior to being able to detect a malignancy. Lastly, when considering available trial data, we are challenged with deciding which cancer incidence rates allow for valid risk comparisons.

In this review I presented comparator data from 2 different sources. The Copaxone sNDA breast cancer rate was higher than the estimate of the breast cancer rate for the general population (SEER data). At the same time, the Copaxone breast cancer rate was similar to the breast cancer rates from the development programs of other recently reviewed MS treatments. Therefore, it becomes important to decide which data yields the most valid comparison.

The use of general population data, in this case SEER data, is appealing, given its availability, but can be associated with difficulties. I believe 2 factors could impact any conclusions based on this comparison. First, there are preliminary data suggesting that breast cancer risk in women with MS may be elevated compared to the general population. Although this has not yet been proven, if true, any comparison of MS treatment program breast cancer rates to background could merely reflect an elevated risk related in the population, rather

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[4] Kingwell, E, Bajdik C, Phillips N, Zhu F, Oger J, Hashimoto S, Tremlett H. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. Brain 2012: 135;2973-2979.

[5] Achiron A, Barak Y, Gail M, Mandel M, Pee D, Ayyagari R, Rotstein Z. Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments. Breast Cancer Research and Treatment 2005; 89;265-270.

than the treatment. Second, it is possible that there are other differences between clinical trial subjects and the general population (frequency of physician visits, other exposures, etc.) that could complicate comparisons to general population data.

Recent MS clinical trial data, suggests that the breast cancer risk in the Copaxone sNDA is similar to the risk observed in other development programs. While I acknowledge the difficulty in making risk comparisons across development programs, this approach does address a concern regarding the use of general population data for comparison. All of the women in these trials have MS, eliminating any concerns about the potential effect of underlying disease on breast cancer risk. In addition, one could assume that clinical trial subjects may be more alike to each other, in terms of overall experiences and exposures compared to the general population. In addition, if one is concerned that the results represent a situation where all drugs equally increase risk breast cancer risk, the inclusion of several different drugs, with different characteristics, would seem to suggest a “class effect” is unlikely.

For these reasons, I believe that comparison of breast cancer rates with Copaxone to the rates in other MS treatment development programs are the most appropriate. Based on these comparisons, Copaxone appears to have a similar breast cancer rate as other MS treatments. Admittedly, these data are incapable of proving that Copaxone does not increase breast cancer risk. The MS clinical trial data do not provide any information regarding longer exposures (years to decades) and are unable to address effects manifesting at a time many years following exposure. The data do provide some comfort in that for similar exposure and observation periods, the observed risk with Copaxone is comparable to the risk with other recently reviewed MS treatments.

Recommendations
I do not recommend any regulatory action based on the data in this review.

Note: I presented these findings to the clinical review team during a 11/19/13 meeting.

Appendix
Calculation of breast cancer incidences in MS development programs

Dalfampridine
Through the 120 day safety update, among females in the integrated MS safety database, there were 3 (3/596) breast cancers reported (all SAEs). The dalfampridine SU submission (6/22/09) documented that the average exposure duration was 87.3 weeks. I used this data to estimate that there was 1000PY exposure in female MS patients. 3/1000PY

Dimethyl fumarate
In the dimethyl fumarate NDA (204063), in the MS controlled trials, 2 PBO female patients (2/594) had breast cancer compared to none in the BG12 BID group (0/538), 1 in the BG12 TID group (1/601) and none in the GA group (0/246). In the integrated MS controlled and uncontrolled trials studies, there were a total of 3 breast cancer diagnoses among 1764 dimethy fumarate treated females. The SU reported that for all 2513 were exposed for 4306 years, yielding an average exposure of 1.7 years. I multiplied the average exposure times the number of females to arrive at an exposure estimate of 3022PYs.

PEGylated interferon beta-1a
In the PEGylated interferon beta 1-a BLA (125499) through the 120 day safety update, there were 2 breast cancer cases. The total exposure was 2386PYs and 71% of study subjects were female, yielding a female exposure time of 1694PYs. This yields a breast cancer rate in females of 1.2/1000PYs (2/1694).

Fingolimod
The fingolimod data were provided by Dr. Villalba. In the fingolimod NDA, there were 5 breast cancer cases in 2427 female PYs. This yields a breast cancer rate of 2/1000PYs.

Teriflunomide
The teriflunomide data were provided by Dr. Mentari. She contacted Sanofi for the breast cancer cases and female exposure. In the teriflunamide NDA, through the 120 day safety update, there were 2 breast cancer cases in 3038 female PYs. This yields a breast cancer rate of 0.7/1000PYs.

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/s/

GERARD A BOEHM
11/22/2013

SALLY U YASUDA
11/22/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DATE: January 8, 2014

TO: NDA 20-622/S-089

THROUGH: Martha R. Heimann, Ph.D., CMC Lead, ONDQA/DNDQA-1

FROM: Kavita A. Vyas, Ph.D., CMC Reviewer, ONDQA/DNDQA-1

SUBJECT: Addendum to CMC Review Dated 12/20/2013

Only the Environmental Assessment Section for the above supplement is covered here.

Environmental Assessment:

The applicant claimed a categorical exclusion from performing an environmental assessment in accordance with 21 CFR 25.31(c). In accordance with 21 CFR 25.15(d), to the best of the applicant's knowledge, no extraordinary circumstances exist.

The applicant's categorical exclusion statement is **Acceptable.**

All other CMC issues were resolved in Review 1 dated 12/20/2013.

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/s/

KAVITA A VYAS
01/08/2014

MARTHA R HEIMANN
01/08/2014

Chemistry Review: # 1	**Division:** **DNP**	**NDA Number: 20-622**
Name and Address of Applicant: Teva Pharmaceuticals USA 425 Priver Road, PO Box 1005 Horsham, PA 19044	**4. Supplement(s): S** **Number:** 089 **Date(s): Letter Date: 3/29/2013**	
5. Name of Drug: Copaxone ®	**6. Nonproprietary name: Glatiramer acetate**	
7. Supplement Provides for: Efficacy supplement to add new strength 40 mg/mL and dosing regimen for DP.		**8. Amendment(s):** 12/18/13
9. Pharmacological Category:	**10. How Dispensed:** R_x	**11. Related Documents:** (b) (4)
12. Dosage Form: INJECTABLE	**13. Potency:** 40 mg/mL	

14. Chemical Name and Structure: Acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with avg molar fraction 0.141, 0.427, 0.095, and 0.338, respectively. Avg MW: 5,000 – 9,000 daltons. Structural formula: (Glu, Ala, Lys, Tyr)*x*●*x*CH3COOH
(C5H9NO4●C3H7NO2●C6H14N2O2●C9H11NO3n (b) (4)● (b) (4)C2H4O2
CAS - 147245-92-9

15. Comments: This efficacy supplement proposes the same indication and patient population, but different dosing strength and treatment regime (Approved: 20 mg/mL, daily. Proposed: 40 mg/mL, three times a week). No changes are proposed in DS, excipients, CCS (PFS). The manufacturing process for Drug Product (DP) (40 mg/mL) is similar to that for approved strength except for differences in (b) (4) (b) (4) (b) (4) (v) Container label, carton and PI labeling to include the proposed strength and dosing regimen.

In support, the applicant provided (i) Pharmaceutical development data. (ii) Details of manufacturing Process, IPC, facilities, and Process Validation data. (iii) Batch Analyses and stability data for 9 batches made using the proposed process. (iv) Executed Batch Records.

The clinical trials to support the proposed strength were performed using the approved process (b) (4) and primary registration stability studies were conducted using the proposed process (b) (4) The data provided indicate consistency in quality (based on comparability of the release specifications) in batches produced by the approved and proposed processes, and those used in clinical trials and registration stability studies. Batch data indicate that all batches remain within specifications at release for all the measured parameters, and that they resemble approved product (based on release specifications).

(b) (4) (b) (4) An IR was sent (12/13/13 by

Nicole Bradley) recommending that the applicant harmonize the DP specifications both strengths with those currently approved for the 20 mg/mL strength. The applicant revised the DP release and stability specifications for 40 mg/mL strength to match those approved for the 20 mg/mL strength (amendment dated 12/18/13).

Proposed shelf life and storage temperature for 40 mg/mL strength are the same as for 20 mg/mL: 24 months, at 5±3ºC is supported by data provided and is acceptable. No CMC issues are pending.

Microbiology reviewer recommends approval from a Microbiology point of view. DMEPA reviewer concluded that carton and container labels are acceptable (see review by Jacqueline Sheppard dated 12/10/13). The OC gave an overall Acceptable recommendation for the proposed site based on district recommendation on 12/18/13. All CMC issues are resolved.

16. Conclusion: Recommend Approval for NDA 20-622 S-089 from a CMC point of view.

17. Name: **Signature:** **Date: 11/15/13**
Kavita A. Vyas, Ph.D., Chemist

18. Concurrence: **Signature:** **Date:**
Hasmukh B. Patel, Ph.D., Branch Chief, Div., VI, ONDQA

Chemistry Review Notes:

I. Proposed Changes and Regulatory History:

NDA 20-622 was approved in 1996 for slowing progression of disability and reducing frequency of relapses in patients with multiple sclerosis who have experienced a 1st clinical episode and have MRI features with Multiple Sclerosis.

This efficacy supplement proposes the same indication and patient population, but different dosing strength and treatment regime.

- Approved: 20 mg/mL, subcutaneous, **daily.**
- **Proposed: 40 mg/mL,** subcutaneous, **three times a week.**

In addition:

- **No changes are proposed in DS** (the applicant refers to approved NDA).
- **No change in the excipient** (mannitol, WFI; or amounts (same as for approved strength).
- **No change in the Container Closure System** (Prefilled syringes).
- **Comparability protocol is proposed for changes in receiving vessels.**
- **Manufacturing process for Drug Product (DP) (40 mg/mL) mirrors that for the approved strength**, with the following minor differences (b) (4) (b) (4)
- **Container labels, Carton labeling** for DP 40 mg/mL, and **modified PI labeling to include the proposed strength and dosing regimen.**

Although not specified in the cover letter (or QOS), the following are changed.

(b) (4)

- Clinical trials to support the proposed strength were performed using the approved process (b) (4) and primary registration stability studies were conducted using the proposed process (b) (4) data indicating the equivalence quality/stability for batches made using the approved and proposed processes are provided.

II. Supporting Data:

In support, the applicant provided the following data.

1. **Pharmaceutical development**.
2. **Details of the manufacturing Process, IPC, and facilities, and Process Validation data.**
3. **Details of the Method Validation** (all DP methods are validated for the proposed strength).
4. **Batch Analyses data.**
5. **Stability data**
6. **Executed Batch Records (both sites, Kfar Saba and Runcom).**

III. Issues Identified and their Impact on the Proposed Changes:

1. (b) (4)
2.

An IR letter was sent to the applicant (by Nicole Bradley, dated 12/13/13) stating: (b) (4) (b) (4) We recommend that you harmonize your proposed Drug Product specifications for the 40 mg/mL strength to be consistent with those currently approved for the 20 mg/mL strength. Provide updated specification table as an amendment to your application".

The applicant responded on 12/18/13 by harmonizing the proposed DP specifications (release and stability. See Supplementary Materials sections)**.** In this amendment, the applicant also provided:

- Revised DP release and stability specifications, harmonized for both strengths.
- Details and validation data for the (b) (4)
- Revised Justification of Specifications.
- Data for 9 Clinical trial batches, tested for (b) (4). All batches meet acceptance criteria.
- (b) (4)

All CMC issues related to the proposed 40 mg/mL strength are resolved.

IV. The following information was reviewed.

3.P. DRUG PRODUCT

3.2.P.2.1. Description and Composition of the Drug Product

The proposed formulation is based on that approved. The only difference is that DS is present at double the concentration (see Tables below).

Table 1: Quantitative Composition of GA Injection 40 mg/ mL

Raw Material	Quantity per Dosage Unit	Unit	Function	Reference to Standard
Active Ingredient				
Glatiramer Acetate (GA)	40.0[1]	mg	Active	In-house specification
Other Ingredients				
Mannitol	40.0	mg	(b) (4)	
Water for Injection(s)	q. s. to 1.0[2]	mL		

(b) (4)

Table 5: Composition of the Approved and Proposed Drug Product

Components	Content per mL	
	Commercial Copaxone® Injection 20 mg/mL	GA Injection 40 mg/mL
Glatiramer Acetate[1]	20.0 mg	40.0 mg
Mannitol USP/Ph.Eur.	40.0 mg	40.0 mg
Water for Injection USP/Ph.Eur/JP	q.s. to 1.0 mL	q.s. to 1.0 mL

[1] Calculated on the dry basis and 100% assay

Reviewer's Evaluation. Adequate.

3.2.P.2.2. Pharmaceutical Development

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 20622/089	**Sponsor:**	TEVA PHARMS USA
Org. Code:	120		400 CHESTNUT RIDGE RD
Priority:	1S		WOODCLIFF LAKE, NJ 07677
Stamp Date:	29-MAR-2013	**Brand Name:**	COPAXONE
PDUFA Date:	29-JAN-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	GLATIRAMER ACETATE
District Goal:	25-DEC-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		002; SOLUTION, INJECTION; GLATIRAMER ACETATE; (b) (4) 001; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED, WITH ADDITIVES; GLATIRAMER ACETATE; 20MG/1VIL	

FDA Contacts:	K. VYAS	Prod Qual Reviewer		3017964787
	T. BOUIE	Product Quality PM		3017961649
	N. BRADLEY	Regulatory Project Mgr	(HFD-120)	3017961930
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	ACCEPTABLE	on 18-DEC-2013	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 13-AUG-2013	by EES_PROD		

Establishment:	**CFN:** 9610275	**FEI:** 3002721084	
	TEVA PHARMACEUTICAL INDUSTRIES, LTD. 18 ELI HURVITZ ST, IND. ZONE KFAR SABA, , ISRAEL 44102		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** 3003925187	
	TEVA RUNCORN (IVAX) ASTON LANE NORTH, WHITEHOUSE CHESHIRE, , UNITED KINGDOM		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

VII. List Of Deficiencies To Be Communicated: NONE

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/s/

KAVITA A VYAS
12/20/2013

NALLAPERUM CHIDAMBARAM
12/20/2013
for Dr. Hasmukh Patel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 20622
Supplement #:	089
Drug Name:	Copaxone® (glatiramer acetate)
Indication(s):	Multiple Sclerosis
Applicant:	TEVA Neuroscience
Date(s):	Submission Date: March 29, 2013
	PDUFA Due Date: January 29, 2014
Review Priority:	Standard Review
Biometrics Division:	Division I
Statistical Reviewer:	Sharon Yan
Concurring Reviewers:	Kun Jin, Team Leader
	James Hung, Division Director
Medical Division:	Division of Neurology Products
Clinical Team:	Jody Green, Clinical Reviewer
	Evelyn Mentari, Safety Reviewer
	Billy Dunn, Acting Deputy Director
	Eric Bastings, Acting Division Director
Project Manager:	Nicole Bradley

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

This sNDA is for an additional dosing strength and regimen (glatiramer acetate, 40 mg/1ml, TIW sc) to the currently marketed Copaxone® (glatiramer acetate, 20 mg/1ml, daily, sc) to provide a therapeutic option for subjects with RRMS.

The proposed dosing strength and regimen is supported by data from clinical trial MS-GA-301 (Study GALA), a 12-month, randomized, double-blind, placebo-controlled study. Statistically significant treatment difference has been achieved for the primary endpoint, annualized relapse rate (ARR), showing benefit of treatment with 40 mg TIW over placebo.

2 INTRODUCTION

2.1 Overview

Copaxone® (glatiramer acetate, GA) is an immunomodulator indicated for reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis (RRMS). The currently marketed dose of Copaxone is 20 mg/mL solution for injection administered subcutaneously daily. This supplemental New Drug Application (sNDA) provides a new dosing strength and regimen for GA: 40 mg/mL administered three times a week (TIW).

One randomized, double-blind, placebo-controlled, parallel-group clinical trial MS-GA-301 was conducted in subjects with RRMS to assess the efficacy, safety and tolerability of GA 40 mg sc administered TIW compared to placebo. The primary efficacy endpoint is the total number of confirmed relapses observed during the 12-month double-blind placebo-controlled treatment period. Table 1 presents a summary of Study MS-GA-301.

Table 1 List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
GA 301 (GALA)	Phase 3, randomized, double-blind, placebo-controlled	12 months	Variable	Placebo: 461 GA 40 mg: 943	Patients with RRMS

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents and datasets of this NDA is listed below:

\\Cdsesub1\evsprod\NDA020622\0083

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submission was complete. The analysis of the primary endpoint is based on relapse data. Relapse data are considered original with no derivation. There is no reason to believe that relapse data were not accurately transcribed from the case report form (CRF). No data quality issues have been identified.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study GA-301 was a multinational, multicenter, randomized, double-blind, parallel-group study performed in subjects with RRMS to assess the efficacy, safety and tolerability of GA 40 mg sc administered TIW compared to placebo.

The study consisted of 3 phases: a screening phase of up to 1 month, a placebo-controlled (PC) phase of 12 months, and an open-label extension phase.

Approximately 1350 subjects were planned to be randomized in a 2:1 ratio to receive sc treatment with either GA 40 mg TIW (900 subjects) or placebo (450 subjects). In total, 1404 subjects were randomized at 155 sites over 17 countries. Among them, 86 subjects were randomized in US sites.

Subjects were evaluated at study sites for a total of 7 scheduled visits at screening, baseline, and at months 1, 3, 6, 9, and 12 (end of PC phase). MRI scans were performed at months 0, 6, and 12 (termination/early discontinuation).

The study enrolled patients who were 18 to 55 years in age, diagnosed of MS based on updated McDonald criteria, had at least one documented T1 Gd-enhancing lesion in an MRI performed within 12 months prior to screening, had EDSS score of 0.0 to 5, and had $\geq$ 2 MS attacks occurring in the prior 24 months and $\geq$ 1 MS attack in the prior 12 months.

