CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020622Orig1s119

Trade Name:	COPAXONE
Generic or Proper Name:	glatiramer acetate
Sponsor:	Teva Pharmaceuticals USA
Approval Date:	January 22, 2025
Indication:	For the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

020622Orig1s119

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 020622/S-118
NDA 020622/S-119

SUPPLEMENT APPROVAL

Teva Pharmaceuticals USA
Attention: Angela Randall
Director, Regulatory Affairs Labeling, Branded Products
145 Brandywine Parkway
West Chester, PA 19380

Dear Angela Randall:

Please refer to your supplemental new drug applications (sNDAs) dated and received July 22, 2024, and August 28, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Copaxone (glatiramer acetate injection), for subcutaneous use, 20 mg/mL and 40 mg/mL prefilled syringe.

Prior Approval sNDA 118 provides for revisions to Section 8.1 (Pregnancy) of the Prescribing Information (PI) and to the patient labeling pertaining to available data in pregnant women.

Prior Approval sNDA 119 provides for revisions to the PI to include a new Boxed Warning and an associated Warnings and Precautions subsection (5.1), as well as revisions to Section 6.2 (Postmarketing Experience), Section 17 (Patient Counseling Information), and patient labeling, to reflect the risk of anaphylaxis. The Patient Package Insert was also converted to a Medication Guide.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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)] in Microsoft Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes. To facilitate review of your submission(s), 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, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton labeling submitted on January 8, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 020622/S-119**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because none of these criteria apply to your supplemental applications, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in these supplements, including any new safety-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Kristen Haslam, Senior Regulatory Project Manager, by email at kristen.haslam@fda.hhs.gov or by phone at (240) 402-4246.

Sincerely,

{See appended electronic signature page}

Alice T.D. Hughes, MD
Deputy Director for Safety
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALICE HUGHES
01/22/2025 09:49:01 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020622Orig1s119

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

WARNING: ANAPHYLACTIC REACTIONS

See full prescribing information for complete boxed warning.

Life-threatening and fatal anaphylaxis, which can occur at any time following initiation of therapy (from as early as after the first dose, up to years after initiation of treatment), has been reported in patients receiving COPAXONE.

- **Make patients aware of the symptoms of anaphylaxis, which may overlap with those of an immediate post-injection reaction. Prompt identification of anaphylaxis is important to avoid a delay in treatment (5.1).**
- **COPAXONE is contraindicated in patients with a history of hypersensitivity reactions to COPAXONE, including anaphylaxis (4).**

RECENT MAJOR CHANGES

Boxed Warning	1/2025
Contraindications (4)	1/2025
Warnings and Precautions (5.1, 5.2, 5.5)	1/2025

INDICATIONS AND USAGE

COPAXONE is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (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, tachycardia, anxiety, dyspnea, throat constriction, and/or urticaria), may occur within seconds to minutes after injection and are generally transient and self-limiting (5.2)
- Chest pain, usually transient (5.3)
- Lipoatrophy and skin necrosis may occur. Instruct patients in proper injection technique and to rotate injection sites (5.4)
- COPAXONE can modify immune response (5.5)
- Hepatic Injury: if signs or symptoms of hepatic dysfunction occur, consider discontinuing COPAXONE (5.6)
- Glatiramer Acetate Products and Administration Errors: Using an optional autoinjector that is not compatible for use with TEVA's COPAXONE may increase the risk for medication errors, such as dose omission or administration of a partial dose. (5.7)

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 Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

WARNING: ANAPHYLACTIC REACTIONS

Cases of life-threatening and fatal anaphylaxis have been reported with COPAXONE. Anaphylaxis can occur at any time following initiation of therapy, from as early as after the first dose, up to years following initiation of therapy.

- **Make patients aware of the symptoms of anaphylaxis, which may overlap with those of an immediate post-injection reaction; instruct them to seek immediate medical care should these symptoms occur. Prompt identification of anaphylaxis is important to avoid a delay in treatment *[see Warnings and Precautions (5.1)]*.**
- **COPAXONE is contraindicated in patients with a history of hypersensitivity reactions to COPAXONE, including anaphylaxis. If an anaphylactic reaction occurs, treatment with COPAXONE must be immediately discontinued. Unless a clear alternative etiology is identified, COPAXONE must be permanently discontinued *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

COPAXONE is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

COPAXONE is for subcutaneous use only *[see Dosage and Administration (2.2)]*. 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.

Using an autoinjector that is not compatible for use with TEVA's COPAXONE may increase the risk for medication errors, such as dose omission or administration of a partial dose *[see Warnings and Precautions (5.7)]*.

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. Reactions have included anaphylaxis *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactic Reactions

Life-threatening and fatal anaphylaxis has been reported with COPAXONE *[see Adverse Reactions (6.2)]*. COPAXONE is contraindicated in patients with a history of hypersensitivity reactions to COPAXONE, including anaphylaxis *[see Contraindications (4)]*. Anaphylaxis can occur at any time following initiation of COPAXONE therapy, from as early as after the first dose, up to years after initiation of treatment. Anaphylaxis occurred within an hour of a COPAXONE injection in most of the reported cases.

Some signs and symptoms of anaphylactic reactions may overlap with those of immediate post-injection reactions *[see Warnings and Precautions (5.2)]*. All patients receiving treatment with COPAXONE and caregivers should be informed about the signs and symptoms of anaphylactic reactions, and that they must seek immediate emergency medical care in case of experiencing such symptoms. If an anaphylactic reaction occurs, treatment with COPAXONE must be immediately discontinued. Unless a clear alternative etiology is identified, COPAXONE must be permanently discontinued *[see Contraindications (4)]*.

5.2 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 that may occur immediately (within seconds to minutes, with the majority of symptoms observed within 1 hour) after injection and included at least two of the following: flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria. These events are termed immediate post-injection reactions.

The symptoms of an immediate post-injection reaction may overlap with those of anaphylaxis; prompt identification of anaphylaxis is important to avoid a delay in treatment. In general, symptoms of an immediate post-injection reaction have 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 developed fatal anaphylaxis and/or 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.

5.3 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.

5.4 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 postmarketing 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.

5.5 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 has been reported with COPAXONE *[see Warnings and Precautions (5.1)]*.

5.6 Hepatic Injury

Cases of hepatic injury, some severe, including liver failure and hepatitis with jaundice, have been reported with COPAXONE. Hepatic injury has occurred from days to years after initiating treatment with COPAXONE. If signs or symptoms of liver dysfunction occur, consider discontinuation of COPAXONE.

5.7 Glatiramer Acetate Products and Administration Errors

Medication errors have occurred when glatiramer acetate products are administered with incompatible autoinjectors. Some glatiramer acetate products can be administered by an optional compatible autoinjector, should one be available; however, not all glatiramer acetate products have a marketed optional compatible autoinjector for administration *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*.