The primary efficacy endpoint was the total number of confirmed relapses observed during the 12-month double-blind PC treatment period.

Secondary endpoints were rank ordered as follows:

1. The cumulative number of new/enlarging T2 lesions taken at Month 6 and Month 12
2. The cumulative number of enhancing lesions on T1-weighted images taken at Months 6 and 12

3. Brain atrophy as defined by the percentage brain volume change from baseline to Month 12

3.2.2 Statistical Methodologies

The ITT population, consisted of all subjects who were randomized, was to be used as the primary patient population in efficacy analyses.

The principal analysis for the number of confirmed relapses was to be based on a Negative Binomial Regression model with an "offset" based on the log of subject's exposure to treatment. The factors and covariates included in the model were treatment, geographic region, baseline EDSS score, log of prior 2-year relapse number, T2 lesion volume at baseline, and status of T1 Gd-enhancing activity at baseline.

For secondary endpoints, hierarchical approach based on the given rank order (Section 3.2.1) was to be used to control for multiplicity.

The analysis for the accumulated number of new/enlarging T2 lesions and the cumulative number of T1 Gd-enhancing lesions was to be based on a Negative Binomial Regression with an "offset" employing the log of the proportion of the number of the available post-baseline scans to adjust for missing MRI scans (if any). The model was to include covariates of the number of enhancing lesions on T1-weighted images at baseline and country or geographic region (CGR).

The analysis of brain atrophy, as defined by the percentage change in normalized brain volume from baseline to Month 12, was to be based on a baseline-adjusted ANCOVA. SIENAX normalized brain volume at baseline, the number of enhancing lesions on T1-weighted images at baseline and CGR were to be included in the model.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 1404 subjects were randomized: 461 subjects in the placebo group and 943 subjects in the GA 40 mg TIW group. Among those subjects, 31 (6.7%) subjects in the placebo group and 84 subjects (8.9%) in the GA 40 mg TIW group discontinued the study (Table 2). The most common single reason for early discontinuation was withdrawal of consent. The following table presents the distribution of subject treatment discontinuation.

Table 2 Distribution of Reasons for Subject Treatment Discontinuation during (Source: Table 7 of Clinical Study Report)

GALA (MS-GA-301)	Placebo (N=461)		GA 40 mg (N=943)		All (N=1404)	
	N	%	N	%	N	%
Total Number of Randomized Subjects	461	100.0	943	100.0	1404	100.0
Total Number of Subjects Completed PC phase	430	93.28	859	91.09	1289	91.81
Total Number of Treatment Discontinuation	31	6.72	84	8.91	115	8.19
Death	1	0.22	.	.	1	0.07
Adverse Event	6	1.30	29	3.08	35	2.49
Subject Withdrew Consent	17	3.69	34	3.61	51	3.63
Request of Primary Care Physician or Investigator	1	0.22	1	0.11	2	0.14
Non-Compliance with Study Drug	.	.	2	0.21	2	0.14
Protocol Violation	.	.	2	0.21	2	0.14
Pregnancy	4	0.87	7	0.74	11	0.78
Failed to Return / lost to follow-up	1	0.22	5	0.53	6	0.43
Refused to Re-Sign Informed Consent after Relapse	1	0.22	4	0.42	5	0.36

The treatment groups were comparable with respect to sex, race, and age. Overall, the majority of subjects were female (67.9%), with a mean age of 37.6 years. Almost all patients (97.6%) were Caucasian.

Baseline MS characteristics are summarized in Table 3. Treatment groups were comparable in baseline MS characteristics.

Table 3 Distribution of Baseline MS Characteristics (ITT population) (Source: Table 9 of Clinical Study Report)

GALA (MS-GA-301)		Placebo (N=461)	GA 40 mg TIW (N=943)	All (N=1404)
Time from first Symptom (Years)				
	Mean (SD)	7.6 (6.4)	7.7 (6.7)	7.7 (6.6)
	Median	6.1	5.7	5.9
	Min, Max	0.4, 31.0	0.3, 38.8	0.3, 38.8
Time from Diagnosis (Years)				
	Mean (SD)	3.9 (4.7)	3.7 (5.0)	3.8 (4.9)
	Median	1.8	1.4	1.5
	Min, Max	0.0, 26.7	0.0, 38.8	0, 38.8
Time from Onset of Last Relapse (Years)				
	Mean (SD)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
	Median	0.4	0.4	0.4
	Min, Max	0.1, 2.2	0.1, 2.1	0.1, 2.2
No. of Relapses in the Last Year				
	Mean (SD)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
	Median	1.0	1.0	1.0
	Min, Max	0.0, 4.0	0.0, 6.0	0.0, 6.0
No. of Relapses in the Last 2 Years				
	Mean (SD)	1.9 (0.9)	1.9 (0.9)	1.9 (0.9)
	Median	2.0	2.0	2.0
	Min, Max	1.0, 6.0	1.0, 11.0	1.0, 11.0
Baseline EDSS score				
	Mean (SD)	2.7 (1.2)	2.8 (1.2)	NA
	Median	2.5	2.5	NA
	Min, Max	0.0, 5.5	0.0, 5.5	NA

Baseline MRI parameters are presented in Table 4. Baseline characteristics of MRI parameters were generally similar between the two groups.

Table 4 Distribution of Baseline MRI Parameters (ITT Population) (Source: Table 10 of Clinical Study Report)

GALA (MS-GA-301)		Placebo (N=461)	GA 40 mg TIW (N=943)	All (N=1404)
Number of T_1 GdE Lesions at BL	Mean (SD)	1.4 (3.7)	1.7 (4.7)	1.6 (4.4)
Proportion of Subjects with No T_1 GdE Lesions at BL	N (%)	307 (66.6)	607 (64.4)	914 (65.1)
Proportion of Subjects with One T_1 GdE Lesion at BL	N (%)	53 (11.5)	126 (13.4)	179 (12.7)
Proportion of Subjects with Two T_1 GdE Lesions at BL	N (%)	29 (6.3)	52 (5.5)	81 (5.8)
Volume T_1 GdE Lesions (mL) at BL	Mean (SD)	0.1 (0.5)	0.2 (0.8)	0.2 (0.7)
Number of T_2 Lesions at BL	Mean (SD)	36.7 (26.7)	38.0 (26.3)	37.5 (26.5)
Volume T_2 Lesion (mL) at BL	Mean	17.4 (17.4)	19.7 (20.7)	19.0 (19.7)
Number of T_1 Hypointense Lesions at BL	Mean (SD)	20.4 (18.1)	23.7 (21.9)	22.6 (20.7)
Volume T_1 Hypointense Lesions (mL) at BL	Mean (SD)	4.7 (6.6)	5.3 (7.7)	5.1 (7.3)

3.2.4 Results and Conclusions

The results presented in this section mostly represent the ones reported by the sponsor and confirmed by the reviewer. Additional analyses performed by the reviewer are also presented.

3.2.4.1 Analysis of the Primary Efficacy Endpoint – Relapse Rate

Among the 943 patients treated with GA 40 mg, 726 (77.0%) patients were free of relapse by the end of the study compared to 302 of the 461 (65.5%) patients treated with placebo. Descriptive statistics of relapse data are presented in the following table.

Table 5 Descriptive Statistics of Relapse Data by Treatment Group (reviewer's analysis)

	Placebo N=461	GA 40 mg N=943
N (%) free of confirmed relapse **Total number of confirmed relapse**	302 (65.5%) 212	726 (77.0%) 283
N (%) free of all relapses **Total number of confirmed & unconfirmed relapses**	294 (63.8%) 227	702 (74.4%) 318

The adjusted ARR from the primary negative binomial model was 0.331 for GA 40 mg group and 0.505 for the placebo group, representing a risk ratio of 0.656 (p<.0001) to have a confirmed relapse for patients treated with GA 40 mg versus the patients treated with placebo (Table 6).

Pre-defined supportive analyses of the primary endpoint were carried out by applying alternative statistical models to the ITT, completers (CO), and evaluable (EV) analysis population. The results appeared to be robust and consistent. When covariates are removed from the negative binomial model, the estimates of ARR are slightly lower for both treatment groups, but the p-values remains to be 0.0001. The lower ARR is likely due to the regional difference, which is discussed in more detail in 4.1. Table 5 presents a summary of analyses of relapse rate.

Table 6 Summary of Analyses of Relapse (Source: Table 11 of Clinical Study Report)

Analysis Population	Analysis Model	Covariates	Adjusted Mean Estimates	Treatment effect GA 40 mg vs. Placebo [95% CI]	P-value
Principal Analysis					
ITT	Total No. of Confirmed Relapses: Negative Binomial Regression (Principal Model)	1) EDSS at BL 2) Status of GdE T_1 activity at BL 3) Volume T_2 lesions at BL 4) Log of prior 2-year number of relapses 5) CGR	GA 40 mg TIW=0.331 Placebo=0.505	Risk Ratio: 0.656 [0.539; 0.799]	<0.0001
Robustness Analyses					
ITT	Total No. of Confirmed Relapses: Negative Binomial Regression (Unadjusted)	Treatment only	GA 40 mg TIW=0.322 Placebo=0.482	Risk Ratio: 0.669 [0.546; 0.821]	0.0001
	Total No. of Confirmed Relapses: Quasi-Likelihood (Over-Dispersed) Poisson Regression	1) EDSS at BL 2) Status of GdE T_1 activity at BL 3) Volume T_2 lesions at BL 4) Log of prior 2-year number of relapses 5) CGR	GA 40 mg TIW=0.327 Placebo=0.497	Risk Ratio: 0.657 [0.553; 0.780]	<0.0001
	Individual Annualized Relapse Rate: ANCOVA	1) EDSS at BL 2) Status of GdE T_1 activity at BL 3) Volume T_2 lesions at BL 4) Log of prior 2-year number of relapses 5) CGR	GA 40 mg TIW=0.469 Placebo=0.635	Adjusted Mean Difference: -0.166 [-0.262; -0.070]	0.0007
	Individual Annualized Relapse Rate: Wilcoxon's test	NA	NA	NA	<0.0001

Cross Reference: Tables 15.7.1.1.2-15.7.1.1.4; Tables 15.7.1.4.2 and 15.7.1.4.3.
Abbreviations: TIW, three times/week; BL, baseline; EDSS, Expanded Disability Status Scale; CGR, country/geographical region; Gd, gadolinium; ANCOVA, analysis of covariance; CI, confidence interval.

Analyses of other relapse related endpoints, such as time to first confirmed relapse by Cox model (hazard ratio=0.603; p<.0001) and percentage of relapse-free patients by logistic regression (p<.0001), further confirmed results of the primary analysis.

A total of 73 patients (51 in 40 mg GA group and 22 in placebo group) had at least one relapse not confirmed. The estimated annualized relapse rate for all relapses (confirmed and unconfirmed) was 0.592 for the placebo group and 0.406 for the GA 40 mg TIW group, with risk ratio of 0.685 (p<.0001) for having a relapse for GA 40 mg-treated patients versus placebo-treated patients.

3.2.4.2 Analysis of Secondary Efficacy Endpoints

The Cumulative Number of New/Enlarging T2 Lesions taken at Month 6 and Month 12.

The number of new/enlarging T2 lesions decreased from Month 6 to Month 12 for both treatment groups. The cumulative number of new/enlarging T2 lesions at Month 12 was significantly lower in the GA 40 mg group than in the placebo group. The adjusted mean was 3.65 for the GA 40 mg group and 5.59 for the placebo group, representing a risk ratio of 0.653 (p<.0001) for having a new/enlarging T2 lesions for GA 40 mg-treated patients compared to placebo-treated patients. Table 6 presents the results from analysis of new/enlarging T2 lesions at Months 6 and 12.

Table 7 Number of New/Enlarging T2 Lesions taken at Month 6 and Month 12 (reviewer's analysis)

	Placebo N=461	GA 40 mg N=943
Month 6		
N	440	883
Mean (SD)	3.50 (6.09)	2.98 (6.00)
Median	1.0	1.0
Month 12		
N	426	855
Mean (SD)	2.78 (4.82)	1.75 (4.32)
Median	1.0	0.0
Cumulative Number		
N	441	884
Mean (SD)	6.18 (9.31)	4.67 (9.37)
Median	3.0	2.0
Adjusted mean	5.59	3.65
Risk ratio		0.653
p-value		<.0001

The Cumulative Number of Enhancing Lesions on T1-Weighted Images Taken at Month 6 and Month 12

The cumulative mean number of Gd-enhancing lesions on T1-weighted images at Months 6 and 12 was lower in the GA 40 mg TIW group (0.91) compared to the placebo group (1.64) (p<.0001). The GA 40 mg TIW group had larger decrease in the T1 lesion number at both Month 6 and Month 12 than the placebo group (Table 7).

Table 8 Change from baseline in the number of Gd-enhancing T1 lesions (reviewer's analysis)

	Placebo N=461	GA 40 mg N=943
Month 6		
N	440	883
Mean (SD)	1.24 (3.17)	0.91 (2.73)
Median	0.0	0.0
Mean change from baseline	-0.20	-0.84
Month 12		
N	426	855
Mean (SD)	1.01 (2.63)	0.60 (2.21)
Median	0.0	0.0
Mean change from baseline	-0.38	-1.14
Cumulative Number		
N	441	884
Mean (SD)	2.22 (4.84)	1.49 (4.41)
Median	0.0	0.0
Adjusted mean	1.64	0.91
Risk ratio		0.552
p-value		<.0001

Brain Atrophy - Percent Brain Volume Change from Baseline to Month 12

More patients had available data in brain atrophy than what were included in the sponsor's analysis, resulting a slightly different analysis result of brain atrophy between the one obtained by the reviewer and the one reported by the sponsor. The difference is minimal and would have no impact on the interpretation or conclusion of the results.

At the end of the study, the adjusted mean percent change in brain volume was -0.63 in the placebo group and -0.70 in the GA 40 mg TIW group. Results did not demonstrate a statistically significant treatment effect of GA 40 mg TIW over placebo at Month 12 (p=.1852; Table 8).

Table 9 Brain Atrophy defined as percentage brain volume change from baseline to Month 12 (reviewer's analysis)

	Placebo N=461	GA 40 mg N=943
N	435	870
Baseline Mean (SD)	1538 (111)	1535 (110)
Mean % change from baseline	-0.62 (.89)	-0.71 (.89)
Adjusted mean change	-0.63	-0.70
p-value		.1852

3.2.4.3 Analysis of Other Efficacy Endpoints

Confirmed progression of EDSS was defined as 1 point increase from baseline in EDSS score if baseline EDSS score was between 0 and 5.0, or 0.5 point increase from baseline EDSS score if baseline EDSS score was higher than 5.0, confirmed 3 months later.

Statistical analysis of this exploratory endpoint based on a logistic model did not find effect for GA 40 mg TIW over placebo (odds ratio: 1.182; p=.5726).

No treatment difference was found in the change from baseline in EDSS scores as well (p=.2449 from ANCOVA analysis).

3.3 Evaluation of Safety

Refer to Evaluation of Safety by Dr. Jody Green.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analyses of relapse by sex and age group were performed. Annualized relapse rate is lower in males than in females for both treatment groups. No significant discrepancies were found in efficacy results in the subgroups of sex and age.

Table 10 Summary of relapse analysis by sex and age group (reviewer's analysis)

	Placebo N=461	**GA 40 mg N=943**
Sex		
Male		
N	148	302
Estimated ARR	0.367	0.298
Risk Ratio (nominal p-value)		0.812 (p=.250)
Female		
N	313	641
Estimated ARR	0.564	0.345
Risk Ratio (nominal p-value)		0.613 (p<.0001)
Age (years)		
< 38		
N	226	509
Estimated ARR	0.562	0.382
Risk Ratio (nominal p-value)		0.687 (p=.008)
≥ 38		
N	235	434
Estimated ARR	0.430	0.261
Risk Ratio (nominal p-value)		0.606 (p<.001)

The study was conducted at 155 sites over 17 countries. A total of 86 subjects (6.1%) came from the USA. Except Croatia, results appear to be generally consistent in countries with at least 30 patients.

The estimated relapse rate is lower in US patients than in patients from other countries for both treatment groups. The numerical treatment difference in relapse rate is also smaller in US patients compared to patients from other countries. In Croatia, patients treated with GA 40 mg had higher relapse rate than patients treated with placebo on average. Due to the small size of patient number, it is difficult to draw any conclusions with respect to regional difference. The following table presents the results from analysis of relapse by US and Non-US countries. Relapse rate in Croatia is also presented.

Table 11 Summary of relapse analysis by region (reviewer's analysis)

Country	Placebo N=461	GA 40 mg N=943
US		
N	25	61
Estimated ARR	0.294	0.230
Risk Ratio (nominal p-value)		0.785 (p=.688)
Non-US (including Croatia)		
N	436	882
Estimated ARR	0.494	0.320
Risk Ratio (nominal p-value)		0.647 (p<.0001)
Croatia		
N	39	72
Estimated ARR	0.305	0.397
Risk Ratio (nominal p-value)		1.304 (.465)

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major issues were identified in Study GA-301.

5.2 Collective Evidence

Study GA-301 has showed robust results in the primary endpoint of annualized relapse rate with or without pre-planned adjustments of covariates and from alternative analysis methods. The results are consistent across ITT, completers, and evaluable patient populations as well as in other relapse related endpoints. The estimated ARR for for GA 40 mg TIW is in line of the ARR for daily GA 20 mg, which is the marketed dose.

5.3 Conclusions and Recommendations

The reviewer concludes that efficacy in annualized relapse rate has been established in this single pivotal phase 3 trial.

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/s/

XIAORONG YAN
12/11/2013

KUN JIN
12/11/2013
I concur with the review.