Using an optional autoinjector that is not compatible for use with TEVA’s COPAXONE may increase the risk for medication errors, such as dose omission or administration of a partial dose.

If using an optional autoinjector for administration, ensure the device is compatible for use with the specific glatiramer acetate product by referring to the autoinjector labeling. The availability of compatible autoinjectors for each glatiramer acetate product may change with time.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Anaphylactic Reactions *[see Warnings and Precautions (5.1)]*
- Immediate Post-Injection Reaction *[see Warnings and Precautions (5.2)]*
- Chest Pain *[see Warnings and Precautions (5.3)]*
- Lipoatrophy and Skin Necrosis *[see Warnings and Precautions (5.4)]*
- Potential Effects on Immune Response *[see Warnings and Precautions (5.5)]*
- Hepatic Injury *[see Warnings and Precautions (5.6)]*

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 practice.

Incidence in Controlled Clinical Trials

COPAXONE 20 mg per mL per day

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 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
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), breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

COPAXONE 40 mg per mL three times per week

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 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 reactions have been identified during postapproval use of COPAXONE. 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.

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

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

Hepatobiliary Disorders: cholelithiasis; liver function abnormality; cirrhosis of the liver; hepatitis; hepatic injury *[see Warnings and Precautions (5.6)]*

Immune System Disorders: hypersensitivity reactions (including anaphylactic reactions) *[see Boxed Warning and Warnings and Precautions (5.1)]*.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from pharmacovigilance and published observational studies over decades of use with glatiramer acetate during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes *(see Data)*. Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on embryofetal or offspring development *(*see *Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Data from pharmacovigilance and published observational studies have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes when glatiramer acetate was used during pregnancy. However, the published comparative observational studies have methodological limitations, such as short exposure duration during pregnancy, confounding, selection bias, and exposure misclassification.

Animal Data

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryofetal 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 Lactation

Risk Summary

There are no data on the presence of glatiramer acetate in human milk. Based on the low systemic exposure because of substantial local hydrolysis of glatiramer acetate following subcutaneous administration, breastfeeding is not expected to result in clinically relevant exposure of the infant to the drug *[see Clinical Pharmacology (12.3)]*. There are no data on the effects of glatiramer acetate on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COPAXONE and any potential adverse effects on the breastfed infant from COPAXONE or from the underlying maternal condition.

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:

$$(\text{Glu, Ala, Lys, Tyr})_x \bullet x\text{CH}_3\text{COOH}$$

$$(\text{C}_5\text{H}_9\text{NO}_4 \bullet \text{C}_3\text{H}_7\text{NO}_2 \bullet \text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \bullet \text{C}_9\text{H}_{11}\text{NO}_3)_x \bullet x\text{C}_2\text{H}_4\text{O}_2$$

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 (5.5)]*.

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

Carcinogenesis

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.

Mutagenesis

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.

Impairment of Fertility

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 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

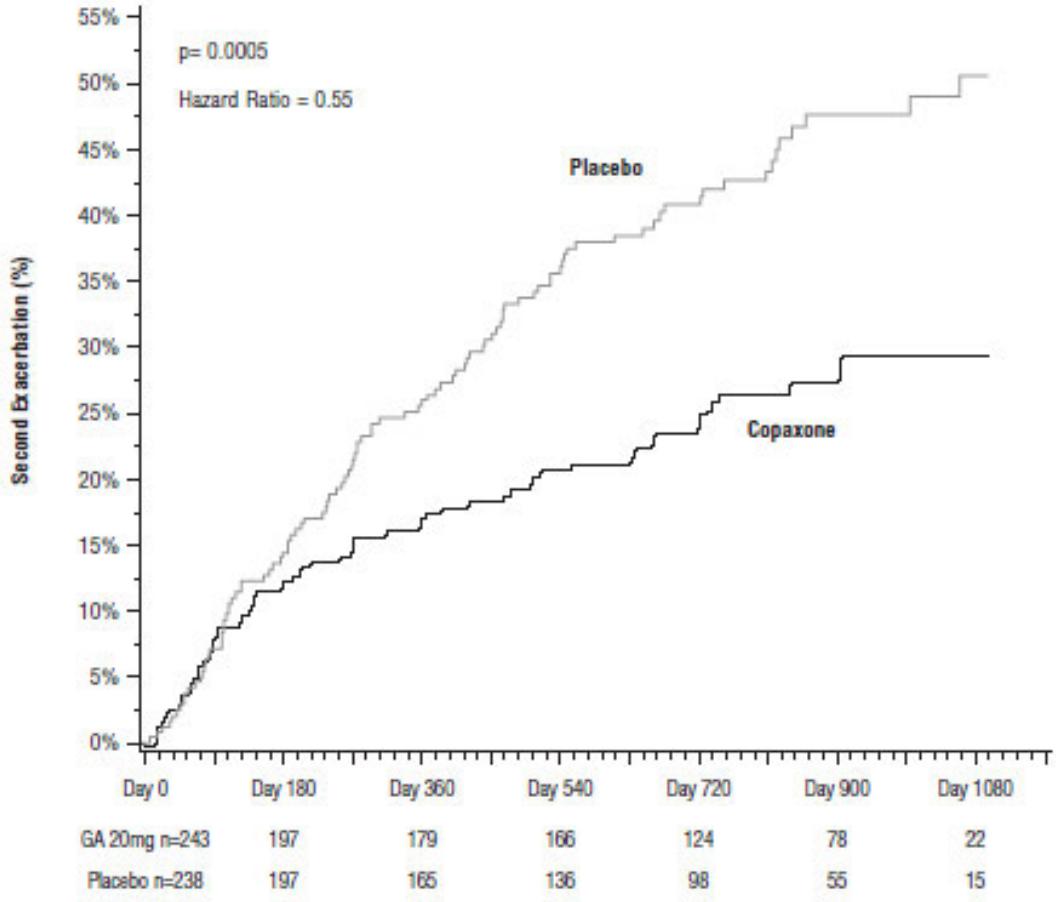
	COPAXONE 20 mg/mL (n=125)	**Placebo (n=126)**	**P-Value**
Mean No. of Relapses	1.19/2 years	1.68 /2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+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; $p = 0.0001$).