HSIEN MING J HUNG
12/12/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

24 JUL 2013

NDA: 20-622/S-089

Drug Product Name
Proprietary: Copaxone (b) (4)
Non-proprietary: Glatiramer acetate

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
28 MAR 2013	29 MAR 2013	29 MAR 2013	29 MAR 2013
17 JUL 2013	17 JUL 2013	N/A	N/A

Applicant/Sponsor
Name: Teva Neuroscience, Inc.
Address: 425 Privet Road
PO Box 1005
Horsham, PA 19044
Representative: Dennis Ahern
Telephone: 610-786-7379

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Efficacy Supplement

2. SUBMISSION PROVIDES FOR: 40 mg strength and three times a week dosing regimen

3. MANUFACTURING SITE: Teva sites Runcorn, UK and Kfar Saba, Israel

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- 20 mg/mL (approved) and 40 mg/mL (proposed)
- Subcutaneous injection
- Sterile solution in a pre-filled glass syringe

5. METHOD(S) OF STERILIZATION: (b) (4) (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of multiple sclerosis

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This submission is in the eCTD format. The following information request was sent to the applicant on 17 June 2013 and a response was received on 17 July 2013. The responses were incorporated into the relevant sections of this review.

1. Provide the incubation conditions for the biological indicators used for (b) (4) (b) (4) at Kfar Saba and Runcorn. Include a description of the type of indicator that is used (b) (4)
2. Provide the following information on the media fill program at Kfar Saba.
   a. Clarify if the alert level for a media fill with (b) (4) units is (b) (4) units. We believe this to be a typo and refer you to Table D-1 in the process validation package.
   b. Provide a justification for filling the (b) (4).
   c. Indicate which part(s) of the media fill batch (beginning, end, etc.) use water and which part use media for filling.
   d. Provide data to support the adequacy of water-filled syringes to detect potential microbial contamination. (b) (4) (b) (4) (b) (4)
   e. Provide the following information for the media fill results submitted: the number of units filled with water, the number of units filled with media, the number of water and media filled units rejected, and a reason for the rejection.
   f. Provide additional information on the positive unit recovered in (b) (4). What organism was recovered? Was the positive sample a filled unit (water or media) or a bioburden sample?
   g. Describe the retest procedures in (b) (4).
   h. Justify the use of a (b) (4) (b) (4)
3. Describe the growth promotion studies conducted for Runcorn media fills. Include the organisms

used, the inoculum size, the incubation conditions, and acceptance criteria.

filename: N020622S089R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This is an (b) (4) drug product intended for manufacture at two different locations. The drug product is (b) (4) and filled into glass syringes.

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, PhD

B. Endorsement Block _____
Bryan Riley, PhD
Microbiology Team Leader

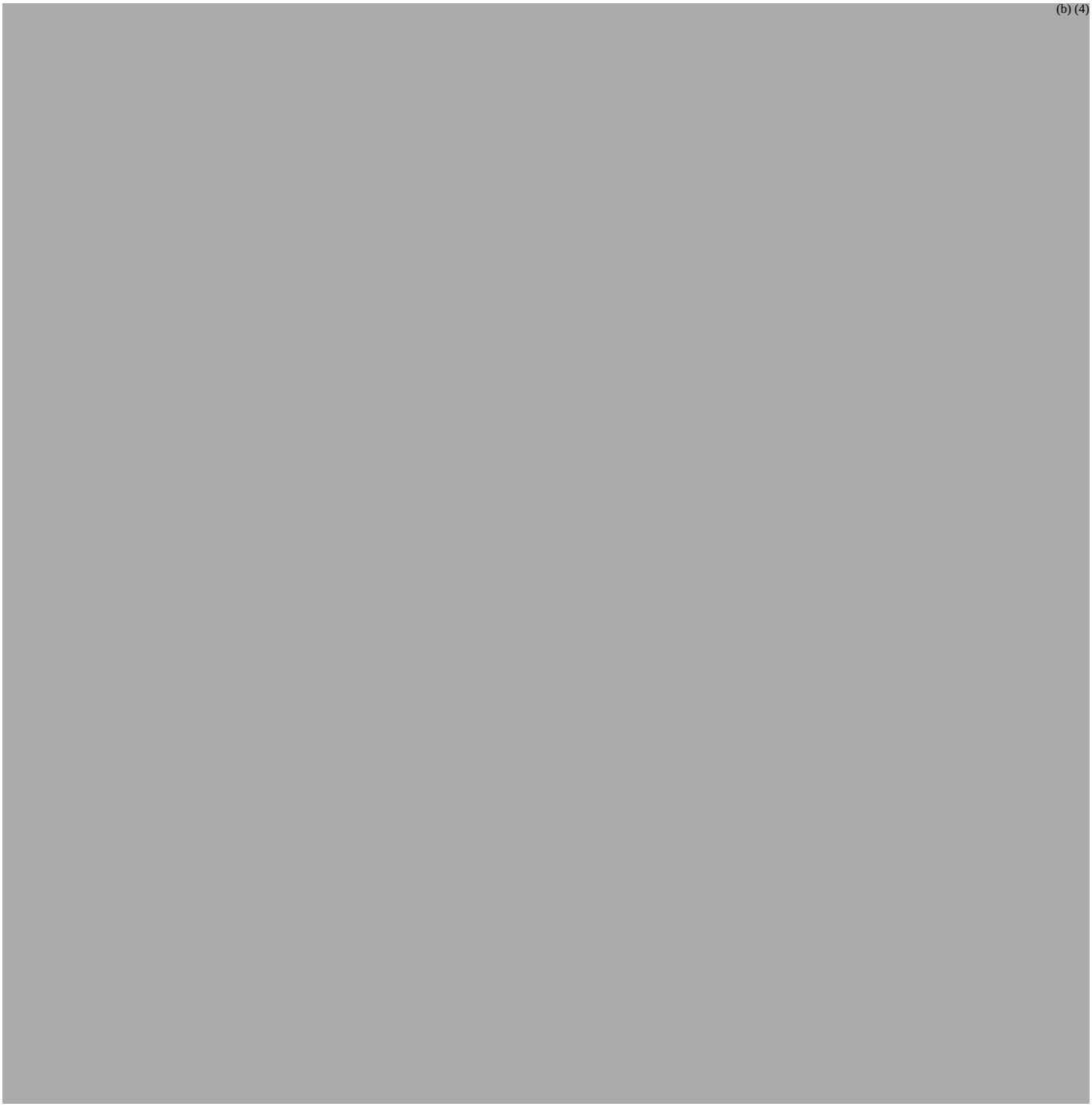
C. CC Block
In DARRTS

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE The drug substance is unchanged.

(b) (4)



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/s/

JESSICA COLE
07/24/2013

BRYAN S RILEY
07/24/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

PRODUCT (Generic Name):	Glatiramer acetate
PRODUCT (Brand Name):	Copaxone®
sNDA:	20,622/s-089
DOSAGE FORM:	Solution for subcutaneous injection
DOSAGE STRENGTHS:	40 mg/ml
INDICATION:	Relapsing-Remitting Multiple Sclerosis
SUBMISSION DATE:	3/29/2013
SPONSOR:	Teva Pharmaceutical Industries Ltd.
CP REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

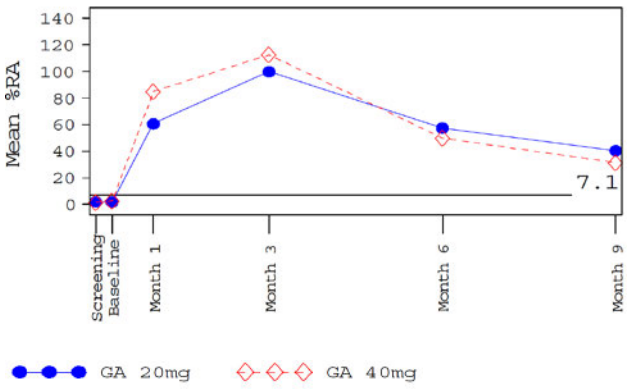
In this supplemental NDA submission, the sponsor seeks the approval of a new dosing regimen for Copaxone®, 40 mg/ml glatiramer acetate (GA) given three times a week (TIW). The submission includes one pivotal trial – Study MS-GA-301 (GALA), which was a randomized, parallel-group study conducted in subjects with relapsing-remitting multiple sclerosis (RRMS) to assess the efficacy, safety, and tolerability of GA subcutaneous injection of 40 mg (N= 943) administered TIW compared to placebo (N=461) in a double-blind design.

Immunogenicity was assessed by measuring anti-GA antibodies in part of the GALA study (ancillary study). Per the protocol, serum samples to detect anti-GA specific antibodies were to be collected from a subset of approximately 400 subjects at participating sites, at Months 0 (baseline), 1, 3, 6, 9, 12 (end of placebo-control phase), 18 and 24. However, in the current submission, there are no immunogenicity results provided for this study. As a response to the information request from the Division, the sponsor informed that they have not analyzed the data and are waiting for the final set of samples which were collected in June of 2013 to be shipped to the lab. The sponsor stated that it would take undetermined time for the results to be available.

An immunogenicity report for a supportive study GA-9006 was submitted and reviewed. GA-9006 was a randomized, double-blind, parallel group study performed in RRMS patients to

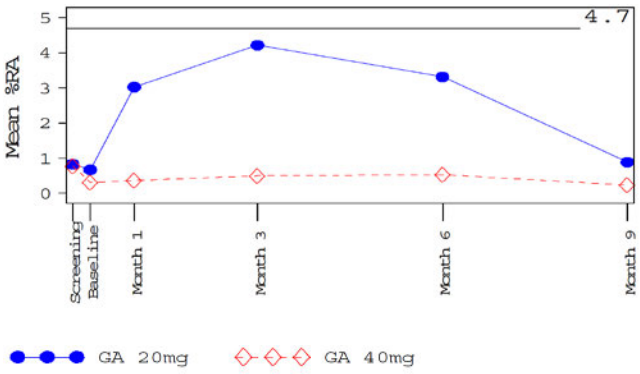
evaluate the efficacy, tolerability and safety of 40 mg (N=46) vs. 20 mg (N=44) GA injection both administered once daily over a 9-month period. Anti-GA IgG antibodies were detected in most of the patients in both groups. The time-profiles of anti-GA IgG antibody were similar between the two groups with slightly higher peak level (observed at month 3) in 40 mg group than 20 mg group. The results for IgG antibodies are generally in line with the description of immune response to 20 mg GA in the current labeling of Copaxone®. The presence of anti-GA IgE antibodies was also detected but in a much smaller number of patients. The 40 mg group had less number of subjects positive for anti-GA IgE antibodies compared to 20 mg group and showed lower levels of IgE antibodies. For 20 mg group, the IgE antibodies appeared between months 1 – 6 and then declined towards baseline at month 9.

Comparison of immunogenicity results from Study GA-9006 and the current labeling of Copaxone®

<table>
<tr><th></th><th>GA-9006</th><th>Current labeling</th></tr>
<tr><td>Anti-GA IgG</td><td>Table 1. Number and percentage of the IgG responders in each treatment group at each tested time point of the treatment
<table>
<tr><th rowspan="2">GA-9006
Time Points</th><th colspan="3">Treatment</th></tr>
<tr><th>GA 20mg</th><th>GA 40mg</th><th>Total</th></tr>
<tr><td>Screening</td><td>1 (2.3%)</td><td>0 (0.0%)</td><td>1 (1.2%)</td></tr>
<tr><td>Baseline</td><td>2 (4.5%)</td><td>1 (2.2%)</td><td>3 (3.3%)</td></tr>
<tr><td>Month 1</td><td>38 (86.4%)</td><td>44 (95.7%)</td><td>82 (91.1%)</td></tr>
<tr><td>Month 3</td><td>42 (97.7%)</td><td>41 (95.3%)</td><td>83 (96.5%)</td></tr>
<tr><td>Month 6</td><td>34 (91.9%)</td><td>39 (97.5%)</td><td>73 (94.8%)</td></tr>
<tr><td>Month 9</td><td>31 (83.8%)</td><td>29 (74.4%)</td><td>60 (78.9%)</td></tr>
</table>
Figure 1. Anti-GA IgG Mean of %RA over time.


%RA (Percent Relative Absorbance) is the percent of the absorbance (optical density) value of the tested serum relative to the values of the System Suitability Tests (SST) positive control of each test run.</td><td>In a controlled trial of 125 RRMS patients given COPAXONE, 20 mg, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype.</td></tr>
</table>

<table>
<tr><td></td><td>The line representing IgG cut-point value crosses the Y-axis at 7.1 point. The samples whose RA% exceeded the cut-point values were considered as positive.</td><td></td></tr>
<tr><td>Anti-GA IgE</td><td>Results from the first testing

Table 2. Number and percentage of the IgE responders in each treatment group at each tested time point of the treatment
<table>
<tr><th rowspan="2">GA-9006 Abs</th><th colspan="3">Treatment</th></tr>
<tr><th>GA 20</th><th>GA 40</th><th>Total</th></tr>
<tr><td>Screening</td><td>3 (7.0%)</td><td>3 (7.0%)</td><td>6 (7.0%)</td></tr>
<tr><td>Baseline</td><td>1 (2.3%)</td><td>0 (0.0%)</td><td>1 (1.1%)</td></tr>
<tr><td>Month 1</td><td>8 (18.6%)</td><td>0 (0.0%)</td><td>8 (9.0%)</td></tr>
<tr><td>Month 3</td><td>6 (14.0%)</td><td>1 (2.3%)</td><td>7 (8.1%)</td></tr>
<tr><td>Month 6</td><td>8 (21.6%)</td><td>2 (5.0%)</td><td>10 (13.0%)</td></tr>
<tr><td>Month 9</td><td>3 (8.1%)</td><td>0 (0.0%)</td><td>3 (4.0%)</td></tr>
</table>
Figure 2. Anti-GA IgE Mean of %RA over time.
 

The line representing IgE cut-point value crosses the Y-axis at 4.7 point. As shown in the above figure, majority of the samples had %RA values lower than the cut-point (values above which are considered as positive).

The sponsor conducted a second testing (reanalysis) of the anti-GA IgE positive serum samples. The presence of anti-GA-reactive IgE antibodies was confirmed in 5 subjects (11.6%) from the 20mg group and in one subject (2.2%) treated with 40mg GA. The %RA values measured in the repeated assay were lower compared to those determined in the first assay, except for one subject. There was no clear relationship between the safety results (lab tests and clinical observations) and anti-GA IgE responses.</td><td>No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, the risk cannot be excluded.</td></tr>
</table>

It should be noted that there are several limitations about the immunogenicity results from Study GA-9006. First, the dosing regimen for 40 mg GA was different from the one for which the sponsor pursues approval in this sNDA (once daily vs. TIW) and the treatment periods were also different (9 months vs. 12 months); Secondly, the number of subjects in Study GA-9006 were small; Lastly, the assay for anti-GA IgE antibodies was optimized but not validated, according to the sponsor, due to unavailability of a true standard, i.e., IgE-positive human serum. In addition, the validation reports for the assays to measure anti-GA IgG or anti-GA IgE antibodies are not provided along with the immunogenicity report.

Considering these factors, no definite conclusions can be made for the immunogenicity of 40 mg GA administered TIW. The agency will review the immunogenicity results from Study GALA when the sponsor submits the data in the future. The following message needs to be conveyed to the sponsor:

In the immunogenicity report for Study GA-9006, there is a signal for the presence of anti-GA IgE antibody. You stated that the assay used to measure IgE is optimized but not validated. You need to develop a validated assay and use that to analyze the samples from the GALA study.

For Study GA-9006, you have provided data for patient IgG responses. To enable the Agency fully understanding the significance of these results, please provide the validation report for the IgG assay.

Xinning Yang, Ph.D.

Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D. Ph.D._____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XINNING YANG
12/06/2013

YUXIN MEN
12/06/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 31436/S89

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	June 26, 2013
Reviewer(s):	Liu (Sue) Liu, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Copaxone (Glatiramer Acetate) Injection 40 mg/mL
Application Type/Number:	NDA 20622/S-089
Applicant/Sponsor:	Teva Neuroscience
OSE RCM #:	2013-800

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CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Copaxone, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 BACKGROUND

Copaxone was approved in December 1996 and is currently marketed as a prefilled syringe containing 1 mL of a 20 mg/mL solution, which is administered once daily. Teva submitted this supplemental New Drug Application (S-085) to seek approval for a new prefilled syringe containing 1 mL of a 40 mg/mL solution, which will be administered three times per week. The new strength will have the same labeled indications as the approved product.

On March 29, 2013, the Applicant submitted a proprietary name request for Copaxone [(b) (4)] along with an external study conducted by [(b) (4)] in support of the modifier [(b) (4)] On June 25, 2013, the Applicant submitted a proprietary name request amendment indicating they wanted the modifier removed and wanted the name 'Copaxone' reviewed by DMEPA. The Applicant confirmed there were no product characteristic changes since their March 29, 2013 submission.

1.2 PRODUCT INFORMATION

The following table includes the product information provided in the March 29, 2013 proprietary name submission as well as comparative information for the currently marketed Copaxone strength.

Table 1: Product Information for Copaxone

	Copaxone (Approved)*	Copaxone (Proposed)*
Active Ingredient	Glatiramer Acetate	Glatiramer Acetate
Indication of Use	Relapsing-remitting multiple sclerosis	(b) (4)
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection	Injection
Strength	20 mg/mL	40 mg/mL
Dose and Frequency	20 mg once daily	40 mg three times weekly, at least 48 hours apart
How Supplied	Prefilled syringe containing 1 mL of a 20 mg/mL solution, with white plunger; 30 count cartons	Prefilled syringe containing 1 mL of a 40 mg/mL solution with blue plunger; 12 count cartons
Storage	Refrigerate at 2°C to 8°C (36°F to 46°F).	Refrigerate at 2°C to 8°C (36°F to 46°F).