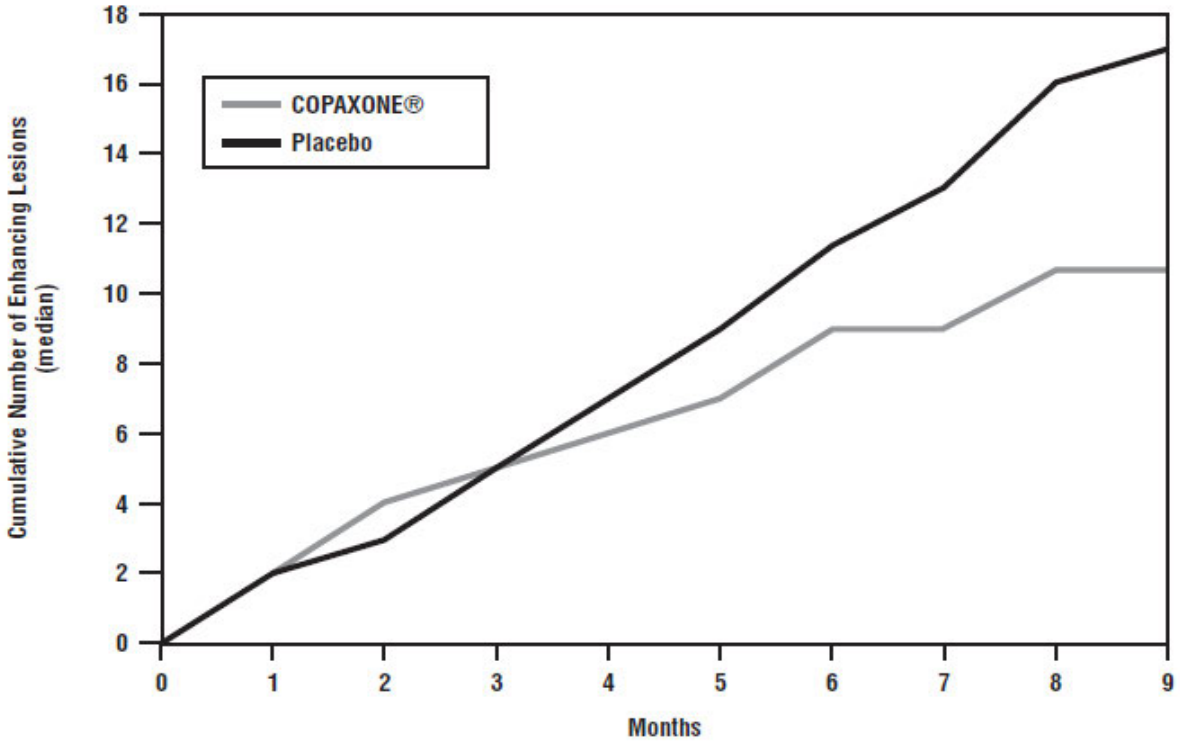
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients 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 48 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			

	COPAXONE 40 mg/mL (n=943)	Placebo (n=461)	P-Value
Cumulative number of new or enlarging T2 lesions at Months 6 and 12			
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).

Some glatiramer acetate products can be administered by an optional compatible autoinjector. Compatible autoinjectors are supplied separately if available, but the availability of compatible autoinjectors may change with time *[see Warnings and Precautions (5.7) and Patient Counseling Information (17)]*.

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

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

Important Administration Instructions

Advise patients with new or existing glatiramer acetate prescriptions to consult their pharmacist or healthcare provider if they would like information about using an optional compatible autoinjector device, if available.

Additionally, advise patients who would like to use an autoinjector for administration, should one be available, that not all available autoinjectors are compatible with all glatiramer acetate products and the availability of compatible autoinjectors may change with time. If you have questions about the availability or compatibility of an autoinjector, contact the manufacturer of the prescribed glatiramer acetate product for more information.

Advise patients that using an optional autoinjector that is not compatible with the glatiramer acetate product may increase the risk for medication errors, such as missing a dose or administration of a partial dose *[see Dosage and Administration (2.2), Warnings and Precautions (5.7)]*.

Anaphylactic Reactions

Advise patients and their caregivers that COPAXONE may cause life-threatening and fatal anaphylactic reactions shortly after injection, and that reactions may occur months to years after initiation of treatment *[see Warnings and Precautions (5.1)]*. Inform patients and their caregivers about the signs and symptoms specific

for anaphylactic reactions, and that signs and symptoms of anaphylactic reactions may overlap with those of immediate post-injection reactions. Instruct them to seek immediate emergency medical care if they experience any signs or symptoms of an anaphylactic reaction *[see Warnings and Precautions (5.1, 5.2)]*. Patients should be advised to also contact their healthcare provider, and that treatment should be discontinued immediately and permanently if anaphylactic reactions occur.

Immediate Post-Injection Reaction

Advise patients that COPAXONE may cause immediate post-injection reactions, characterized by various symptoms after injection, including flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria *[see Warnings and Precautions (5.2)]*. These symptoms occur within seconds to minutes after injection and are generally transient, 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.

Advise patients that the symptoms of an immediate post-injection reaction may overlap with those of an anaphylactic reaction. Advise patients to contact their healthcare provider if they experience any signs or symptoms of an immediate post-injection reaction *[see Warnings and Precautions (5.1, 5.2)]*.

Chest Pain

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation *[see Warnings and Precautions (5.3)]*. 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 *[see Warnings and Precautions (5.4)]*. Instruct patients to follow proper injection technique and to rotate injection areas and sites with each injection to minimize these risks.

Hepatic Injury

Advise patients that hepatic injury, including hepatic failure and hepatitis with jaundice, has been reported with the use of COPAXONE. Educate patients about the signs and symptoms of hepatic injury and instruct patients to report them immediately to their healthcare provider *[see Warning and Precautions (5.6)]*.

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking COPAXONE they should inform their healthcare provider *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed during COPAXONE therapy *[see Use in Specific Populations (8.2)]*.

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.

Manufactured for: Teva Neuroscience, Inc., Parsippany, NJ 07054

COP-013

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

Read this Medication Guide 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 healthcare provider about your medical condition or your treatment.

What is the most important information I should know about COPAXONE?

- **Serious allergic reactions (anaphylactic reactions).** Serious allergic reactions that may be life-threatening or lead to death may happen any time after you start using COPAXONE. These reactions may happen right after your first dose up to years after starting treatment with COPAXONE, even if you never had an allergic reaction before. Many reactions have happened within 1 hour of using COPAXONE. Some signs and symptoms may be the same as those of an immediate post-injection reaction. **See What are the possible side effects of COPAXONE?**
  Stop using COPAXONE and get emergency help right away if you have:
  - widespread rash
  - swelling of the face, eyelids, lips, mouth, throat, or tongue
  - sudden shortness of breath, difficulty breathing, or wheezing
  - uncontrolled shaking (convulsions)
  - trouble swallowing or speaking
  - fainting, feeling dizzy or faint

What is COPAXONE?

COPAXONE is a prescription medicine that is used to treat relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
It is not known if COPAXONE is safe and effective in children under 18 years of age.

Do not take COPAXONE:

- if you are allergic to glatiramer acetate or mannitol. Serious allergic reactions including life-threatening or anaphylactic reactions that can lead to death have happened. See the end of this leaflet for a complete list of the ingredients in COPAXONE.

Before you use COPAXONE, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. Talk to your healthcare provider who will advise if you should take COPAXONE during your pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if COPAXONE passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using COPAXONE.

Tell your healthcare provider 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 healthcare provider 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 healthcare provider 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 healthcare provider tells you to use it.
- Since every body type is different, talk with your healthcare provider about the injection areas that are best for you.
- You should receive your first dose of COPAXONE with a healthcare provider or nurse present. This might be at your healthcare provider's office or with a visiting home health nurse who will teach you how to give your COPAXONE injections.
- Some glatiramer acetate products can be used with an optional compatible autoinjector. Compatible autoinjectors are supplied separately if available, but the availability of compatible autoinjectors may change with time.
  - Check with your healthcare provider when you fill or refill your medicine to make sure the autoinjector you have is meant to be used with your glatiramer acetate product. Not all optional autoinjectors are meant to be used with all glatiramer acetate products. If you use the wrong autoinjector, you might not get the correct dose of your medicine. Contact the manufacturer of your glatiramer acetate product to find out if there is an autoinjector that is meant to be used with your glatiramer acetate product.
- Read your Instructions for Use and talk to your healthcare provider about the best way for you to use COPAXONE.

What are the possible side effects of COPAXONE?

COPAXONE may cause serious side effects, including:

- **Immediate Post-Injection Reactions**. Serious side effects may happen right after or within minutes after you inject COPAXONE at any time during your course of treatment. Some signs and symptoms may be the same as those of a serious allergic reaction (anaphylaxis). **See What is the most important information I should know about COPAXONE?** Call a healthcare provider right away if you have any of these immediate post-injection reaction symptoms including:
  - redness to your cheeks or other parts of the body (flushing)
  - chest pain
  - fast heartbeat
  - anxiety
  - breathing problems or tightness in your throat
  - swelling, rash, hives, or itching

If you have symptoms of an immediate post-injection reaction, do not give yourself more injections until a healthcare provider tells you to.

- **Chest Pain**. You can have chest pain as part of an immediate 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 healthcare provider 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 healthcare provider'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".
- **Liver problems.** Liver problems, including liver failure, can occur with COPAXONE. Call your healthcare provider right away if you have symptoms, such as:
  - nausea
  - loss of appetite
  - tiredness
  - dark colored urine and pale stools
  - yellowing of your skin or the white part of your eye
  - bleeding more easily than normal
  - confusion
  - sleepiness

The most common side effects of COPAXONE are:

- skin problems at your injection site, including:
  - redness
  - pain
  - swelling
  - lumps
  - itching
- rash
- shortness of breath
- flushing (vasodilation)
- chest pain

Tell your healthcare provider 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 healthcare provider 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 your 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 Medication Guide. 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. You can ask your pharmacist or healthcare provider for information about COPAXONE that is written for health professionals.

What are the ingredients in COPAXONE?
Active ingredient: glatiramer acetate
Inactive ingredients: mannitol

Manufactured for: Teva Neuroscience, Inc., Parsippany, NJ 07054

COPMG-001

teva

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

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: January 2025

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 healthcare provider or nurse present. This might be at your healthcare provider'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 healthcare provider will prescribe the correct dose for you.

If you plan to use your glatiramer acetate product with an autoinjector, ask your healthcare provider or pharmacist to make sure that your autoinjector is meant to be used with your glatiramer acetate product. If you use an autoinjector that is not meant to be used with your glatiramer acetate product, you might not get the correct dose of your medicine.

Instructions for Using Your COPAXONE 20 mg Prefilled Syringe:

- **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 your needles and syringes".**

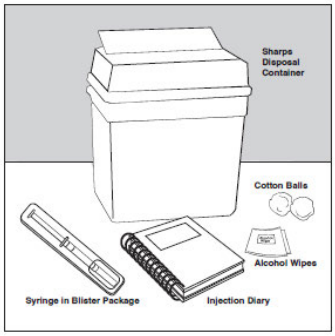


Figure A

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

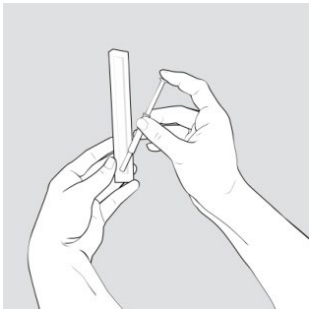


Figure B

- 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 your 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 healthcare provider 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)

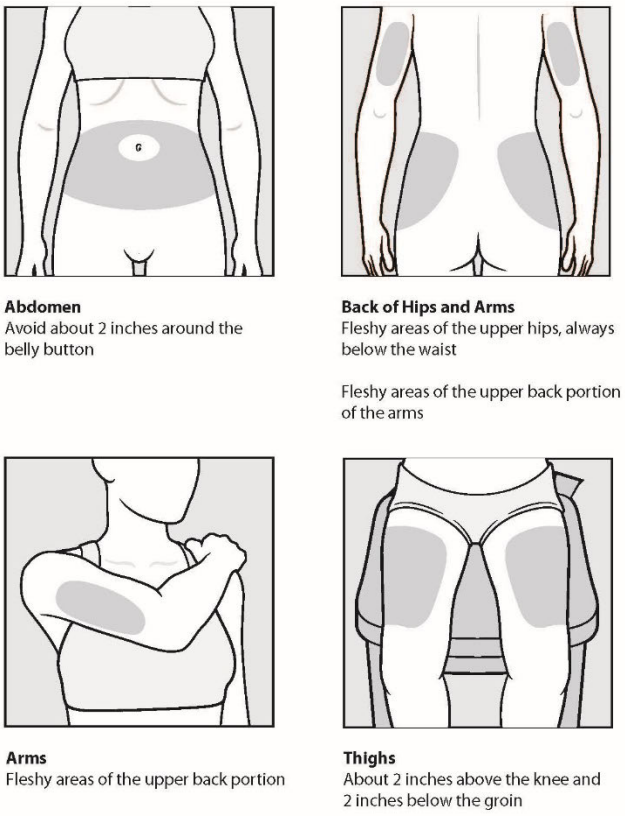


Figure C

- 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.**

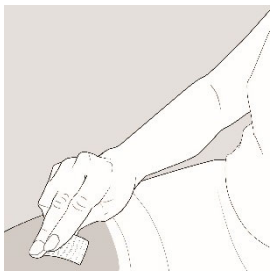


Figure D

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.**

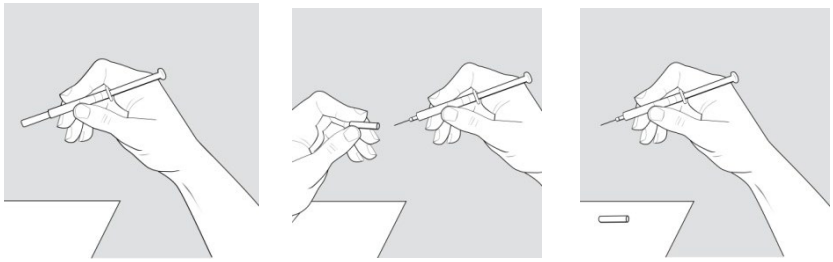


Figure E

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

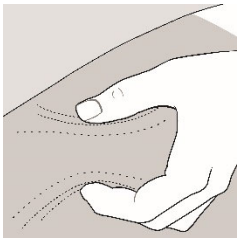


Figure F

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.**

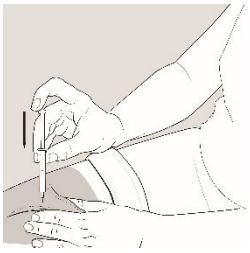


Figure G

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

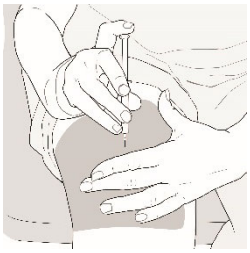


Figure H

Step 10: Give your COPAXONE injection.