* Per email correspondence from the Office of New Drug Quality Assessment (ONDQA), both the approved and proposed Copaxone products are the same formulation, with the only difference being the concentration of glatiramer acetate.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) did not review the amended name, Copaxone; however, Copaxone is already marketed, and there are no identified promotional concerns with this name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) SEARCH

The May 17, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The proposed proprietary name, Copaxone, is the same name that is currently marketed for Teva's Glatiramer Acetate Injection.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database on April 26, 2013 for wrong drug medication errors involving Copaxone.

The (FAERS) search used the following search terms: Copaxone (trade name), Glatiramer Acetate (product active ingredient), Glatiramer (product active ingredient), Copaxone* (verbatim), Glatiramer acetate* (verbatim), product label issues (HLT), product packaging issues (HLT), product quality issues NEC (HLT) and medication errors (HLGT).

This search strategy identified one case describing a wrong drug error where Copaxone was filled with Enbrel (Etanercept). This is a single case, and we cannot confirm the error was due to name confusion. Thus, at this time we have no issues with continuing to market the product with the name Copaxone.

2.2.4 FDA Name Simulation Studies

The FDA name simulation studies were conducted prior to the amendment to retain Copaxone only. We did not conduct additional name simulation studies for Copaxone.

The results of the simulation studies conducted for Copaxone (b) (4) can be seen in Appendix C. The majority of participants in the written studies and verbal study interpreted the root name, Copaxone, correctly. However, more than half of the participants in the inpatient written study omitted the modifier, (b) (4)

2.2.5 Analysis of Need for Modifier

This supplement represents both the addition of a new strength and a change in frequency from what is currently available in the product line. There are no single modifiers currently on the market today that convey both strength and frequency differences. The Applicant proposes to market the product line extension under the existing proprietary name, Copaxone. Due to the product characteristic differences, we evaluated whether a modifier is needed to distinguish the products.

Our evaluation determined there is no need to amend the proprietary name with a modifier because:

- The modifier may be omitted or overlooked
- The product can be differentiated by labeling
- There are currently other marketed products (i.e. Trelstar, Eligard) available in different strengths administered at different frequencies which are managed safely under one insert and one proprietary name
- Copaxone is primarily ordered through the Shared Solutions enrollment form, which already has the full medication name and sig printed

Additionally, the option of a dual proprietary name introduces risk for therapeutic duplication and overdose, and would not be appropriate in this circumstance.

2.2.6 Failure Mode and Effects Analysis of Similar Names

DMEPA conducted searches for potential names of concern prior to receipt of the Applicant's amendment to proprietary name review. Therefore, Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Copaxone (b) (4). Table 1 lists the names identified by the primary reviewer (PR), the Expert Panel Discussion (EPD), and other review disciplines that have potential orthographic, phonetic, or spelling similarity to the proposed proprietary name, Copaxone (b) (4). However, the Applicant amended their request for proprietary name review, and this product line extension will now be marketed under Copaxone. No failure mode and effects analysis was conducted because Copaxone is marketed without reports of confusion with the names listed in Table 1.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines)					
Look Similar (n=35)					
Name	Source	Name	Source	Name	Source
Copegus	EPD	Copperose	EPD	3XB Liquid	PR
Capsaicin	EPD	Loperamide	PR	3XB Powder	PR
Capex	EPD	B-100	PR	ZTO	PR
Coplavix***	EPD	Cetazone T	PR	MTO	PR
Capozide	EPD	Carboxine DM	PR	MTU	PR
Cuvposa	EPD	Carboxine 12 DM	PR	BTO	PR
Ceftriaxone	EPD	Suboxone	PR	Cupric Acetate	PR
Cogentin	EPD	BTD	PR	MT-100***	PR
TW	EPD	MTX Support	PR	MK-4	PR
Capoten	EPD	3TC	EPD	[redacted]	[redacted]
Ceprotin	EPD	Mt-10	PR	[redacted]	[redacted]
Cuprimine	EPD	MZM	PR	[redacted]	[redacted]
Gepirone	EPD	MFA	PR	[redacted]	[redacted]
Sound Similar (n=0)					
Name	Source	Name	Source	Name	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Look and Sound Similar (n=7)					
Name	Source	Name	Source	Name	Source
[redacted] (b) (4)	PR	[redacted] (b) (4)	PR	[redacted] (b) (4)	PR
	PR		PR		EPD
Copaxone	EPD/PR	[redacted]	[redacted]	[redacted]	[redacted]

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the DNP via e-mail on June 21, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DNP on June 24, 2013, they concurred with our finding, and they did not have additional comments.

3 CONCLUSIONS

The proposed proprietary name, Copaxone, is acceptable from both a promotional perspective and safety perspective.

*** This document contains proprietary and confidential information that should not be released to the public.

If you have further questions or need clarifications, please contact Ermias Zerislassie, OSE project manager, at 301-796-0097.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Copaxone, and have concluded this name is acceptable.

The proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA. The results are subject to change. If any of the proposed product characteristics as stated in your March 29, 2013 submission are altered, the name must be resubmitted for review.

4 REFERENCES

1. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)***

   The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. ***Dogpile (www.dogpile.com)***

    Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. ***Natural Standard (http://www.naturalstandard.com)***

    Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[3] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

[3] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Copaxone (b) (4)	**Scripted May Appear as**	**Spoken May Be Interpreted as**
Capital 'C'	A, G, L, O. U	Z, K, S if followed by an i or e
Lower case 'c'	a, e, i, l	Z, K, S if followed by an i or e
Lower case 'o'	a, c, e, u	Oh
Lower case 'p'	yn, ys, g, j, l, q	b
Lower case 'a'	el, ci, cl, d, o, u	Any vowel
Lower case 'x'	a, d, skinny f, k, n, p, r, t, v, y	ks, kz, s, z
Lower case 'o'	a, c, e, u	Oh
Lower case 'n'	m, u, x, r, h, s	dn, gn, kn, mn, pn
Lower case 'e'	a, i, l, o, u,p	Any vowel
(b) (4)		(b) (4)
Letter Strings		
(b) (4)		

Appendix C: Prescription Simulation Samples and Results

Figure 1. Copaxone [(b) (4)] Study (Conducted on April 26, 2013)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Copaxone [(b) (4)] 40 mg subcutaneously	Copaxone [(b) (4)] 40 mg/mL 40 mg subcutaneously three times a week
Outpatient Prescription: Copaxone [(b) (4)] 40mg/mL 40mg subcutaneously 3 times a week	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Copaxone [(b) (4)]

As of Date 5/13/2013

190 People Received Study

73 People Responded

Study Name: Copaxone [(b) (4)]

OUTPATIENT	VOICE	INPATIENT
COPAXONE (5)	COPASONE [(b) (4)] (1)	COPADONE (1)
COPAXONE [(b) (4)] (1)	COPAXAN [(b) (4)] (1)	COPAXONE (15)
COPAXONE [(b) (4)] (1)	COPAXIL (1)	COPAXONE [(b) (4)] (11)
COPAXONE [(b) (4)] (12)	COPAXIL [(b) (4)] (2)	COPAXONE [(b) (4)] (1)
COPAZONE (1)	COPAXONE (3)	
COPAZONE [(b) (4)] (1)	COPAXONE [(b) (4)] (16)	

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Proprietary Name	Active Ingredient	Similarity to 'Copaxone' (b) (4)	Failure preventions
1.	(b) (4)	Glatiramer Acetate	Look and Sound	(b) (4)
2.		Glatiramer Acetate	Look and Sound	
3.		Glatiramer Acetate	Look and Sound	
4.		Glatiramer Acetate	Look and Sound	
5.		Glatiramer Acetate	Look and Sound	
6.	3XB Liquid	Benzoic Acid, Salicyclic Acid	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.
7.	3XB Powder	Bismuth Subnitrate, Boric Acid, Thymol Iodide	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.
8.	ZTO	Zinc Chromate	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.

9.	MTO	Methyl tris (methylethylketoxime) silane	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.
10.	MTU	Alkiron	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.
11.	BTO	Tributyltin Oxide	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.
12.	Cupric Acetate	Copper Acetate	Look	Found in Micromedex, but unable to find product characteristics in commonly used databases.
13.	MT-100***	Metoclopramide, Naproxen	Look	Per Clinical Pharmacology: NDA submitted in August 2003. On May 28, 2004, the FDA issued a not-approvable letter due to inadequate supportive data and safety concerns. On August 4, 2005, an FDA advisory committee concluded that the benefit of the drug as compared with naproxen alone was not enough to outweigh the risk of tardive dyskinesia with metoclopramide; naproxen. Due to the committee's findings, clinical development of metoclopramide; naproxen by Pozen has ceased
14.	MK-4	Menatetrenone (Vitamin K2)	Look	Found in Micromedex and Facts and Comparison, but unable to find product characteristics in commonly used databases (i.e. strength).
15.	Copegus	Ribavirin	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
16.	Capsaicin	(Established Name)	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
17.	Capex	Fluocinolone Acetonide	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)

*** This document contains proprietary and confidential information that should not be released to the public.

18.	Coplavix***	Clopidogrel bisulfate, Aspirin	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
19.	Capozide	Capozide; Hydrochlorothiazide	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
20.	Cuvposa	Glycopyrrolate	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
21.	Ceftriaxone	(Established Name)	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
22.	Cogentin	Benztropine Mesylate	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
23.	(b) (4)		Look	This is a not a pharmaceutical product. Med Lexicon states this is an abbreviation for (b) (4)
24.	Capoten	Captopril	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
25.	Ceprotin	Protein C Concentrate (Human) Lyophilisate	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
26.	(b) (4)	Glatiramer Acetate	Look and Sound	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
27.	Cuprimine	Penicillamine	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
28.	Gepirone	(Established Name)	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
29.	Copperose	Corn Poppy	Look	Name lacks sufficient orthographic similarity to Copaxone (b) (4)
30.	Loperamide		Look	No FMEA conducted since product can be managed under existing name
31.	B-100	Vitamin B Complex	Look	No FMEA conducted since product can be managed under existing name

*** This document contains proprietary and confidential information that should not be released to the public.

32.	Cetazone T	Acetaminophen, Phenyltoloxamine citrate, Salicylamide	Look	No FMEA conducted since product can be managed under existing name
33.	Carboxine DM	Carbinoxamine Maleate, Dextromethorphan Hydrobromide, Pseudoephedrine Hydrochloride	Look	No FMEA conducted since product can be managed under existing name
34.	Carboxine 12 DM	Carbinoxamine Tannate, Dextromethorphan Tannate, Pseudoephedrine Tannate	Look	No FMEA conducted since product can be managed under existing name
35.	Suboxone	Buprenorphine Hydrochloride, Naloxone Hydrochloride	Look	No FMEA conducted since product can be managed under existing name
36.	BTD	Chemotherapy Regimen for Multiple Myeloma	Look	No FMEA conducted since product can be managed under existing name
37.	MTX Support	Cyanocobalamin, Folic Acid	Look	No FMEA conducted since product can be managed under existing name
38.	3TC	Lamivudine	Look	No FMEA conducted since product can be managed under existing name
39.	Mt-10	Multivitamin	Look	No FMEA conducted since product can be managed under existing name
40.	MZM	Methazolamide	Look	No FMEA conducted since product can be managed under existing name
41.	MFA	Lactobacillus	Look	No FMEA conducted since product can be managed under existing name
42.	Copaxone	Glatiramer Acetate	Look and Sound	Name is the subject of this review

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/s/

LIU LIU
06/26/2013

IRENE Z CHAN
06/27/2013

IRENE Z CHAN on behalf of CAROL A HOLQUIST
06/27/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

OTHER REVIEW(S)

Division of Neurology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 020622/S-089

Name of Drug: Copaxone (glatiramer acetate injection) for subcutaneous use

Applicant: Teva Pharmaceuticals

Labeling Reviewed

Submission Date: March 28, 2013

Receipt Date: March 29, 2013

Background and Summary Description:

Copaxone (NDA 020622) is currently approved for 20 mg/ml administered once a day. NDA 020622/S-089 is a prior-approval efficacy supplement providing for Copaxone 40 mg/ml administered three times a week.

The Copaxone label has been revised for supplement 89 to include information in support of the 40 mg/ml administered three times a week dosing regimen.

Review

This review compares the currently approved labeling for Copaxone, dated March 8, 2013, to the final, agreed-upon label between FDA and Teva which is being approved under S-089.

1. For Supplement 89, the following sections of the label have been updated to add the 40 mg/ml administered three times a week data:
    a. Dosage and Administration
    b. Dosage Forms and Strengths
    c. Warnings and Precautions
    d. Adverse Reactions
    e. Description
    f. Clinical Studies
    g. How Supplied
    h. Patient Counseling Information
    i. Patient Information – This section has also been updated to conform with the current Patient Information format.
    j. Instructions for Use (IFU) – This section has also been updated to conform with

the current IFU format. Per DMEPA, the sponsor has updated the instructions for use to include illustrations for all steps outlined

2. A side by side review found no changes other than those agreed upon between the sponsor and FDA.

3. Appended to this review is a tracked changes version of the full prescribing information that uses the currently approved label (dated, March 8, 2013) as the base document and the tracked changes illustrate the information added for Supplement 89.

Recommendations

Approval.

Nicole Bradley, PharmD

Regulatory Project Manager Date

Jacqueline Ware, PharmD

Chief, Project Management Staff Date

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/s/

NICOLE L BRADLEY
01/27/2014

JACQUELINE H WARE
02/26/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

M E M O R A N D U M

From:	Donna Snyder, MD, Medical Officer Pediatric and Maternal Health Staff (PMHS)
Through:	Hari Cheryl Sachs, MD, Team Leader Lynne Yao, MD, OND Associate Director, Pediatric and Maternal Health Staff (PMHS)
To:	Division of Neurology Products (DNP)
NDA:	20622
Drug:	Glatiramer acetate injection (Copaxone®)
Sponsor:	Lundbeck, Inc.
Approved indications:	Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with MS.
Consult Question:	PMHS was asked to attend team meetings for this efficacy supplement to the NDA and assist with preparation of the Pediatric Review Committee (PeRC) paperwork.

Materials Reviewed

- PMHS consult request dated March 29, 2013, (DARRTS Reference ID: 3285153)
- Pediatric waiver request submitted by the sponsor on March 29, 2013

- Copaxone® (glatiramer acetate injection) labeling from Drugs@ FDA
- Cross-Discipline Team Leader Review and Medical Review dated February 26, 2006 to expand indication to include patients who have had a first clinical episode of MS and have MRI features consistent with MS
- Approval letters from Drugs@FDA for Aubagio (teriflunomide, NDA 202992), Gilenya® (fingolimod, NDA 22527) and Tecfidera (dimethyl fumarate, NDA 204063)
- PMHS consult review by B. Durmowicz, dated March 28, 2012, (DARRTS Reference ID: 3113986)

Background and Regulatory History: originally approved on December 20, 1996.
Glatiramer acetate injection (Copaxone®) is indicated for the reduction of frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have had a first clinical episode and have MRI features consistent with MS. Glatiramer acetate consists of the acetate salts of synthetic polypeptides containing the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. The drug is thought to act by modifying the immune processes that are responsible for Multiple Sclerosis (MS), however the exact mechanism of action is not known.

Glatiramer acetate injection (Copaxone®) was approved on December 20, 1996, for the treatment of RRMS. Glatiramer acetate was originally granted orphan status; however this orphan designation expired on December 20, 2003. The original approval predates the Pediatric Research and Equity Act (PREA). On February 27, 2009, the indication was expanded to allow treatment of patients with RRMS who have experienced a first clinical episode and have MRI features consistent with MS. DNP determined that PREA did not apply since this was an expansion of the current indication and not a new indication.

On March 29, 2013, the sponsor submitted a supplemental application to the NDA containing study data to support modifying the dosing regimen. Currently, glatiramer acetate is dosed subcutaneously at 20 mg once a day (QD) using a 20 mg/ml formulation. This supplement includes data to support dosing at 40 mg subcutaneously three times a week (TIW) with a more concentrated 40 mg/ml dosage form. According to PREA, section 505B(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a], any application which includes a new active ingredient, new indication, new dosage form, new dosing regiment or new route of administration is required to submit a pediatric assessment or a request for a waiver of pediatric studies. This supplemental application triggers PREA as a new dosing regimen. (b) (4) The applicant has not conducted any studies in the pediatric population to date.

Of note, a pediatric Written Request (WR) was issued on January 3, 2000, but was declined by the sponsor. In December 2011, the sponsor submitted a (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4)

(b) (4)

Discussion:
The criteria for a full or partial waiver under the Pediatric Research and Equity Act (PREA) are the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).

2. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information must be included in labeling.

3. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed. If ultimately, the sponsor cannot produce an appropriate pediatric formulation, the partial waiver will only include those age ranges that would require a different formulation. The information on the sponsor's attempts to produce an appropriate pediatric formulation will be posted publically on the FDA website.

The sponsor's rationale for the (b) (4) is that studies are impossible or highly impracticable because of the low prevalence of the disease in the pediatric population and supplied epidemiologic data on prevalence to support the assertion.

(b) (4) a partial waiver would be appropriate for pediatric patients from birth to 9 years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small. However, based on discussions with academia, DNP has determined that studies in MS in pediatric patients ages 10 to 17 years of age are possible and that studies will provide a public health benefit, especially since there are no approved therapies for pediatric patients with MS.[1] This requirement for studies is evidenced by the current PREA postmarketing requirements (PMRs) for Aubagio® (teriflunomide, NDA 202992), Gilenya® (fingolimod, NDA 022527) and Tecfidera® (dimethyl fumarate, NDA 204063).

Additionally, in the case of glatiramer acetate, there are no specific safety concerns that preclude a study in the pediatric population. Glatiramer acetate is currently used off-label

[1] Chitnis T et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. Neurology: 2013. Mar 19;80(12):1161-8.

in pediatric patients with MS as first-line therapy and is relatively well tolerated.[2] Studies for glatiramer acetate are needed in the pediatric population to confirm that dosing is appropriate and that glatiramer acetate is efficacious in the pediatric population. DNP will require a study in for pediatric patients with MS 10 to 17 years of age and will request that the sponsor submit a plan and timelines for the study. PMHS concurs that none of the criteria for a partial waiver apply for pediatric patients between 10 and 16 years of age and agrees that a study should be performed under PREA.

Conclusion:
PMHS participated in the filing, mid-cycle and wrap-up meetings and assisted DNP with the review of the paperwork needed for the Pediatric Review Committee (PeRC) Meeting. DNP met with the PeRC on December 4, 2013. PeRC agreed to the pediatric plan for a partial waiver for pediatric patients ages 0 to 10 years of age and to a deferral of pediatric studies for ages 10 to 17 years of age because the product is ready for approval in adults before pediatric studies have been completed. PeRC recommended that DNP determine whether a juvenile toxicology study is needed for the product and if a study is not needed, that the proposed timelines be moved up. PeRC also recommended that the division consider issuing a Written Request to the sponsor to encourage completion of studies under PREA. However, this reviewer notes that the sponsor's patents will expire in May 2014, so completion of studies in order to be eligible for any additional exclusivity will not likely be feasible.

[2] Yeh, A. Management of Children with Multiple Sclerosis. Pediatric Drugs 2102; 14 (3): 165-177.

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/s/

DONNA L SNYDER
12/19/2013

HARI C SACHS
12/20/2013

LYNNE P YAO
12/22/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**COPAXONE (glatiramer acetate injection) for subcutaneous use**
Applicant	TEVA
Application/Supplement Number	NDA 20622/S-089
Type of Application	Efficacy Supplement
Indication(s)	treatment of patients with relapsing-forms of multiple sclerosis
Office/Division	ODE I/DNP
Division Project Manager	Nicole Bradley
Date FDA Received Application	March 29, 2013
Goal Date	January 29, 2014
Date PI Received by SEALD	December 13, 2013
SEALD Review Date	December 16, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *The horizontal line between TOC and FPI is missing.*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *A reference is missing at the end of the summarized statement in I&U.*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

Selected Requirements of Prescribing Information

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

NO 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *The subsection headings and corresponding numerical identifiers are missing. Based on placement of the vertical lines in the FPI (see SRPI item #34), the RMC subsections include 2.1, 2.2, 5.1 and 5.2. This section should state: Dosage and Administration, Recommended Dose (2.1) 01/2014 followed by Dosage and Administration, Instructions for Use (2.2) 01/2014 on the next line. Similarly, the two Warnings and Precautions subheadings and subsection numbers (5.1 and 5.2) would follow on separate lines.*

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

Selected Requirements of Prescribing Information

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

YES 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *There is currently a vertical line next to the RMC section of HL; this should be removed. Only corresponding text in the FPI should have a vertical line in the left margin.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *The statement has been modified but, if agreed to by the review divison, is acceptable.*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Although there is reference made to patient labeling in this section, the Patient Counseling Information section guidance recommends: "Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)".*

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH A DONOHOE
12/16/2013

ERIC R BRODSKY
12/16/2013
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Memo

Date:	December 9, 2013
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Julie Neshiewat, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Copaxone (Glatiramer Acetate) Injection
Application Type/Number:	NDA 020622/S-089
Applicant/sponsor:	Teva Neuroscience
OSE RCM #:	2013-801

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised syringe label, blister pack labeling, and carton labeling for Copaxone, NDA 020622/S-089, received via e-mail on December 5, 2013 from the Applicant (Appendices A through J). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-801 dated September 14, 2013, November 1, 2013 and November 27, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling received via e-mail on December 5, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-801 dated September 14, 2013, November 1, 2013, and November 27, 2013.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. DMEPA concludes that the revised labels and labeling are acceptable.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

5 Page(s) of Draft Labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

JACQUELINE E SHEPPARD
12/09/2013

JULIE V NESHIEWAT
12/10/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Memo

Date:	November 27, 2013
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Copaxone (Glatiramer Acetate) Injection 20 mg/ml and 40 mg/ml
Application Type/Number:	NDA 020622/S-089
Applicant/sponsor:	Teva Neuroscience
OSE RCM #:	2013-801

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised syringe blister pack labeling and carton labeling for Copaxone NDA 103471/S-5125, received on November 7, 2013 from the Applicant (Appendices A through H). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-801 dated September 24, 2013 and November 1, 2013.

2 MATERIALS REVIEWED

DMEPA reviewed the labels and labeling received on November 7, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-801 dated September 24, 2013 and November 1, 2013.

3 RESULTS

Review of the revised labels and labeling determined that the Applicant addressed our previous recommendations; however, as confirmed by the Office of New Drug Quality Assessment (ONDQA), the expression of the strength should be mg/ml, not as (b) (4) This should be applied to all labels and labeling for this application.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that an additional revision is required for all the labels and labeling of this product.

Based on this review, DMEPA advises the recommendations below be implemented prior to approval of this NDA supplement. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

4.1 COMMENTS TO THE APPLICANT

A. General Comment, all labels and labeling (20 mg/ml, 40 mg/ml)

1. Change "20 (b) (4) and "40 (b) (4) to "20 mg/ml" and "40 mg/ml" to comply with the current USP requirements for the labeling of injectable products

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/s/

JACQUELINE E SHEPPARD
11/27/2013

IRENE Z CHAN
11/27/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Memo

Date:	November 1, 2013
Reviewer:	Jacqueline Sheppard, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Copaxone (Glatiramer Acetate) Injection 20 mg/ml and 40 mg/ml
Application Type/Number:	NDA 020622/S-089
Applicant/sponsor:	Teva Neuroscience
OSE RCM #:	2013-801

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised syringe blister pack labeling, carton labeling, and syringe label for Copaxone NDA 103471/S-5125, received on October 10, 2013 from the Applicant (Appendices A through H). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-801 dated September 24, 2013.

2 MATERIALS REVIEWED

DMEPA reviewed the labels and labeling received on October 10, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-801 dated September 24, 2013.

3 RESULTS

Review of the revised labels and labeling determined that the Applicant addressed most of our previous recommendations; however, there are additional areas that can be improved from a medication error perspective. This includes placement of the route of administration and frequency of administration statements for increased prominence. Additionally, as confirmed by the Office of New Drug Quality Assessment (ONDQA), the term (b) (4) on the carton labels should be replaced by "single dose."

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the revised labels and labeling can be improved for safe use of the product.

Based on this review, DMEPA advises the recommendations below be implemented prior to approval of this NDA supplement. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

4.1 COMMENTS TO THE APPLICANT

A. Carton Labeling, retail and professional sample (20 mg/ml, 40 mg/ml)

   1. Change (b) (4) to "single dose" to comply with the current USP requirements for the labeling of injectable products

B. Blister Pack Labeling, retail and professional sample

   (20 mg/ml, 40 mg/ml)

   1. Move the route of administration and frequency of administration statements closer to the proprietary name, established name, and strength by switching its place with the NDC number.

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/s/

JACQUELINE E SHEPPARD
11/01/2013

IRENE Z CHAN
11/04/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: October 24, 2013

To: Nicole Bradley, PharmD.
Regulatory Project Manager
Division of Neurology Products (DNP)
Office of Drug Evaluation (ODE)-1

From: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, PharmD
Team Leader OPDP

Subject: OPDP's comments on NDA 020622 (supplement 089)
COPAXONE (glatiramer acetate injection) solution for subcutaneous use injection

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Background

On May 30, 2013, DNP consulted OPDP to review the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for COPAXONE (glatiramer acetate injection) solution for subcutaneous use (Copaxone) pursuant to labeling supplement 089 which provides for a 40 mg dose delivered three times a week.

OPDP reviewed the proposed substantially complete version of the PI, PPI, and IFU for Copaxone provided by DNP on October 15, 2013. OPDP also reviewed the proposed carton and container labeling submitted to the electronic document room (eDR) on October 10, 2013 and we have no comments. The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the PPI and IFU under separate cover. Our comments on the PI are provided below.

Thank you for your consult. If you have any questions, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.

21 Page(s) of Draft Labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

MELINDA W MCLAWHORN
10/24/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 24, 2013
To:	Eric Bastings, M.D. Acting Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Mathilda Fienkeng, PharmD Team Leader **Office of Prescription Drug Promotion (OPDP**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs**
	Melinda Mclawhorn, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	COPAXONE (glatiramer acetate injection)
Dosage Form and Route:	injection for subcutaneous use
Application Type/Number:	NDA 20-622
Supplement Number:	089
Applicant:	Teva Neuroscience

1 INTRODUCTION

On March 29, 2013, Teva submitted for the agency's review a Supplemental New Drug application (S-089) for COPAXONE (glatiramer acetate injection) for subcutaneous use. Supplement 089 included a request for proprietary name review, for COPAXONE (b) (4) (glitiramer acetate) injection. On June 25, 2013, the Applicant submitted a proprietary name request amendment requesting removal of the modifier and requesting 'Copaxone'. Copaxone is already marketed, and the Division of Medication Error Prevention and Analysis (DMEPA) found no identified promotional concerns with this name. Supplement 089 also proposed an additional dosing strength of 40mg/1mL, injected subcutaneously three times weekly to provide additional therapeutic options for patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

COPAXONE (glatiramer acetate injection) for subcutaneous use was approved on December 20, 1996, and is indicated for the treatment of patients with relapsing forms of multiple sclerosis**.** COPAXONE is currently marketed as a prefilled syringe containing 1 mL of a 20 mg/mL solution, which is administered once daily.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on May 14, 2013 and May 30, 2013, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for COPAXONE (glitiramer acetate) injection 40mg/1mL.

2 MATERIAL REVIEWED

- Draft COPAXONE (glatiramer acetate) injection PPI and IFU received on June 25, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on May 14, 2013
- Draft COPAXONE (glatiramer acetate) injection PPI and IFU received on June 25, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on October 15, 2013
- Draft COPAXONE (glatiramer acetate) injection, Prescribing Information (PI) received on June 25, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on October 15, 2013
- Draft COPAXONE (glatiramer acetate) injection, Prescribing Information (PI) received on June 25, 2013 revised by the Review Division throughout the review cycle, and received by OPDP on October 15, 2013

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the prescribing information (PI)
- rearranged information due to conversion of the PI to PLR format
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PI and IFU.

Please let us know if you have any questions.

9 pages of Draft Labeling have been withheld as b4 (CCI/TS) immediately following this page.

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/s/

TWANDA D SCALES
10/24/2013

LASHAWN M GRIFFITHS
10/24/2013

MELINDA W MCLAWHORN
10/24/2013

ROBIN E DUER
10/24/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 020622 **Applicant: Teva Pharmaceuticals** **Stamp Date: 03/29/2013**

Drug Name: Copaxone (b) (4) **NDA/BLA Type: NDAs083**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			Application is a 505 (b) (2) application Reference drug is Copaxone 20 mg/mL
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	Drug is already approved.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? yes Pivotal Study #1 MS-GA301 (GALA) A multinational, multicenter, randomized, parallel-group	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	study performed in subjects with RRMS to assess the efficacy, safety and tolerability of glatiramer acetate (GA) injection 40 mg administered three times a week compared to placebo in a double-blind design. Indication: RRMS Pivotal Study #2 N/A Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		This is not required.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	This drug is already approved.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			Safety assessment is complete for the 40 mg dose; it was not requested for the 20 mg dose at this time.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			They are using MedDRA 15.0 for

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					MS-GA-301; version 11.0 for GA-9016 Version 8.1 for GA-9006.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	Not aware of any.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Initial documentation inadequate. Requested and now adequate.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	Has statement stating not necessary.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	All studies submitted were IND studies.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Not initially, but did so with request.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			Yes, after request resubmitted.
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			No additional ones requested.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	x			Discussed with team

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				leader. Willing to forgo those from studies GA9016 and GA9006. For MS GA 301 sponsor has only provided 4 disclosures as well as a statement indicating nothing more to disclose.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JODY E GREEN
05/20/2013

WILLIAM H Dunn
10/24/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 020622 BLA#	NDA Supplement #:S- 089 BLA Supplement #	Efficacy Supplement Type SE- 2
Proprietary Name: Copaxone (b) (4) Established/Proper Name: glatiramer acetate injection Dosage Form: Injection Strengths: 40mg/ml administered sc three times per week		
Applicant: Teva Pharmaceuticals USA Agent for Applicant (if applicable):		
Date of Application: March 28, 2013 Date of Receipt: March 29, 2013 Date clock started after UN:		
PDUFA Goal Date: January 29, 2014	Action Goal Date (if different):	
Filing Date: May 28, 2013	Date of Filing Meeting: May 14, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Dosage strength and regimen		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 027998

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: No ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X			

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			Completed waiver and certifications provided 23-April-2013 after Information Request
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			Copaxone (b) (4)
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined?			X	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 31-October-2012 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 14-May-2013

BLA/NDA/Supp #: NDA 020622 / S-089

PROPRIETARY NAME: Copaxone (b) (4)

ESTABLISHED/PROPER NAME: glatiramer acetate injection

DOSAGE FORM/STRENGTH: 40mg/ml administered SC three times per week

APPLICANT: Teva Pharmaceuticals USA

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Dosage strength and regimen

BACKGROUND:
Copaxone® (GA 20 mg/mL in a pre-filled syringe) is a first-line therapy indicated for reduction of the frequency of relapses in patients with RRMS, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. The recommended dosing and administration for Copaxone® is 20mg/mL, injected subcutaneously once daily.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nicole Bradley	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Billy Dunn		Y
Clinical	Reviewer:	Jody Green	Y
	TL:	Billy Dunn	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial*	Reviewer:		

products)			
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:	Sharon Yan	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Kavita Vyas	Y
	TL:	Martha Heimann	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Jessica Cole	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Liu (Sue) Liu	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Donna Snyder (Pediatrics Reviewer) Hari Sachs (Pediatrics TL)		Y Y
Other attendees	Twanda Scales (DMPP) Melissa Hulett (DMPP TL)		Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: OSI stated an inspection was unnecessary	☐ YES ☒ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Evaluation request to be sent by CMC	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**:	 ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Nicole Bradley, Pharm.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): August 13, 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE L BRADLEY
05/31/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 020622/S-089

Application Type: Efficacy Supplement

Name of Drug: Copaxone (glatiramer acetate injection)

Applicant: Teva Pharmaceuticals

Submission Date: March 28, 2013

Receipt Date: March 29, 2013

1.0 Regulatory History and Applicant's Main Proposals

The currently approved dosing for NDA 020622 is 20 mg/ml administered subcutaneously daily. This supplemental application proposes an additional dosage strength and regimen (40 mg/ml administered subcutaneously three times per week).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 28, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Length of HL is more than one-half page*

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Headings not presented in the center of a horizontal line*

NO 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Indications and Usage section does not include reference*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *Statement needs to be bolded*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

NO 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment: *Wrong cross-reference for Dosage and Administration*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

N/A 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

NO 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *Vertical line not added for Dosage and administration and warnings and precautions*

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Missing statement "See FDA-approved patient labeling (Patient Information and Instructions for Use"*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE L BRADLEY
05/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20622/S89

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 020622 SUPPL # S-089 HFD # 120

Trade Name Copaxone

Generic Name glatiramer acetate

Applicant Name Teva Pharmacueticals

Approval Date, If Known January 28, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020622 Glatiramer acetate

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study MS-GA-301 (GALA): A multinational, multicenter, randomized, parallel-group study performed in subjects with RRMS to assess the efficacy, safety and tolerability of GA injection 40 mg administered three times a week compared to placebo in a double-blind design.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the

effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study MS-GA-301 (GALA): A multinational, multicenter, randomized, parallel-group study performed in subjects with RRMS to assess the efficacy, safety and tolerability of GA injection 40 mg administered three times a week compared to placebo in a double-blind design.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 027998 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Nicole L. Bradley, PharmD
Title: Regulatory Project Manager

Date: January 28, 2014

Name of Office/Division Director signing form: Billy Dunn, MD
Title: Acting Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE L BRADLEY
01/28/2014

WILLIAM H Dunn
01/28/2014

Action Package Checklist

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 020622 BLA #	NDA Supplement # S-089 BLA Supplement #	If NDA, Efficacy Supplement Type: SE2
Proprietary Name: Copaxone Established/Proper Name: glatiramer acetate Dosage Form: Injection		Applicant: Teva Pharmaceuticals Agent for Applicant (if applicable):
RPM: Nicole Bradley		Division: Division of Neurology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 29, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

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- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval – January 28, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included Final: January 28, 2014
• Original applicant-proposed labeling	March 28, 2013
• Example of class labeling, if applicable	NA

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	March 28, 2013
• Example of class labeling, if applicable	NA
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included – December 13, 2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	June 27, 2013 June 27, 2013
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 5/17/2013 ☒ DMEPA 11/04/2013 11/27/2013 12/10/2013 ☒ DMPP/PLT 10/24/2013 ☒ OPDP (DDMAC) 10/24/2013 ☒ SEALD 12/16/2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM filing review 5/31/2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC December 4, 2013 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Version: 12/09/2013

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10/31/2012
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 01/28/2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 01/26/2014
PMR/PMC Development Templates *(indicate total number)*	☐ None 2
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review (01/26/2014)
• Clinical review(s) *(indicate date for each review)*	Primary clinical: 01/27/2014 Safety consult: 11/22/2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review (Section 3.3)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Pediatrics: 12/22/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 12/12/2013
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/06/2013
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/20/2013 01/08/2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 07/24/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	01/08/2014
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 12/18/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY GRACE LUBAO
02/05/2014

Pediatric Page

DARRTS
An ADMS Affiliate

PEDIATRIC PAGE REPORT

November 20, 2013 4:00:37 PM GMT-05:00

Selection Criteria:

Appl Type Number:	**NDA 20622**
Submission Type(s):	**SUPPL**
Sort Order:	**Appl Type No**

<Reports start from Page 2>

Organization: DNP **Product Name:** COPAXONE
Appl Type No: NDA 20622 **Applicant:** TEVA PHARMACEUTICALS USA
Submission Type #: SUPPL - 89 **Submission Status:** PENDING

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
3/29/2013	POWDER, FOR INJECTION SOLUTION, LYOPHILIZED, WITH ADDITIVES	N	3/29/2013	1/29/2014	DOSING	(b) (4) (b) (4) PATIENTS WITH (b) (4) MULTIPLE SCLEROSIS.