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

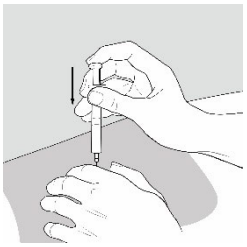


Figure I

Step 11: Remove the needle.

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

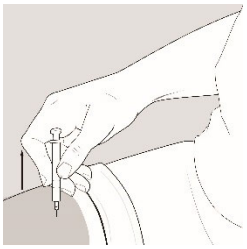


Figure J

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.**

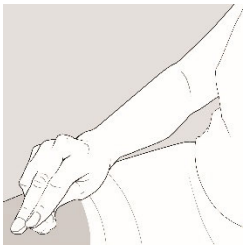


Figure K

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.

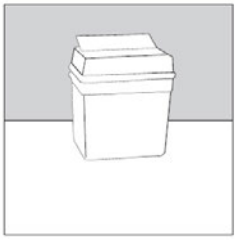


Figure L

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

teva

Manufactured for: Teva Neuroscience, Inc., Parsippany, NJ 07054

COPIFU-008
Revised: November 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020622Orig1s119

CLINICAL REVIEW(S)

CLINICAL SAFETY REVIEW

NDA number	020622
Application holder	Teva
US product trade name(s)	COPAXONE
Product established name	Glatiramer acetate
Topic	Anaphylaxis with delayed cases
Medical reviewer/Division	Gerard Boehm, MD, MPH/DN2

This memo summarizes information regarding the risk of anaphylaxis, including cases occurring more than a year after initiating treatment, with Glatiramer acetate (GA) and supports the labeling supplement submitted on 08/28/2024.

Background

Although there is no specific WARNINGS AND PRECAUTIONS statement regarding anaphylaxis in current GA labeling, WARNINGS and PRECAUTIONS statement 5.4, Potential effects on immune response, includes the following sentence "Anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded". The term "anaphylactoid reaction" is also listed under Body as a whole in section 6.2 of labeling. GA has a WARNINGS AND PRECAUTIONS statement describing post injection reactions which is provided below. The symptoms listed here overlap with the symptoms of anaphylaxis and are described as "transient and self-limited and did not require treatment; however, there have been reports of patients with similar symptoms who received emergency medical care".

> 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 that may occur immediately (within seconds to minutes, with the majority of symptoms observed within 1 hour) after injection and included at least two of the following: flushing, chest pain, palpitations, tachycardia, 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.

Division of Pharmacovigilance Review

In a 07/18/2024 memo, the Division of Pharmacovigilance (DPV) completed a review of FDA Adverse Event Reporting System (FAERS) cases of anaphylaxis with GA as requested by the Division of Neurology-2 (DN2). DN2 requested this review after learning from a Periodic Safety Update Report (PSUR) that the European Medicine's Agency (EMA) added to the "Special warnings and precautions" section of approved labeling, new language regarding risk for anaphylactic reactions with description of cases occurring "months or years after treatment initiation".[1]

I refer the reader to the DPV memo which contains detailed findings and recommendations. Briefly, DPV identified 82 cases of anaphylaxis with GA including 19 cases that occurred more than 1 year after initiating GA. Outcomes included 6 deaths along with cases describing intensive care unit admission, mechanical ventilation, and cardiopulmonary resuscitation. DPV noted the limitations of available data in examining whether gaps in treatment administration or history of adverse events with GA impacted the risk for anaphylaxis. DPV felt that the temporal relationship and biological plausibility supported a causal association between anaphylaxis and GA.

DPV recommended labeling changes and a Drug Safety Communication to convey to prescribers and patients risk information regarding anaphylaxis with GA. Specifically, DPV recommended a BOXED WARNING and updates to the WARNINGS AND PRECAUTIONS section of GA labeling. To support their recommendation, DPV cited the FDA Guidance or Industry, which states that BOXED WARNINGS should be used when there is "an adverse reaction so serious in proportion to the potential benefit from the drug such as fatal or life threatening that it is essential that it be considered in assessing the risks and benefits of using the drug or there is serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug." DPV also pointed to the precedent of a BOXED WARNING with Omalizumab, a subcutaneously injected drug with cases of anaphylaxis that have occurred more than 1 year after regular administration.

TEVA Supplement Clinical Expert Statement

On 8/28/2024, Teva submitted a Clinical Expert Statement review discussing anaphylaxis risk with GA and proposed labeling to describe this risk. TEVA stated that their proposed labeling changes reflected changes they made to their Core Company Safety Information for GA after concluding " there is enough evidence to suggest a causal association between administration of COPAXONE and the occurrence of anaphylactic reaction after months or years since the first dose administered."

Safety Database Cases

Teva's review focused on "long latency" anaphylaxis cases with GA. Teva searched their global pharmacovigilance databases using the preferred terms "anaphylactic reaction", "anaphylactic shock", "anaphylactoid reaction", and "anaphylactoid shock". Teva limited review to cases occurring at least 31 days after initiation of therapy and those that resulted in hospitalization and/or death.

[1] NISS 1005345 was opened for this issue on 5/29/24 (and moved to evaluation phase on 5/31). The sponsor was notified of the NISS on 9/6/24.

Teva identified 248 cases from their query and after excluding unrelated[2] cases (n=30), and cases with insufficient information to allow assessment (n=65), there were 153 cases for review. Teva provided a table with select data for these cases. Teva felt 3 cases were "certain", 17 "probable", and 133 "possible". 148 cases were from postmarketing reports and 5 from uncontrolled studies. Teva felt 113 of 148 postmarketing report cases described anaphylaxis (using WAO criteria). 40 cases occurred 1-3 months after starting GA, 50 occurred 3-12 months after starting GA, 12 occurred 1-2 years after starting GA and 11 occurred >2years after starting GA. Outcomes for the 113 cases included 1 death and 112 hospitalizations. Treatments included "adrenaline" (n=20), corticosteroids (n=41), antihistamines (n=7), IV fluids, oxygen, and symptomatic treatment (n=6).