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
2,207	DEFERRED	YEARS	10	18	PRODUCT IS READY FOR APPROVAL IN ADULTS		10/31/2020
2,207	WAIVED	YEARS	0	9	NECESSARY STUDIES ARE NOT FEASIBLE	MS (MULTIPLE SCLEROSIS) IS A RARE CONDITION IN THE PEDIATRIC POPULATION AND IS CONSIDERED EXCEPTIONAL IN THE PREPUBERTAL AGE GROUP (BEFORE 10 YEARS OF AGE).	

Orga	Product	Appl Typ	Subm Ty	Applic	Subm	FDA Rec	Dosag	Orph	Subm	Goal Du	Submi	Su	Pe	PREA S	Pediat	Min Va	Max V	Waive	Waive	Study
DN	COPAX	NDA	SUPPL	TEV	PEN	3/29/20	PO	N	3/29/	1/29/2	DOS	R	2	DEFE	YEA	10	18	PRO		10/3
DN	COPAX	NDA	SUPPL	TEV	PEN	3/29/20	PO	N	3/29/	1/29/2	DOS	R	2	WAIV	YEA	0	9	NEC	MS	

Bradley, Nicole

From: Bradley, Nicole
Sent: Sunday, March 02, 2014 1:36 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Final Printed Labeling

Hi Ron,

Reference is made to NDA 020622 and to the February 21, 2014, submission providing final printed carton and container labeling for Supplement 89, approved on January 28, 2014. Additional reference is made to my December 4, 2013, email stating that it was acceptable for you to exhaust your current supple of carton labeling before implementing the revised language.

Can you clarify whether the final labeling submitted on February 21, 2014, reflect the labels that you plan to use until the supply is exhausted?

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
03/02/2014

PMR/PMC Development Template for NDA 020622/S-089
COPAXONE (glatiramer acetate)

PMR # 2114-1

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA: A randomized, controlled, parallel group superiority study in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of glatiramer acetate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/2017
Study/Trial Completion:	08/2020
Final Report Submission:	12/2021
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a PREA requirement. A waiver has been given for children under from birth to nine years of age because necessary studies are impossible or highly impracticable due to the small number of patients less than 10 years old with multiple sclerosis. A deferral has been given for those ages 10 up to 17; it is appropriate for a PMR because the drug is about to be approved and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this study is to evaluate the safety and efficacy of glatiramer acetate in pediatric patients ages 10 through 17 compared to an appropriate control for treatment of relapsing forms of multiple sclerosis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Deferred pediatric study under PREA: A randomized, controlled, parallel group superiority study in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of glatiramer acetate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
PREA pediatric clinical trial

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for NDA 020622/S-089
COPAXONE (glatiramer acetate)

PMR # 2114-2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A juvenile animal toxicology study in rat to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	02/2015
	Study/Trial Completion:	11/2016
	Final Report Submission:	01/2017
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This product is ready for approval for use in adults and pediatric studies have not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of glatiramer acetate on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile animal toxicology study in rat to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

SALLY U YASUDA
01/08/2014

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, December 23, 2013 12:08 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622

Hi Ron,

Reference is made to NDA 020622 and to your December 18, 2013, response to the Agency's December 9, 2013, information request. We have the following comments:

As stated in, "Guidance for Industry - Assay Development for Immunogenicity Testing of Therapeutic Proteins (2009)":

> *"for products that induce allergic responses, assays that can specifically measure IgE may be important for helping predict and prepare for anaphylactic reaction in the clinic."*

The Copaxone labeling states that drug hypersensitivity occurs, and therefore, on a risk basis, IgE evaluation may be important. However, you have been unable to develop an IgE positive control, so it is not possible to evaluate the significance of the IgE results. You may wish to consider alternative methods for the development of an IgE positive control. Alternatively, you may wish to consider the use of skin testing (refer to Guidance for Industry, Immunogenicity Assessment for Protein Therapeutic Product (2013)).

The IgG assay needs to have a control for sensitivity. Without a sensitivity evaluation, it is very difficult to assess the levels of patient antibody responses. In addition, since there is substantial immunological disturbance in MS patients, we recommend that you confirm the cut-point and the matrix interference using sera from MS treatment-naïve patients, which may give different responses than normal sera.

Thanks,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
12/23/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Friday, December 13, 2013 1:21 PM
To: Ron.Carnal@tevapharm.com
Cc: Bouie, Teshara; Bradley, Nicole
Subject: NDA 020622/S-089 Information Request

Importance: High

Hi Ron,

Please note that the following are not approved for the [redacted] (b) (4)

[redacted] (b) (4)

[redacted] We recommend that you harmonize your proposed Drug Product specifications for the 40 mg/mL strength to be consistent with those currently approved for the 20 mg/mL strength. Provide updated specification table as an amendment to your application.

[redacted] (b) (4)

Please provide this information at your earliest convenience.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

APPEARS THIS WAY
ON ORIGINAL

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/s/

NICOLE L BRADLEY
12/16/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, December 11, 2013 12:06 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Post-Marketing Requirements

Hi Ron,

Reference is made to NDA 020622/S-089, submitted on March 29, 2013, and to your April 23, 2013, request for full pediatric waiver. The Agency has reviewed your request and has made the following decisions:

1. We are waiving the pediatric study requirement from birth to 9 years of age because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

2. In accordance with section 505B(a) of the Federal Food, Drug, and Cosmetic Act, we are deferring submission of your pediatric study for ages 10 through 17 years of age. This required study and associated milestone dates are listed below:

   A randomized, controlled, parallel-group, superiority trial in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of glatiramer acetate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis

   Final Protocol Submission: 09/2017
   Study/Trial Completion: 08/2020
   Final Report Submission: 12/2021

3. We are requiring the following non-clinical study:

   A juvenile rat toxicology study to evaluate the effects of glatiramer acetate on growth, reproductive development, and neurological and neurobehavioral development

   Final Protocol Submission: 02/2015
   Study/Trial Completion: 11/2016
   Final Report Submission: 01/2017

We request that you submit the draft protocols for the deferred pediatric study and the juvenile animal toxicology study at least 3 months prior to the final protocol submission dates to allow for review and agreement on the protocol design.

Please submit, as an amendment to supplement 89, your agreement to the pediatric plan outlined above by Tuesday December 17, 2013. When doing so, clearly mark your submission, “Pediatric Plan”.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
12/16/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, December 16, 2013 2:55 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Labeling Format comments

Hi Ron,

Reference is made to NDA 020622/S-089 and to your December 13, 2013, submission that contains the final, agreed upon labeling. As I previously mentioned, we have additional PLR-formatting comments that are provided in this email. Please update your label with these changes and resubmit it (both clean and tracked changes versions) as an amendment to the supplement.

Labeling Formatting Deficiencies

1. The horizontal line between the Table of Contents and the Full Prescribing Information is missing

2. In Highlights, a reference is missing at the end of the summarized statement in the Indications and Usage section

3. Under Recent Major Changes in Highlights, the subsection headings and corresponding numerical identifiers are missing. Based on placement of the vertical lines in the FPI (see also comment #4), the RMC subsections include 2.1, 2.2, 5.1 and 5.2. This section should state: Dosage and Administration, Recommended Dose (2.1) 01/2014 followed by Dosage and Administration, Instructions for Use (2.2) 01/2014 on the next line. Similarly, the two Warnings and Precautions subheadings and subsection numbers (5.1 and 5.2) would follow on separate lines.

4. There is currently a vertical line next to the RMC section of HL; this should be removed. Only corresponding text in the FPI should have a vertical line in the left margin.

5. In the Full Prescribing Information: When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

   "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

6. Under the Patient Counseling Information in the Full Prescribing Information: Although there is reference made to patient labeling in this section, the Patient Counseling Information section guidance recommends: "Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)".

Additional Labeling Format Recommendations

7. 21 CFR 201.57(a)(2) requires that the established names of the drugs and the dosage form to be included in the product title in HL. Page 4 of the Labeling Review Tool (LRT) contains some of these format recommendations. Based on the regulations and the recommendations in the LRT, consider the revision below :

   COPAXONE (glatiramer acetate) injection, for subcutaneous use

8. Currently, the TOC starts at the top of the second page and FPI starts at the top of the third page. This results in a large amount of white space; for improved readability, consider moving TOC to page 1 after HL and start FPI at the top of page 2.

9. The current PI has "Iss. 01/2014" following Section 17; this should be removed as the only revised date in the PI should be the Revised Date at the end of HL.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
12/16/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, December 10, 2013 8:55 PM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 FDA Labeling Revisions_December 10, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We also refer to your email dated December 5, 2013, containing the revised carton and container labeling and to your email dated December 9, 2013, containing Teva's proposed labeling revisions for the Package Insert, Patient Package Insert, and Instructions for Use. We have reviewed all documents and have the following comments:

1. **Carton and Container labeling:** We have no further comments. Submit, as an amendment to the supplement, the carton and container labeling that is identical to the carton and container labeling contained in your December 5, 2013, email.

2. **Package Insert:** We have no further comments and agree with [redacted] (b) (4). I have accepted all changes and have attached the clean version below. Submit this version as an amendment to the supplement.

3. **Patient Package Insert and Instructions for Use:** Our comments and revisions are provided in the attached document. Please note, I have accepted the language we agree with and our revisions are in tracked changes. If you agree with our changes, please submit this document along with the other documents as a formal submission to the supplement. If you disagree, you can send me your counter-proposal via email.

Package Insert

Patient Package Insert and Instructions for Use

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930

Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

From: Ron Carnal [mailto:Ron.Carnal@tevapharm.com]
Sent: Monday, December 09, 2013 10:27 AM
To: Bradley, Nicole
Subject: RE: NDA 020622/S-089 FDA Labeling Revisions_November 26, 2013

Nicole,
Attached are files containing our revised labeling as response to your email on November 26. These files include Word and pdf versions of clean and track changes. All requested illustrations for the IFU are included.

Teva is challenging the inclusion of the statement regarding the [redacted] (b) (4)

We are including our argument/justification for why this statement should not be included.

Ron Carnal Mgr, Reg Affairs
Tel: 610-727-6132 Cell: 215-317-8197
Ron.Carnal@tevapharm.com sip:Ron.Carnal@tevapharm.com www.tevapharm.com

---

From: Bradley, Nicole [mailto:Nicole.Bradley@fda.hhs.gov]
Sent: Tuesday, November 26, 2013 11:10 AM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 FDA Labeling Revisions_November 26, 2013
Importance: High

Hi Ron,

Reference is made to NDA 020622/S-089. We also refer to our November 5, 2013, proposed labeling revisions and to your November 15, 2013, response.

As discussed during yesterday's teleconference, attached are our labeling revisions.

Please note the following:

- We have accepted all tracked changes for which we are in agreement with.
- The outstanding tracked changes are either changes we disagree with or changes that are being introduced for the first time in this version of the label.

Prescribing Information

Patient Information and Instructions for Use

We request that either agreement or additional revisions to the label be provided by Noon on Monday, December 9, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Senior Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
12/10/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, November 27, 2013 3:12 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Labeling Comments_November 27, 2013

Hi Ron,

Reference is made to NDA 020622/S-089 and to the carton and container labeling submitted on November 7, 2013. After review, we have the following comment which should be incorporated into your revisions to the package insert, PPI/IFU, and all carton and container labeling (20 mg/ml, 40 mg/ml):

- Change [redacted] (b) (4) to "20 mg/ml" and "40 mg/ml" to comply with the current USP requirements for the labeling of injectable products

Please provide the revised labeling as soon as possible.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Senior Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
11/27/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, November 04, 2013 12:45 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Carton and Container Labeling Comments_November 4, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We also refer to your carton and container labeling submitted on October 10, 2013, in response to our September 26, 2013, comments. After reviewing the submission, we have the following comments:

A. Carton Labeling, retail and professional sample (20 mg/ml, 40 mg/ml)
1. Change (b) (4) to "single dose" to comply with the current USP requirements for the labeling of injectable products

B. Blister Pack Labeling, retail and professional sample (20 mg/ml, 40 mg/ml)
1. Move the route of administration and frequency of administration statements closer to the proprietary name, established name, and strength by switching its place with the NDC number.

Please incorporate these comments and submit your revised carton and container labeling as an amendment to NDA 020622/S-089 by November 18, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
11/04/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, October 30, 2013 12:44 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_October 30, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following information request:

Submit the DSMB minutes for clinical studies GA-301-GALA, GA-9016, and GA-9006, or let us know where in the submission they are located.

Please provide this information by November 7, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Senior Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
10/30/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Thursday, September 26, 2013 6:15 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Carton and Container Labeling Comments_September 26, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We also refer to your carton and container labeling submitted on August 7, 2013 and August 15, 2013 . We have the following comments:

A. General Comment (20 mg/mL and 40 mg/mL)

1. There is inadequate strength differentiation between Copaxone 40 mg/mL and Copaxone 20 mg/mL since both utilize a (b) (4). Therefore, we recommend you select a different (b) (4) for the Copaxone 40 mg/mL, and carry that (b) (4) differentiation throughout the labels and labeling.

B. Syringe Blister Pack Labeling and Carton Labeling (20 mg/mL and 40 mg/mL)

1. Add the statements “three times a week” for the 40 mg strength and “once daily” for the 20 mg strength to help minimize wrong frequency errors.

C. Syringe Blister Pack Labeling (20 mg/mL and 40 mg/mL)

1. The established name is ½ the size of the proprietary name, but it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

2. Move the strength expression immediately to the right of the proprietary name and established name so it is not separated by the “Each pre-filled syringe…” statement and NDC number.

3. We recommend all numbers are followed by its associated unit of measure and all hyphens replaced with the word “to” for clarity. For example, consider revising “36°-46°F/2°-8°C” to “36°F to 46°F/2°C to 8°C”.

4. The ‘Teva Neuroscience’ logo is a redundant statement, is overly prominent, and clutters the label. We recommend removing this logo.

5. In order to minimize wrong route errors, include the statement ‘For subcutaneous injection only’.

6. Reduce the font size of the ‘Rx Only’ statement so it is less prominent than the established name.

D. Syringe Blister Pack Labeling (20 mg/mL)

1. The statement ‘(b) (4) contains a trailing zero. Trailing zero can lead to 10 fold errors in dosing. We recommend removing the trailing zero.

2. Ensure the labeling includes the expiration date and lot number.

E. Carton Labeling (20 mg/mL and 40 mg/mL)

1. Increase the prominence of the existing route of administration statement by moving it beneath the established name.

2. See recommendations C(2) above.

3. The 'Teva Neuroscience' logo is a redundant statement, is overly prominent, and clutters the label. We recommend removing this logo or minimizing it.

4. The back panel looks too similar to the Principal Display Panel (PDP) and may lead to the wrong side being displayed on a pharmacy shelf. We recommend revising the back panel so it does not look similar to the PDP.

5. On the Principal Display Panel (PDP) move the statement [redacted] (b) (4) to the upper right hand corner immediately above the statement "Each syringe…"

6. Revise the usual dosage statement from "See package insert…" to reflect actual dosage and administration for the product (i.e. Inject 20 mg once daily or Inject 40 mg three times a week).

Please incorporate these comments and submit your revised carton and container labeling as an amendment to NDA 020622/S-089 by October 10, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
09/30/2013

From:	Bradley, Nicole
To:	Ron.Carnal@tevapharm.com
Cc:	Bradley, Nicole
Subject:	NDA 020622/S-089 Information Request_August 12, 2013
Date:	Monday, August 12, 2013 2:32:28 PM

Hi Ron,

Reference is made to NDA 020622/S-089.

Please clarify if you are proposing revisions to the currently marketed Copaxone 20 mg/mL labels and labeling. If so, please submit all proposed labels and labeling for the currently marketed 20 mg/mL strength under supplement 089. Your submission should be accompanied by a document that outlines what changes you are proposing, along with your rationale for each change, for the labels and labeling for Copaxone 20 mg/mL.

Due to our review timelines, please provide a response by COB Wednesday, August 14, 2013.

Thank you,

Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/12/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Thursday, August 01, 2013 4:56 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_August 1, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following requests for information:

1. There appears to be a discrepancy between a narrative and the data found in the datasets of LB and ADLB for patient 301/592408. The narrative seems to imply that this is a case that met Hy's rule criteria. Please explain this discrepancy.

   Your narrative: 301/592408
   Severe toxic hepatitis was reported for subject #592408, a 46–year old male, resulting in termination from the study. Peak values were measured at month 1 with AST of 13.6xULN, ALT of 6.8xULN and total bilirubin of 5.2x ULN. At early termination visit, AST was within normal limits and ALT and bilirubin were slightly elevated, 1.19 X ULN and 1.86 X ULN, respectively.

2. Patient profiles are requested for several subjects.

   The following four patients that experienced AE due to liver injury:
   GA 9016 101605
   GA 9016 511013
   GA 301 592408
   GA 301 506012
   GA 9016 500204

   A profile should include all laboratory data and other results in single place. These profiles should include all the information recorded for that patient, including but not limited to:
   - Age
   - Sex
   - Dates of screening, randomization and starting therapy
   - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   - Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   - Prior medications and concomitant medications with dates of start and end
   - Vital signs and laboratories, sorted by date, with reference ranges *
   - Full reports for radiologic studies, MRI, and special studies with dates and reference ranges *

   * Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results. If it is known if these patients had work-up for their liver dysfunction please submit the results of such a work-up which might include hepatitis A, B, and C antibody screening, herpes simplex, varicella zoster serologies, CMV IgG, p-ANCA, and alpha-1 antitrypsin, actin, iron/ferritin, ceruloplasmin, tests of autoimmunity and AIH such as antinuclear

autoantibody (ANA), liver/kidney microsome (LKM) autoantibodies, smooth muscle autoantibodies (SM-as) anti-Ma antibodies (MAs) and history to include use of alcohol or other drugs that could induce liver injury.