Literature Review

Teva searched Embase for publications about anaphylaxis occurring >31 days after starting GA and identified 7 relevant articles. One publication described 2 cases that were included in the database review above. The remaining 6 publications described 12 cases. Teva summarized these cases in a table. The interval between first dose of GA and anaphylaxis for these cases ranged from 1-30 months. The outcomes were recovered (n=4) and unknown (n=8).

Teva Discussion/Conclusion

After summarizing their findings regarding identified anaphylaxis cases with GA, Teva noted that immediate post injection reactions did not appear to predict anaphylactic reactions, and discussed potential mechanisms for anaphylaxis cases, and estimated anaphylaxis frequency with GA (0.2%-0.3%) from limited uncontrolled trial data. Teva concluded that "there is enough evidence to suggest a causal association between administration of GA and the occurrence of anaphylactic reaction after months or years since the first dose administered." Teva proposed labeling changes consisting of a new WARNINGS AND PRECAUTIONS statement along with plans for a Dear Healthcare letter to describe this GA associated risk information.

Reviewer Discussion

Both Teva and the review team agree that GA treatment is causally associated with anaphylaxis. The reviewed reports included events that occurred in patients who had been treated with GA for months to years prior to experiencing anaphylaxis. As noted, the symptoms of anaphylaxis can overlap with the symptoms of immediate post injection reactions, AEs that can be common and are currently described in labeling as "transient and self-limited" and not requiring treatment. The review team is concerned or the potential for confusion of immediate post injection reactions with anaphylaxis resulting in delay of appropriate care and risk to patients.

The review team concluded that to best address these concerns, the GA labeling should be updated to include a BOXED WARNING for Anaphylaxis along with a WARNINGS AND PRECAUTIONS statement, changes to section 17 (Patient Counseling), and a Drug Safety Communication to explain these changes to prescribers and patients. The review team forwarded proposed labeling to Teva on 10/11/2024. In addition, the review team presented the findings and recommendations at a Drug Safety

[2] Cases deemed unrelated after applying WHO criteria, mostly due to other identified causal explanations.

Communication Planning meeting on 10/16/2024 and the participants at this meeting agreed with the plan.

In an 11/1/2024 submission, Teva responded to the Division's labeling proposal. Although Teva accepted many of the Division's proposed labeling updates, Teva disagreed with the need for a BOXED WARNING. Teva argued that anaphylaxis cases with GA are rare, based on clinical trial data and (no cases of long latency anaphylaxis in 1455 exposures) and post marketing report data (over 3-million-person years use with only 260 reports of severe long latency anaphylaxis). Teva also highlighted other MS drugs that do not have BOXED WARNINGS despite associations with both anaphylaxis and post injection reactions or infusion related reactions that have overlap of symptoms.

After reviewing the Division's responses their arguments, Teva agree to the BOXED WARNING and negotiated final labeling for anaphylaxis with GA.

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/s/

GERARD A BOEHM
01/21/2025 07:04:29 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020622Orig1s119

OTHER REVIEW(S)

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:	December 6, 2024
To:	Kristen Haslam Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
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:	for subcutaneous use
Application Type/Number:	NDA 020622
Supplement Number:	S-119
Applicant:	Teva Pharmaceuticals USA

1 INTRODUCTION

On August 28, 2024 Teva Pharmaceuticals USA submitted for the agency's review a prior approval labeling supplement for COPAXONE (glatiramer acetate injection) for the treatment of patients with relapsing forms of multiple sclerosis. The purpose of this supplement is to provide proposed labeling changes for alignment with changes in Teva's company core safety information (CCSI). Teva's CCSI was recently revised following a signal evaluation that concluded there is enough evidence to suggest a causal association between administration of COPAXONE and the occurrence of anaphylactic reaction after months or years since the first dose administered. Labeling changes are proposed in the Highlights, Section 5.2 (New; Anaphylactic Reactions), Section 6.1 (Clinical Trials Experience), Section 6.2 (Postmarketing Experience), Section 17 (Patient Counseling Information), and Patient Information. After the review and archiving of the patient labeling on December 4, 2024 the review division requested the PPI be revised to a Medication Guide based on the inclusion of a Boxed Warning.

This review is written by the Division of Medical Policy Programs (DMPP) of the Patient Package Insert (PPI) and Instructions for Use (IFU) for COPAXONE (glatiramer acetate injection).

2 MATERIAL REVIEWED

- Draft COPAXONE (glatiramer acetate injection) PPI and IFU received on August 28, 2024, and received by DMPP and OPDP on November 22, 2024.

- Draft COPAXONE (glatiramer acetate injection) Prescribing Information received on August 28, 2024, revised by the review division and received by DMPP and OPDP on November 22, 2024.

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.

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.
In our review of the PPI and IFU we:

- changed the PPI to a MG

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

4 CONCLUSIONS

The MG is acceptable with our recommended changes. There are no recommended changes to the IFU.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP and regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/06/2024 12:02:29 PM

LASHAWN M GRIFFITHS
12/06/2024 12:27:11 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 5, 2024

To: Daniela Pimentel Maldonado
Division of Neurology Products II (DN2)

Kristen Haslam, Regulatory Project Manager, (DN2)

Tracy Peters, Associate Director for Labeling, (DN)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Taylor Burnett Mmagu, Team Leader, OPDP

Subject: OPDP Labeling Comments for Copaxone (glatiramer acetate injection), for subcutaneous use

NDA: 020622/Supplement-119

In response to DN2 consult request dated September 15, 2024, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU) for Copaxone (glatiramer acetate injection), for subcutaneous use. This supplement (S119) provides for changes to PI to include the risk of the occurrence of anaphylaxis reaction after months or years since the first dose administered.

PI:
OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN2 on November 22, 2024, and are provided below.

PPI and IFU:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on December 4, 2024.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

SAMUEL A FASANMI
12/05/2024 12:19:24 PM

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:	December 4, 2024
To:	Kristen Haslam Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samuel Fasanmi, PharmD 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:	for subcutaneous use
Application Type/Number:	NDA 020622
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Applicant:	Teva Pharmaceuticals USA

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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 II (DN2) on September 15, 2024 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for COPAXONE (glatiramer acetate injection).

2 MATERIAL REVIEWED

- Draft COPAXONE (glatiramer acetate injection) PPI and IFU received on August 28, 2024, and received by DMPP and OPDP on November 22, 2024.

- Draft COPAXONE (glatiramer acetate injection) Prescribing Information received on August 28, 2024, revised by the review division and received by DMPP and OPDP on November 22, 2024.

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.

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.