For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted to IND.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

Please provide this information by August 9, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
08/01/2013

From:	Bradley, Nicole
To:	Ron.Carnal@tevapharm.com
Cc:	Bradley, Nicole
Subject:	NDA 020622/S-089 Information Request_July 25, 2013
Date:	Thursday, July 25, 2013 12:16:54 PM

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following information request:

In the pivotal trial (MS-GA-301, GALA), serum samples were collected from a subset of patients (approximately 400 per protocol) to measure anti-GA specific antibodies at different time points to see whether there was a difference in the kinetics of the antibodies and in the titer between the two treatment arms. You stated that "The results of this study will be presented in a separate report". Please clarify when these results will become available.

As such information is needed for our review, please submit it within next 2 weeks.

Thank you,
Nicole

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/s/

NICOLE L BRADLEY
07/25/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, July 22, 2013 4:08 PM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_July 22, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following requests for information:

1. Please perform an analysis of dropouts due to lack of efficacy for the ISS Double Blind and Open Label cohorts. This should also include a data listing including the unique subject identifier of all such cases with links to their narratives.

2. In your analysis of Adverse Events of special interest (as described in Post Text Table 1 in the ISS), is this search based on broad or narrow SMQ?

3. Please perform a query and analysis for the category "chest pain" for the two safety cohorts, Double Blind and Open Label. Please link to any narratives in Appendix 2 if reported as an SAE or Discontinuation already and provide a listing as you have done for other AEs of special interest in Appendix 4.2.

4. For the pivotal trial MS-GA-301 please perform an analysis of adverse events stratified by country similar to Table 20 in the CSR. Please also perform this analysis for Eastern Europe vs. ROW.

GA- MS-GA-301 n subjects		Placebo		GA 40 mg TIW	
		N subjects With AE	% Subjects	N subjects With AEs	% Subjects
Country	N subjects				
BGR					
CZE					
DEU					
EST					
GBR					
GEO					
HRV					
HUN					
ISR					
ITA					
LTU					
POL					
ROU					
RUS					
UKR					
ZAF					
Total # Subjects with AEs					
Total # Subjects					

GA- MS-GA-301 n subjects		Placebo		GA 40 mg TIW	
		N subjects With AE	% Subjects	N subjects With AEs	% Subjects
Region	N subjects				
Eastern Europe					
ROW					

5. Please submit a narrative for those cases of embolism/thrombosis which are not yet in Appendix 2 (see list below) and update the three narratives that have been submitted to include the following information if not previously provided.

   GA 9006-025-2518
   GA 9016-311-1-311105
   GA9016-321-2-321202
   GA9006-025-2518
   GA9016-322-4-322411
   GA9016-321-9-321902
   GA 301-3265-32650
   GA 301-5379-53790

   Narratives should include, but not be limited to:
   a. Age
   b. Sex
   c. Dates of screening, randomization, and start of therapy
   d. Whether the patient completed or did not complete the study, with dates and reason for termination
   e. Narrative evaluating the listed adverse event, as well as any related adverse events
   f. A list of other adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not, and action taken with drug)
   g. Whether the subject had a history of hypercoagulability, any risk factors for embolic or thrombotic disease, or other vascular risk factors
   h. Prior medications and concomitant medications with dates of start and end
   i. Full reports for radiologic studies or other studies used to evaluate the adverse event (with dates and reference ranges) *
   j. Whether the adverse event was preceded by prolonged immobility
   k. Whether the cause of the adverse event was assessed, and, if so, the likely cause according to the treating physician(s) and/or investigator
   l. Whether the subject received any treatment or corrective action

   * Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included. Available baseline study results should also be included.

Please provide this information by July 29, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD

Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
07/23/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 020622/S-089

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Teva Neuroscience, Inc
41 Moores Road
PO Box 4011
Frazer, PA 19355

Attention: Dennis Ahern
Senior Director, Regulatory Affairs

Dear Mr. Ahern:

Please refer to your supplemental New Drug Application (sNDA) dated March 28, 2013, received March 29, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 40 mg/mL.

We also refer to:

- Your correspondence dated March 28, 2013, and received March 29, 2013, requesting review of your proposed proprietary name, Copaxone (b) (4)
- Your Proprietary Name Amendment, dated and received on June 25, 2013, requesting that the modifier (b) (4) be removed from the name request and the name Copaxone alone be reviewed by DMEPA

We have completed our review of the proposed proprietary name, Copaxone, and have concluded that it is acceptable.

The proposed proprietary name, Copaxone, will be re-reviewed 90 days prior to the approval of the sNDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your March 29, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Nicole Bradley, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

ERMIAS ZERISLASSIE
06/27/2013

IRENE Z CHAN on behalf of CAROL A HOLQUIST
06/27/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, June 17, 2013 4:05 PM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_June 17, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following requests for information:

1. Provide the incubation conditions for the biological indicators used for (b) (4) at Kfar Saba and Runcorn. Include a description of the type of indicator that is used (b) (4)
2. Provide the following information on the media fill program at Kfar Saba.
   a. Clarify if the alert level for a media fill with (b) (4) units is (b) (4) units. We believe this to be a typo and refer you to Table D-1 in the process validation package.
   b. Provide a justification for (b) (4)
   c. Indicate which part(s) of the media fill batch (beginning, end, etc.) use water and which part use media for filling.
   d. Provide data to support the adequacy of water-filled syringes to detect potential microbial contamination. (b) (4) (b) (4)
   e. Provide the following information for the media fill results submitted: the number of units filled with water, the number of units filled with media, the number of water and media filled units rejected, and a reason for the rejection.
   f. Provide additional information on the positive unit recovered in (b) (4). What organism was recovered? Was the positive sample a filled unit (water or media) or a bioburden sample?
   g. Describe the retest procedures in (b) (4)
   h. Justify the use of a (b) (4).
3. Describe the growth promotion studies conducted for Runcorn media fills. Include the organisms used, the inoculum size, the incubation conditions, and acceptance criteria.

Please provide this information by EOB July 8, 2013.

Thanks,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
06/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE
Attn: Ermias Zerislassie

FROM:
Eric Bastings, Deputy Director
Billy Dunn, Team Leader
Jody Green, Clinical Reviewer
Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 30, 2013		20622	Efficacy supplement	March 28, 2013

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Copaxone	None	Multiple Sclerosis	December 6, 2013

NAME OF FIRM: Teva Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: OSE consult (except proprietary name reviews)

We have received a new efficacy supplement. DMEPA participation is requested for labeling. Reviewers have already been assigned.

NDA 020622/S-089 Copaxone (glatiramer acetate)

New Efficacy Supplement

- Supplement 89
- Includes CMC and Clinical data to support the proposed labeling changes for a new strength and dosing regimen - 40 mg/ml administered subcutaneously three times a week
- Note: The currently recommended dosing is 20 mg/ml administered subcutaneously once daily

Application Links:
Submission EDR link: \\Cdsesub1\evsprod\NDA020622\0083
Submission Global Submit link: \\Cdsesub1\evsprod\NDA020622\020622.enx

eRoom link (which includes sponsor proposed label):
http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0_16b0a

Key Dates based on 21st Century Review:
Receipt date: March 29, 2013
Day 60 (Filing Decision): May 28, 2013
Day 74 (Filing comments): June 11, 2013
Reviews due: December 6, 2013
PDUFA goal date: January 29, 2014

Thanks,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

The regulatory project manager is Nicole Bradley. Jody Green is the clinical reviewer.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

NICOLE L BRADLEY
05/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
May 30, 2013		NDA 020622/S-089	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Copaxone (b) (4) (glatiramer acetate injection)	Standard	Multiple Sclerosis	Approx. December 3, 2013

NAME OF FIRM:
Teva Pharmaceuticals USA

PDUFA Date: January 29, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:
\\Cdsesub1\evsprod\NDA020622\0083

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: May 14, 2013
Labeling planning meeting: August 27, 2013
Labeling Meetings: TBD
Wrap-Up Meeting: December 10, 2013

SIGNATURE OF REQUESTER
Nicole L. Bradley, PharmD 301-796-1930

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

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/s/

NICOLE L BRADLEY
05/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020622/S-089

FILING COMMUNICATION

Teva Pharmaceuticals USA
Attention: Dennis Ahern
Senior Director, Regulatory Affairs
41 Moores Road, PO BOX 4011
Frazer, PA 19355

Dear Mr. Ahern:

Please refer to your Supplemental New Drug Application (sNDA) dated March 28, 2013, received March 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Copaxone (glatiramer acetate injection).

This supplemental application proposes an additional dosage strength and regimen (40 mg/ml administered subcutaneously three times per week).

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is January 29, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 1, 2014.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The length of Highlights (HL) must be less than or equal to one-half page.

2. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

3. White space must be present before each major heading in HL.

4. The HL Limitation Statement, "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**," must be on the line immediately beneath the HL heading and **bolded**.

5. If Recent Major Changes are listed in HL, the corresponding new or modified text in the Full Prescribing Information sections or subsections must be marked with a vertical line on the left edge.

6. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

   "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

7. At the beginning of Section 17, you must reference any FDA-approved patient labeling using one of the following statements:
   - "See FDA-approved patient labeling (Medication Guide)"
   - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
   - "See FDA-approved patient labeling (Patient Information)"
   - "See FDA-approved patient labeling (Instructions for Use)"
   - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

We request that you resubmit labeling that addresses these issues by June 28, 2013. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a (b) (4) of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b) (4) request is denied and a pediatric drug development plan is required.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ERIC P BASTINGS
05/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Nicole L. Bradley, PharmD, Regulatory Project Manager

Division of Neurology Products

REQUEST DATE:

May 8, 2013

NDA/BLA NO.:

NDA 020622/S-089

TYPE OF DOCUMENTS: See below

(PLEASE CHECK OFF BELOW)

NAME OF DRUG:

Copaxone (glatiramer acetate)

PRIORITY CONSIDERATION:

Standard

CLASSIFICATION OF DRUG:

Multiple Sclerosis

DESIRED COMPLETION DATE

(Generally 2 Weeks after receiving substantially complete labeling)

Approx. November 6, 2013

SPONSOR:

Teva

PDUFA Date: January 29, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

☒ PATIENT PACKAGE INSERT (PPI)

☒ MEDICATION GUIDE

☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

☐ ORIGINAL NDA/BLA

☒ EFFICACY SUPPLEMENT

☐ SAFETY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ MANUFACTURING (CMC) SUPPLEMENT

☐ PLR CONVERSION

REASON FOR LABELING CONSULT

☐ INITIAL PROPOSED LABELING

☒ LABELING REVISION

NDA 020622/S-089 Copaxone (glatiramer acetate)

New Efficacy Supplement

- Includes CMC and Clinical data to support the proposed labeling changes for a new strength and dosing regimen - 40 mg/ml administered subcutaneously three times a week
- Note: The currently recommended dosing is 20 mg/ml administered subcutaneously once daily
- Applicant: Teva
- Cover letter

Application Links:

Submission EDR link: \\Cdsesub1\evsprod\NDA020622\0083

Submission Global Submit link: \\Cdsesub1\evsprod\NDA020622\020622.enx

eRoom link (which includes sponsor proposed label):
http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0_16b0a

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: A substantially complete labeling will be provided to DMPP.

Filing/Planning Meeting: May 14, 2013

Mid-Cycle Meeting: August 13, 2013

Labeling Meetings: TBD

Wrap-Up Meeting: December 10, 2013

SIGNATURE OF REQUESTER
Nicole L. Bradley, PharmD 301-796-1930

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL (BLAs Only) ☐ DARRTS

Version: 12/9/2011

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/s/

NICOLE L BRADLEY
05/08/2013

From:	Bradley, Nicole
To:	Ron Carnal
Cc:	Bradley, Nicole
Subject:	NDA 020622/S-089 Information Request_May 8, 2013
Date:	Wednesday, May 08, 2013 4:02:41 PM

Hi Ron,

Reference is made to NDA 020622/S-089.

Some of your datasets included in your submission require clarification. In order to confirm data in the individual trials we are reviewing the datasets for the three trials provided in section 5.3.5.1

Trial GA 9006 and Trial 9016

Both trials independently have 3 associated datasets. For these datasets the SDTM data was converted from original data. One dataset is the analysis Legacy dataset. There are also two datasets that appear to be the data tabulation datasets entitled Legacy tabulation dataset and data listing data. There appears to be some redundancy between the Legacy data tabulation and the data listing data; both used SDTM variables. Please explain the difference between these datasets and in particular the utility of the data listing data.

Trial MS-GA-301

The data tabulation legacy dataset and the analysis dataset legacy are both labeled MS-GA-301 (used to confirm efficacy and safety of this trial). In order to confirm data in the ISE/ISS provided in section 5.3.5.3 we expect that all data would be provided in analysis data sets since the data came from three trials. Since you additionally provided data tabulation dataset Legacy (which is also labeled MS-GA-301) for the ISE/ISS we are unsure about the utility of this dataset since the data set in 5.3.5.3 has the same name and is similar to but not identical to that in section 5.3.5.1. Please clarify which of the two datasets labeled MS-GA-301 in section 5.3.5.1 and in section 5.3.5.3 is to be used to confirm safety and efficacy for study MS-GA-301, what the utility of the other dataset is, and the differences between the two datasets.

Please provide this information no later than Friday May 10, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
05/08/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Friday, May 03, 2013 2:30 PM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_May 3, 2013

Importance: High

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following requests for information:

1. Clarification is needed regarding a reviewer's guide for the ISS/ISE. We cannot find one labeled as such, but there are two MS-GA-301 reviewer's guides which are different. Please let us know if one of these is the ISS/ISE reviewer's guide, but with the wrong title, or, if it was inadvertently not submitted, please submit it.

2. In order to verify and perform analyses please submit a modified set of datasets. You used an EPOCH variable in some datasets (i.e., SE, DS, TA) but not in others where it would be very helpful to have the EPOCH variable present. Please resubmit the AE, CM, VS, and LB datasets with the EPOCH variable (Double-blind treatment) for the MS-301 GALA trial and for the GA-9016 trial.

3. For the ISS/ISE ADAM and GALA ADAM datasets, please add a treatment emergent flag to the ADAE and ADLB datasets to allow determination of events that occurred on or off treatment.

4. In addition to the SAS programs that were provided and used for each of the tables, please provide the step-by-step algorithms (including the variables and values) that were used for the ISS datasets to populate all of the tables in the ISS. For example, for the SAE Incidence Table for the double-blind study pool by treatment arm, an algorithm should be similar to the following:

1) To subset the database to the Safety Population, use the DM dataset with _____=Y.
2) To subset to the adverse events occurring in the double-blind portions of the trials, use the __ dataset and the following variables ___.
3) To subset to only the treatment emergent adverse events, use the ___dataset and the following variables ___.
4) To subset the TEAEs to serious adverse events, use the AE dataset with AESER=Y.
5) For the rows, use the AE dataset variables "Body System or Organ Class" and "Dictionary-Derived Term."
6) For the columns, use the AE dataset variable "Actual Treatment Arm."

Please provide this information no later than close of business May 10, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
05/03/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Tuesday, April 23, 2013 6:38 PM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_April 23, 2013

Hi Ron,

Reference is made to NDA 020622/S-089. We have the following information request:

Please provide financial disclosures for the studies contributing to your safety database, namely studies GA-9016 and GA09006 or let us know where in the NDA this can be located. In section 1.3.4, we currently see only disclosures for those who participated in study MS-GA-301.

Please provide these disclosures no later than May 5.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
04/23/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, April 17, 2013 2:52 PM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 20622/S-089 Information Request_April 17, 2013

Hi Ron,

Reference is made to NDA 20622/S-089. We have the following information request:

Submit the dataset for the GALA study that provides a complete history of relapses for each patient during the study in order to verify the data as well as to perform analyses. The dataset should have a single line listing for each patient without relapses and multiple line listing per patient for patients with relapses, with each line representing a record of a relapse or censoring. The dataset needs to include the following variables, in addition to the variables currently available: date of relapse, confirmed relapse flag, time in days to 1st confirmed relapse, censoring indicator (had confirmed relapse or censored), cumulative number of confirmed relapse, cumulative number of all relapse, flag for alternative medication during the double-blind period, time in days to alternative medication, age, gender, race, and site. Some variables, such as PARAM and PARAMCD are no longer needed as they could be derived from other variables. You may choose to modify the current dataset ADCE or to create a separate dataset for review purposes.

Please provide your response by April 23, 2013.

Thank you,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
04/17/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Wednesday, April 03, 2013 10:17 AM
To: Ron Carnal
Cc: Bradley, Nicole
Subject: NDA 020622/S-089 Information Request_April 3, 2013

Hi Ron,

Reference is made to NDA 020622/S-089, submitted on March 29, 2013. We note in your submission (Section 1.9.1) a request (b) (4) of pediatric studies which includes reference to a submission dated April 25, 2008, submitted under IND 027998. The reference of a submission to support a request (b) (4) is inadequate. You will need to provide a formal submission, as an amendment to the supplement, that includes a justification/evidence for requesting a (b) (4) For further information on how to prepare the submission, please refer to the Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07956.pdf

Please provide your response by EOB April 23, 2013.