In our review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- 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 IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and

Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes. There are no recommended changes to the IFU.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP and regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

20 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

SHARON W WILLIAMS
12/04/2024 12:53:52 PM

SAMUEL A FASANMI
12/04/2024 12:59:55 PM

LASHAWN M GRIFFITHS
12/04/2024 01:20:43 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Brief Drug Utilization Review

Date:	October 25, 2024
Reviewer:	John Rhee, Pharm.D. Drug Utilization Analyst Division of Epidemiology II (DEPI II)
Team Lead:	Yuze Yang, PharmD. Drug Utilization Team Leader, DEPI II
Deputy Director:	Rajdeep Gill, Pharm.D. Deputy Director for Drug Utilization, DEPI II
Subject:	Glatiramer utilization patterns from 2019-2023
Product Names:	Copaxone, Glatopa, Glatiramer acetate
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2024-11371

1 INTRODUCTION

1.1 BACKGROUND

The U.S. Food and Drug Administration (FDA) is planning to issue an additional box warning about the risk for a rare but serious allergic reaction with glatiramer acetate (Copaxone, Glatopa) following a case of fatal delayed anaphylaxis reported on February 14, 2024. In addition, the Department of Pharmacovigilance (DPV) has identified several related FAERS reports which have led to an evaluation of this newly identified safety signal (NISS). In light of this NISS, the Drug Utilization team in the Department of Epidemiology II (DEPI-II) will support the efforts of DPV to formulate a drug safety communication (DSC) by providing utilization data for glatiramer products, which will help illuminate the scope and context in which these products are dispensed and available to patients.

2 MATERIALS AND METHODS

2.1 DATA SOURCE

We used IQVIA's National Sales Perspective™ (NSP) database to ascertain the primary settings of care and channels of distributions to which manufacturers sold glatiramer products in the United States (U.S.) from 2019 through 2023. In addition, we used Symphony Health's Metys® database to determine the estimated annual number of prescriptions for glatiramer products dispensed from U.S. outpatient retail and mail-order pharmacies, as well the estimated annual number of patients dispensed these products from 2019 through 2023. The full database descriptions are available in the **Appendix.**

3 RESULTS

3.1 Settings of Care

In 2023, U.S. manufacturer sales data indicated that approximately (b)(4)% of glatiramer products were distributed to mail-order settings, (b)(4)% to non-retail settings (e.g. long-term care facilities, outpatient clinics, non-federal hospitals, etc.), and (b)(4)% to retail pharmacies.[1] Thus, we focused our analyses of dispensed prescription data from outpatient retail and mail-order pharmacy settings.

3.2 Dispensed Prescription Data

Table 1 below provides the estimated annual number of glatiramer prescriptions dispensed from U.S. outpatient retail and mail-order pharmacies, as well as the number of patients dispensed these products from 2019 through 2023.

[1] IQVIA National Sales Perspective™ (NSP). Study period: 2019-2023. Extracted October 2024. File name: IQVIA Glatiramer Sales (NSP) 2019-2023.xlsx

Table 1: Estimated number of glatiramer prescriptions dispensed and number of patients* receiving glatiramer prescriptions from U.S. outpatient retail and mail-order pharmacies from 2019 through 2023, annually.

	2019	2020	2021	2022	2023
Prescriptions	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Patients	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Source: Symphony Health Metys®. Study period: 2019-2023. Data extracted October 2024. File name: SH Metys Glatiramer TRx Patients 2019-2023.xlsx. *Patient counts are unique and may not be added across time periods, as this could lead to overestimates due to the possibility of double counting patients receiving prescriptions over multiple periods in this analysis.

4 DISCUSSION

Overall, the number of dispensed prescriptions and patient receiving glatiramer prescriptions have both declined by more than half from 2019 to 2023. Glatiramer prescription volumes decreased by (b) (4)% from approximately (b) (4) prescriptions dispensed in 2019 to (b) (4) prescriptions in 2023. The number of patients dispensed with these products have decreased by (b) (4)% from approximately (b) (4) patients in 2019 to (b) (4) patients in 2023.

Drug utilization findings should be interpreted in the context of the known limitations of the databases used. First, the data provided in this review are national estimates, and no statistical tests were performed to determine any significant statistical changes over time or between products. Therefore, all changes over time should be considered approximate. Moreover, the prescription and patient estimates provided for glatiramer products are only generalizable to U.S. outpatient retail and mail-order pharmacy settings and may not represent utilization in other settings of care where these products may be used, such as hospitals, outpatient clinics, medical offices, or long-term care facilities. Additionally, the annual patient counts provided are unique and may not be summed across years due to the risk of double-counting patients dispensed prescriptions over multiple time periods resulting in potential overestimates.

APPENDIX: DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~90% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys®

Powered by IDV®, Metys® is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys® accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions, 74% of all U.S. mail order prescriptions, 73% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level. Metys® Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.

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/s/

JOHN T RHEE
10/29/2024 01:15:25 PM

YUZE YANG
10/29/2024 01:22:24 PM

RAJDEEP K GILL
10/29/2024 01:37:13 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020622Orig1s119

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Haslam, Kristen
Sent: Thu 21 Nov 2024 04:06:22 PM -0500 UTC
To: Angela Randall
Subject: NDA 020622 S-119 PI FDA edits 21Nov2024
Attachments: Copaxone N20622-S119-draft-PI-FDA edits 21Nov2024.docx

Dear Angela,

We refer to CFR 208.1 regarding the purpose of Medication Guides. Specifically, this regulation states:

(c) Patient labeling will be required if the FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.
(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

In our response on November 12, 2024, regarding the inclusion of the Boxed Warning, we noted that, in addition to prescriber awareness, patient awareness of this important safety information is also necessary to prevent misdiagnosis or delays in treatment that could increase the risk to the patient and potentially lead to fatal outcomes.

Therefore, to follow with the inclusion of a BW, the PPI should be converted to a Medication Guide. We have revised this statement per CFR 201.57(a)(14).

Our edits to the patient labeling will follow in approximately two weeks.

In the attached we have accepted the proposed edits with which we agree, and our additional edits are shown in tracked changes. Please use the attached labeling as the base document, accept the revisions with which you agree, and use tracked changes for any additional proposed edits.

We request a response by COB November 25, 2024. Please acknowledge receipt of this message and let me know if you have any questions.

Kind Regards,
Kristen

Kristen Haslam, MS, BSN, RN
CDR, United States Public Health Service
Senior Regulatory Health Project Manager

Center for Drug Evaluation and Research
Office of Regulatory Operations
Division of Regulatory Operations for Neuroscience
Neurology Group 2
U.S. Food and Drug Administration
Tel: 240-402-4246
kristen.haslam@fda.hhs.gov

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/s/

KRISTEN J HASLAM
11/21/2024 05:03:57 PM

From: Haslam, Kristen
Sent: Tue 12 Nov 2024 08:51:15 AM -0500 UTC
To: 'Angela Randall'
Subject: NDA 020622 S-119_FDA Response to Comments_12Nov2024

Dear Angela,

The Division reviewed the arguments you provided in the Response Document, dated November 1, 2024, to support your position against a Boxed Warning for the risk of anaphylaxis in Copaxone labeling, and we are not persuaded to change our position.

We maintain that a Boxed Warning is necessary given the seriousness of anaphylaxis and the overlap in symptoms with those of immediate post injection reactions (IPIRs). IPIRs are currently described in labeling as transient, self-limited, and not requiring treatment. As you noted in your submission, they are "well described in the label and understood by prescribers." It is this prescriber familiarity with the more common and less severe IPIRs, as well as the symptomatic overlap between IPIRs and anaphylaxis, that raise significant safety concerns and warrant a Boxed Warning. Specifically, we are concerned that the overlapping symptoms between IPIRs and anaphylaxis could lead to the misdiagnosis of anaphylaxis as an IPIR and therefore dismissed, leading to potentially serious and life-threatening outcomes. A Boxed Warning also serves to highlight the unexpected cases of delayed anaphylaxis occurring years after initiation of treatment in some patients, similar to the approach taken with labeling for Xolair (omalizumab).

As one of your reasons to not require a Boxed Warning, you stated that cases of anaphylaxis have been and remain uncommon with the use of Copaxone. To support your point, you cited pivotal clinical trial data and extensive postmarketing experience. Although we agree that anaphylaxis appears uncommon with Copaxone, we do not believe that the available data allow for precise estimates of this risk. Moreover, an adverse reaction need not be common to be included in a Boxed Warning.

We acknowledge that labeling for other medications approved for the treatment of multiple sclerosis use Warnings and Precautions statements rather than Boxed Warnings to describe the risk of anaphylaxis (e.g., Ampyra, Vumerity, Ocrevus, Avonex, Tecfidera, Kesimpta, and Tysabri). However, these products are not known to be associated with benign IPIRs, and therefore labeling for these products would not need to prominently communicate this symptomatic overlap that is critical for the safe use of Copaxone. Prescriber and patient awareness of this important safety information is necessary to prevent misdiagnosis or delays in treatment that could increase the risk to the patient and potentially lead to fatal outcomes.

You stated that while the risk of anaphylactic reactions is important, it does not significantly transform the benefit risk profile for Copaxone. You also provided a partial quotation regarding use of Boxed Warnings from the Guidance document, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) when you wrote that the risk for anaphylaxis is not "so serious in proportion" to the drug's benefits to justify a Boxed Warning. Furthermore, you wrote that Boxed Warnings must be reserved for risks that fundamentally shift the risk profile of a product. You claim that such a strict warning would overstate this uncommon risk to prescribers and patients, and could potentially deter

beneficial use of the drug. We disagree with your assessment of the seriousness of this risk, and also maintain that other criteria in the Guidance regarding having a Boxed Warning are met. In particular, anaphylaxis is "serious adverse [reaction] that can be prevented or reduced in frequency or severity by appropriate use of the drug" and a Boxed Warning can be used "to highlight warning information that is especially important to the prescriber."

We have therefore concluded that a Boxed Warning, in addition to the other labeling changes specified in the prescribing information sent to you on October 10, 2024, is justified for the reasons discussed above. The Division agrees that other measures, such as a Dear Healthcare Professional Letter as you have suggested, could be useful to inform prescribers and patients regarding the risk of anaphylaxis with Copaxone.

We request that you submit a labeling supplement amendment that includes the changes we sent to you on October 10, 2024, by *COB* November 18, 2024.

Please acknowledge receipt of this message and let me know if you have any questions.

Kind Regards,
Kristen

Kristen Haslam, MS, BSN, RN
CDR, United States Public Health Service
Senior Regulatory Health Project Manager

Center for Drug Evaluation and Research
Office of Regulatory Operations
Division of Regulatory Operations for Neuroscience
Neurology Group 2
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/s/

KRISTEN J HASLAM
11/12/2024 01:48:27 PM

NDA 020622/S-119

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Teva Pharmaceuticals USA
Attention: Angela Randall
Director, Regulatory Affairs Labeling, Branded Products
145 Brandywine Parkway
West Chester, PA 19380

Dear Angela Randall:

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: S-119

PRODUCT NAME: Copaxone (glatiramer acetate injection), for subcutaneous use, 20mg/mL, and 40mg/mL Pre-filled Syringe

DATE OF SUBMISSION: August 28, 2024

DATE OF RECEIPT: August 28, 2024

This supplemental application proposes labeling changes to align with recent changes to Teva's Company Core Safety Information (CCSI). Teva's CSSI was recently revised following a signal evaluation that concluded there is enough evidence to suggest a casual association between administration of Copaxone and the occurrence of anaphylactic reaction after months or years since first dose administration. Labeling changes are proposed in the Highlights Section 5.2 (New; Anaphylactic Reactions, Section 6.1 (Clinical Trials Experience), Section 6.2 (Postmarketing Experience), Section 17 (Patient Counseling Information), and Patient Information.

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 October 27, 2024, in accordance with 21 CFR: 314.101(a).

If the application is filed, the goal date will be February 28, 2025.

If you have any questions, please contact me by email at kristen.haslam@fda.hhs.gov or by phone at (240) 402-4246.

Sincerely,

{See appended electronic signature page}

Kristen Haslam MS, BSN, RN
Senior Regulatory Health Project Manager
Neurology 2
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

KRISTEN J HASLAM
09/24/2024 02:38:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Kristen Haslam, RPM, DN2

REQUEST DATE:

09/15/2024

NDA 020622
S-119

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

Labeling Supplement

NAME OF DRUG:
Copaxone (glatiramer acetate injection)

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

SPONSOR:
Teva Pharmaceuticals

PDUFA Date: DN2 is targeting early action 11/22/24 due to potential DSC and NISS 1005345 evaluation for delayed anaphylactic reaction. PDUFA goal is 02/28/2025

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/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\evsprod\NDA020622\0692

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:

No meetings scheduled

SIGNATURE OF REQUESTER
Kristen Haslam

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

KRISTEN J HASLAM
09/15/2024 08:53:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Kristen Haslam, RPM, DN2

REQUEST DATE: 0915/2024		NDA 020622 S-119	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Labeling Supplement

NAME OF DRUG: Copaxone (glatiramer acetate injection)	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)

NAME OF FIRM: Teva Pharmaceuticals	PDUFA Date: DN2 is targeting early action 11/22/24 due to potential DSC and NISS 1005345 evaluation for delayed anaphylactic reaction. PDUFA goal is 02/28/2025

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PRESCRIBING INFORMATION (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

For OSE USE ONLY
☐ REMS

EDR link to submission:
EDR Location: \\CDSESUB1\evsprod\NDA020622\0692

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.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

No meetings scheduled at this time.

SIGNATURE OF REQUESTER Kristen Haslam

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ **eMAIL** ☐ HAND

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KRISTEN J HASLAM
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