Thanks,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Office: 301-796-1930
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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/s/

NICOLE L BRADLEY
04/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 020622/S-0089

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Teva Pharmaceuticals USA
Attention: Dennis Ahern
Senior Director, Regulatory Affairs
41 Moores Road, PO BOX 4011
Frazer, PA 19355

Dear Mr. Ahern:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 020622

SUPPLEMENT NUMBER: 0089

PRODUCT NAME: Copaxone (glatiramer acetate injection)

DATE OF SUBMISSION: March 29, 2013

DATE OF RECEIPT: March 29, 2013

This supplemental application proposes the following changes: new dosage strength and regimen (40 mg/ml administered subcutaneously three times per week).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 28, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NICOLE L BRADLEY
04/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**Pediatric and Maternal Health Staff Request for Consultation**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☒ Maternal Health ☐ Both ☐			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Eric Bastings, MD, Deputy Director Billy Dunn, MD, Team Leader Jody Green MD, Clinical Reviewer Division of Neurology Products	
DATE 03/29/2013	IND NO.	NDA/BLA NO. 020622/S-0089	TYPE OF DOCUMENT Efficacy Supplement (new dosing regimen)	DATE OF DOCUMENT March 29, 2013
NAME OF DRUG Copaxone (glatiramer acetate)	NAME OF FIRM Teva		CLASSIFICATION OF DRUG Multiple Sclerosis	PDUFA Goal Date January 29, 2014
Requested Consult Completion Date: December 6, 2013	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☒ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☒ PeRC Preparation Assistance ☐ Other (please explain):	☐ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): **Application Links:** Submission EDR link: \\Cdsesub1\evsprod\NDA020622\0083 Submission Global Submit link: \\Cdsesub1\evsprod\NDA020622\020622.enx eRoom link (which includes sponsor proposed label): http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0_16b0a	Materials to be reviewed: Pediatric waiver submitted by applicant

1. Please briefly describe the submission including drug's indication(s):

NDA 020622/S-089 Copaxone (glatiramer acetate)

New Efficacy Supplement

- Includes CMC and Clinical data to support the proposed labeling changes for a new strength and dosing regimen - 40 mg/ml administered subcutaneously three times a week
- Note: The currently recommended dosing is 20 mg/ml administered subcutaneously once daily
- Applicant: Teva

2. Describe in detail the reason for your consult. Include specific questions:
This efficacy supplement triggers PREA. The applicant includes a request for pediatric waiver.

3. Meeting dates:
TBD

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

N/A	
Review team: Project Manager: Nicole Bradley Clinical reviewer & Team Leader: Jody Green, MD, Clinical Reviewer, Billy Dunn, Team Leader, Eric Bastings, MD Deputy Director Pharmacology/Toxicology reviewer & Team Leader: Rick Houghtling, PhD, reviewer, Lois Freed, PhD, Supervisor Clinical Pharmacology reviewer & Team Leader: Xinning Yang, PhD and Angela Men, PhD	
PRINTED NAME or SIGNATURE OF REQUESTOR:	METHOD OF DELIVERY (Please check) ☐ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 06/01/2011

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/s/

NICOLE L BRADLEY
03/29/2013

Bradley, Nicole

From: Bradley, Nicole
Sent: Monday, December 23, 2013 12:08 PM
To: Ron.Carnal@tevapharm.com
Cc: Bradley, Nicole
Subject: NDA 020622

Hi Ron,

Reference is made to NDA 020622 and to your December 18, 2013, response to the Agency's December 9, 2013, information request. We have the following comments:

As stated in, "Guidance for Industry - Assay Development for Immunogenicity Testing of Therapeutic Proteins (2009)":

> *"for products that induce allergic responses, assays that can specifically measure IgE may be important for helping predict and prepare for anaphylactic reaction in the clinic."*

The Copaxone labeling states that drug hypersensitivity occurs, and therefore, on a risk basis, IgE evaluation may be important. However, you have been unable to develop an IgE positive control, so it is not possible to evaluate the significance of the IgE results. You may wish to consider alternative methods for the development of an IgE positive control. Alternatively, you may wish to consider the use of skin testing (refer to Guidance for Industry, Immunogenicity Assessment for Protein Therapeutic Product (2013)).

The IgG assay needs to have a control for sensitivity. Without a sensitivity evaluation, it is very difficult to assess the levels of patient antibody responses. In addition, since there is substantial immunological disturbance in MS patients, we recommend that you confirm the cut-point and the matrix interference using sera from MS treatment-naïve patients, which may give different responses than normal sera.

Thanks,
Nicole

Nicole L. Bradley, PharmD
Regulatory Project Manager
Division of Neurology Products

Office: 301-796-1930
Mobile: 240-506-7286
Fax: 301-796-9842
Email: nicole.bradley@fda.hhs.gov

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NICOLE L BRADLEY
12/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 027998

MEETING MINUTES

TEVA Branded Pharmaceutical Products R&D
Attention: Ronald J. Carnal
Manager, US Regulatory Affairs
41 Moores Road, PO Box 4011
Frazer, PA 19355-1113

Dear Mr. Carnal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Copaxone (glatiramer acetate) injection.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2012. The purpose of the meeting was to discuss the adequacy of the completed development program (MS-GA-301-GALA) for the new dosing regimen and formulation of Copaxone 40 mg/mL administered three times a week subcutaneously.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	October 31, 2012, at 10:00 AM EST
Meeting Location:	FDA White Oak Campus, Building 22, Room 1311
Application Number:	IND 027998
Product Name:	Copaxone (glatiramer acetate)
Indication:	Multiple Sclerosis
Sponsor/Applicant Name:	TEVA Branded Pharmaceutical Products R&D
Meeting Chair:	Russell G. Katz, MD
Meeting Recorder:	Nicole L. Bradley, PharmD

FDA ATTENDEES

Division of Neurology Products
Russell Katz MD, Director
Eric Bastings, MD, Deputy Director
Billy Dunn, MD, Clinical Team Leader
Jody Green, MD, Clinical Reviewer
Hamet Touré, PharmD, Regulatory Project Manager
Nicole Bradley, PharmD, Regulatory Project Manager
Neda Aghajani Memar, PharmD, Visiting Fellow
Betsy Kurian, Visiting Pharmacy Student

Division of New Drug Quality Assessment I
Martha Heimann, PhD, CMC Team Leader
Kavita Vyas, PhD, CMC Reviewer

Division of Clinical Pharmacology I
Xinning Yang, PhD, Clinical Pharmacology Reviewer

Division of Biometrics I
Kun Jin, PhD, Biostatistics Team Leader
Sharon Yan, PhD, Biostatistics Reviewer

Division of New Drug Microbiology
Jessica Cole, PhD, Senior Regulatory Reviewer

SPONSOR ATTENDEES

TEVA Branded Pharmaceutical Products R&D
Ron Carnal, CNS US Regulatory Leader, Regulatory Affairs
Levana Volovsky, MS, CNS Global Regulatory Leader, Regulatory Affairs
Dennis Ahern, MS, Head CNS Therapeutic Area, Regulatory Affairs
Jon Isaacsohn, MD, Chief Medical Officer
Dan Bar-Zohar, MD, Head CNS Therapeutic Area, Clinical Development
Abi Vainstein, MD, Clinical Leader, CNS & Pain Therapeutic Area
Nissim Sasson, MA, Lead Biostatistician
Youyi Shu, PhD, Director of Biostatistics
Rivka Schwartz, PhD, Project Leader, Global Branded Products
Muhammad Safadi, PhD , Director of Formulation Development
Valerie Mulligan, Senior Director, Regulatory Affairs CMC
Veronique Bellaiche, PhD, Director, Regulatory Affairs CMC
Batya Zak, MA, Medical Writing

1. BACKGROUND

TEVA Branded Pharmaceutical Products R&D submitted an IND meeting request to the Division of Neurology for Copaxone (glatiramer acetate) on July 25, 2012. The meeting request was granted by the Division on August 10, 2012. The purpose of the meeting was to discuss the adequacy of the completed development program (MS-GA-301-GALA) for the proposed dosing regimen and formulation of Copaxone 40 mg/mL administered three times a week subcutaneously. We note Copaxone is currently approved for 20 mg/mL administered once a day subcutaneously

The official meeting minutes are provided below, in the following format:

- FDA's preliminary responses, dated October 30, 2012, denoted in black **bold** font
- Meeting discussion, denoted in black *italic* font

2. DISCUSSION

Question 1:
Teva proposes to submit an application for a new dosing strength and regimen for GA (40 mg/ml TIW). Does FDA consider the GALA clinical study (providing efficacy and safety evidence), supported by additional safety information from GA/9006 and GA/9016 (FORTE) studies, and cross-referencing the non-clinical and other clinical data for Copaxone® (NDA 20-622), provides a sufficient basis to warrant acceptance and review of the application from a nonclinical and clinical perspective?

FDA Preliminary Response to Question 1:

Nonclinical
Based on the available information, cross-referencing the nonclinical data for NDA 20-622 will be sufficient.

Clinical

1. **We are concerned that the SAP was apparently amended (March 22, 2012) after database lock (June 4, 2011). Please clarify whether this was the case.**
2. **On face, the GALA study appears sufficient to support filing and review of a sNDA for the new dosing strength and regimen for GA, but the adequacy of the data will be a matter of review.**
3. **Please provide descriptive efficacy data from the FORTE study. Please note we do not consider these data as contributory to establishing the efficacy of GA 40 mg/mL administered three times a week (TIW).**
4. **Pertaining to the safety data you intend to present, please clarify the extent of exposure with GA 40 mg/ml dosed daily vs. TIW.**
5. **We do not agree with your plans for presenting in your integrated summary of safety a pooled analysis of GA 40 mg, regardless of dosing frequency, as we think**

that analysis would not be interpretable. Instead, separate analyses should be provided for GA 40 mg TIW, GA 40 mg daily, and GA 20 mg daily.

Meeting Discussion:
The sponsor clarified that the date of database lock was actually June 4, 2012. The sponsor agreed to the safety pools for analysis that FDA suggested and intends to email a copy of the shells for use in the ISS pooling prior to submitting the sNDA. FDA will make an effort to briefly review the shells prior to submission.

Question 2:
Does the Agency agree that the pharmaceutical data on the new formulation will be sufficient if fully described in Modules 3.2.P, 3.2.A, 3.2.R and 2.3.P, 2.3.A, 2.3.R, and cross-referencing to the Drug Substance data of Copaxone® NDA 20-622 (GA 20 mg/ml injection, pre-filled syringe)? Note that the drug substance used for the 40 mg/ml formulation is identical to that used for the current 20 mg/ml formulation.

FDA Preliminary Response to Question 2:
Yes.

Meeting Discussion:
None.

Question 3:
A change to the manufacturing process is proposed (b) (4) (b) (4). Does the Agency agree that release results and (b) (4) (b) (4) stability data (at both long-term and accelerated conditions), demonstrating product comparability of production batches produced with the (b) (4) (b) (4) and with the (b) (4) (used for manufacturing of clinical batches), as well as extensive supportive stability data for batches (b) (4) provide a sufficient basis to warrant acceptance and review of the application?

FDA Preliminary Response to Question 3:
Yes, the amount of data proposed is sufficient to file the application. The adequacy of the data will be determined during the review cycle. Please be advised that we may be unable to review any data submitted after mid-cycle.

Meeting Discussion:
None.

Question 4:

An outline of the format and content of the planned submission is provided in section 10.4. Teva plans to submit draft labeling that is inclusive of both the 20 mg and 40 mg strengths. Does FDA find the proposed format and content of the submission and the inclusive labeling acceptable?

FDA Preliminary Response to Question 4:
Labeling content is a review issue. In principle we agree with the inclusion of both the 20 mg/ml and the 40 mg/ml doses in labeling. Please confirm that there will be a 120-Day Safety Update Report for the GALA study.

Table of Contents

- **Please provide Module 1 with your cover letter and if possible, a detailed hyperlinked reviewer's guide which should reside in section 1.2, under the cover letter.**
- **Please use descriptive leaf titles which are short, meaningful, and indicative of the document's content.**
- **Please ensure you provide sufficient navigation (bookmarks, hyperlinks, TOCs) as well as descriptive leaf titles in the index.xml and stf.xml files. The submission**
  needs to comply with FDA and ICH specifications. For example, the tabular listing in module 5.2 and module 2.7.6 should be linked to the referenced studies.
- **To insure proper lifecycle management, eCTD section 2.3 can be submitted in granular format.**
- **Please include a copy of each clinical study protocol as well as each amended protocol.**
- **Please include in your submission an index listing all submitted narratives with links to the narratives.**

Project Management

- **At the time of your NDA submission, please submit a table listing all investigators by country. Please provide in this table the address and contact information for each investigator, the investigator's number, center number, study ID, as well as the number of subjects at each center.**

Dataset issues

- **Each SAS transport file should have a unique patient identifier.**
- **The primary dataset that describes the number of confirmed relapses should also contain a variable of "all relapses". In addition this dataset needs to contain baseline demographic information so that it can be easily merged with other datasets.**
- **Optimize the size of datasets to avoid excessively large data files.**
- **Structure adverse event datasets to include one record per subject per adverse event.**

- **Include accurate, complete, and usable data definitions in a single data definition document. For categorical variables, list the categories within the data definition document.**
- **For each of the study pools, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.**

Safety

Adverse Events

- **Summary of adverse events should either be included in the Integrated Summary of Safety or should be easy to obtain through a linked document. Please ensure that large tables and narratives that are in section 5.3.5.3 are linked to relevant portions of 2.7.4.**
- **The dataset ADAE should be structured as one record/patient/adverse event.**
- **You must provide an analysis of all Serious Adverse Events by SOC and include a discussion of these events.**
- **Please make sure that a coding dictionary with a list of investigator verbatim terms and the preferred terms to which they were matched is submitted as an SAS transport file.**
- **Please make sure that all AEs are presented (and not just those deemed "drug-related").**
- **Please prepare a table of the line listing of all reported treatment emergent AEs, regardless of cause, for all subjects participating in the three trials. The line listing should include trial number, center number, unique subject identifier, age, sex, dose, duration of exposure in days at time of event onset, MedDRA SOC, MedDRA preferred term, MedDRA verbatim term of the adverse event and an indication of whether or not the event met the definition for serious, and where or not it led to withdrawal from study drug.**
- **MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths.**
- **Treatment emergent SAEs and treatment discontinuations should also have a similar line listing.**
- **If an AE listing had a death outcome, it should include the trial number, center number, unique subject identifier, age, sex, dose and duration of exposure in days at time of death.**
- **Line listings should be hyperlinked to the CRFs and narratives.**
- **In addition, deaths, discontinuations and SAE should be linked to a narrative as highlighted below.**
- **All outlier data should have the normative values clearly indicated as well as the thresholds for analysis of outliers. This should include laboratory data, vital signs data and ECG data.**

Narratives

Please provide narrative summaries for deaths, discontinuations, and SAEs using a common template that is easy to review. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following items should be included:

- **Patient age and gender**
- **Signs and symptoms related to the adverse event being discussed**
- **An assessment of the relationship of exposure duration to the development of the adverse event**
- **Pertinent medical history**
- **Concomitant medications with start dates relative to the adverse event**
- **Pertinent physical exam findings**
- **Pertinent test results (e.g., lab data, ECG data, biopsy data)**
- **Discussion of the diagnosis as supported by available clinical data**
- **For events without a definitive diagnosis, a list of the differential diagnoses**
- **Treatment provided**
- **Re-challenge results (if performed)**
- **Outcomes and follow-up information**

If more than one event is contained in a single narrative, there should be a line listing at a minimum for each event. It is preferable, however, especially if events in an individual are separated by 6 months or more, to have separate narratives.

Discontinuations
Please provide both narratives and CRFs for all discontinuations including:

- **SAE**
- **Lost to follow-up**
- **Other**
- **Physician decision**
- **Patient decision**

Please define "premature termination," "dropouts," and "discontinuation" if these terms are used in the context of your NDA.

Pregnancy: **please include a narrative that includes the outcome of the pregnancy, including the reasons for termination if this occurred.**

Incidence data
In safety tables that contain incidence data please describe clearly what is being counted (i.e., # of patients who have an event or # of events.)

Please provide a table of treatment-emergent adverse events and a table of treatment-emergent SAEs reported in ≥ 1% of all Copaxone 40 mg/ml treated

subjects sorted by SOC and MEDRA Preferred Term. This should include separate columns for placebo, for Copaxone 40 mg TIW, and Copaxone 40 mg daily.

Laboratory measurements

- **When available, we request that you use the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for shift tables documenting changes in laboratory values from baseline. Accessed at: (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)**
- **We request that you clearly list the laboratory criteria used for each toxicity grade within the analysis tables.**
- **Any clinically significant laboratory abnormality found in one or more patients should be discussed. Specifically narratives and patient files for any patients with treatment-emergent CTCAE Grade 3 or 4 abnormalities in clinical chemistry assessments should be provided.**

Proposed list of adverse events of special interest

In addition to a complete analysis of AEs, SAEs, discontinuations, death, injection site reactions and IPIRS (Immediate post-injection reactions) please also evaluate the following list of special interest:

- **Lipoatrophy**
- **Hypersensitivity/anaphylaxis**
- **Thrombocytopenia**
- **Hepatitis, liver injury**
- **Breast cancer**
- **Embolic and thrombotic events**

Meeting Discussion:
None.

3. ADDITIONAL PRELIMINARY COMMENTS

Microbiology

1. **The submission should contain (b) (4) validation studies to support adequate sterilization of the 40 mg/mL drug product under the proposed commercial (b) (4) parameters.**
2. **The sterility test verification studies should support the increased drug product concentration.**
3. **(b) (4) validation studies (media fills) may not be needed depending on the validated hold times, filling line, line speeds, etc. If no additional media fills will be conducted to support the 40 mg/mL presentation please provide a justification for not conducting these studies. If media fills are conducted please provide a detailed description of the process with acceptance criteria, number of units filled, number of units rejected, number of units incubated, and number of positive units.**

Meeting Discussion:
None.

Statistics

4. **Please include all relapses (confirmed and unconfirmed) in the relapse dataset and present the analysis of all relapse (using the same model for the confirmed relapse) in the study report.**

Meeting Discussion:
FDA requested that the sponsor present the variables in the define document in the same manner as in Table 1 of the SAP. The sponsor agreed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
12/03/2012