CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020622Orig1s118

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

020622Orig1s118

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020622Orig1s118

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).

---

[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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020622Orig1s118

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

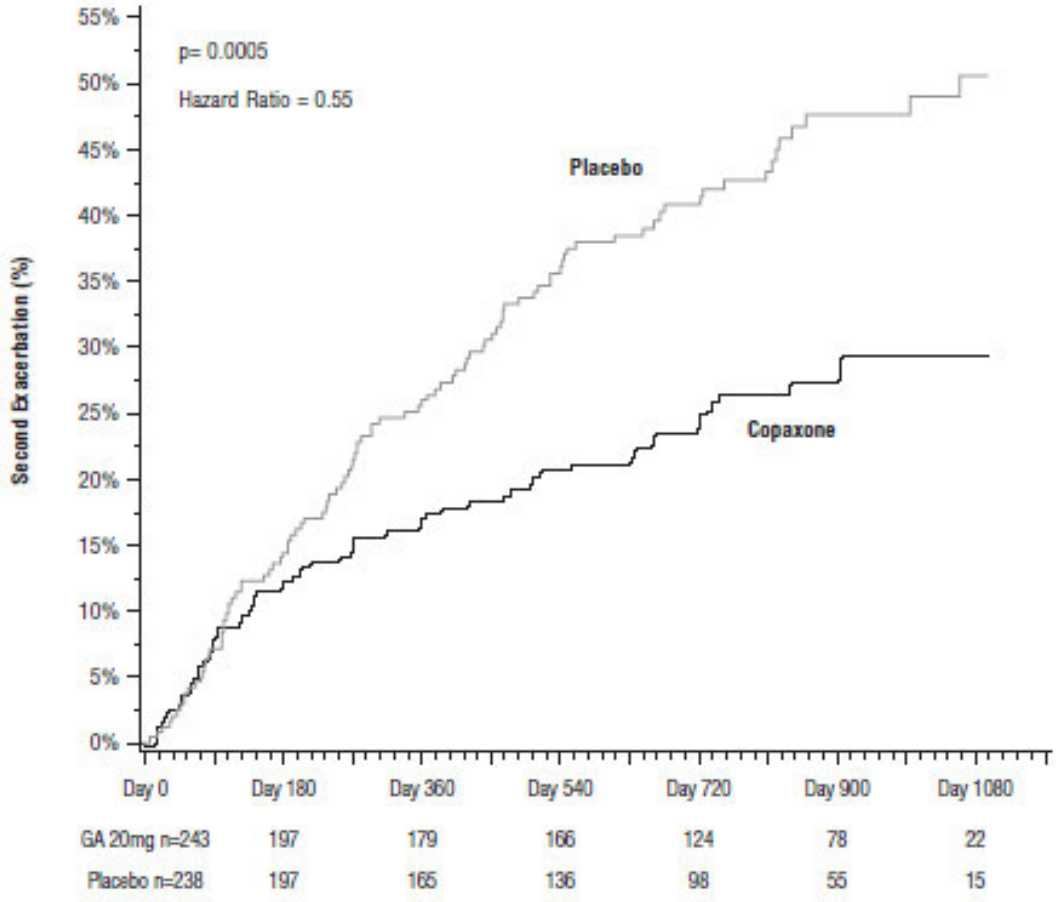
	COPAXONE 20 mg/mL (n=125)	**Placebo (n=126)**	**P-Value**
Mean No. of Relapses	1.19/2 years	1.68 /2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05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

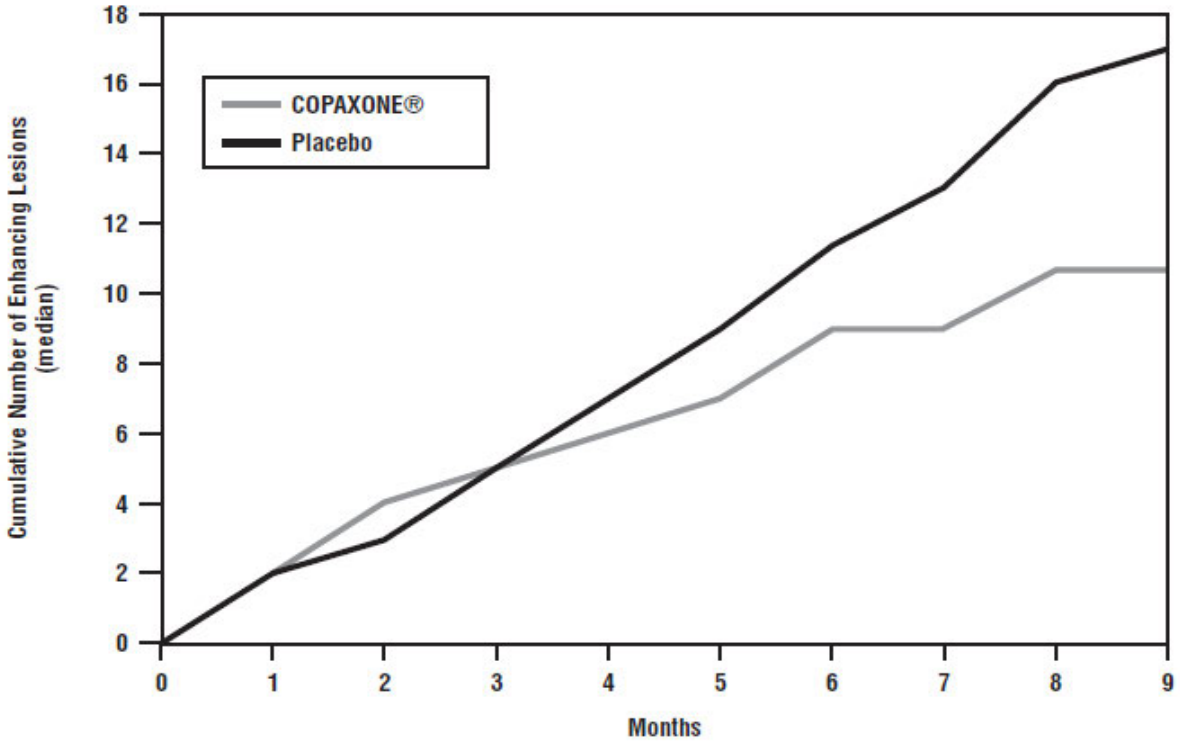
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients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

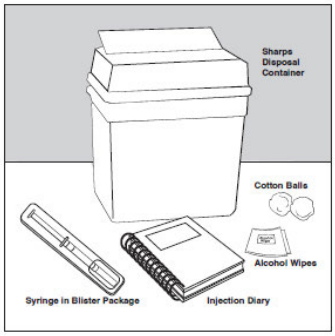


Figure A

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

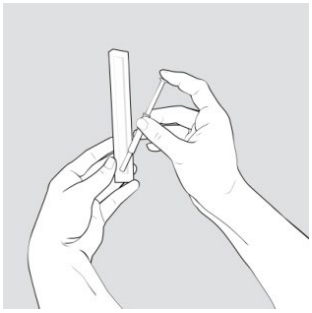


Figure B

- 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)

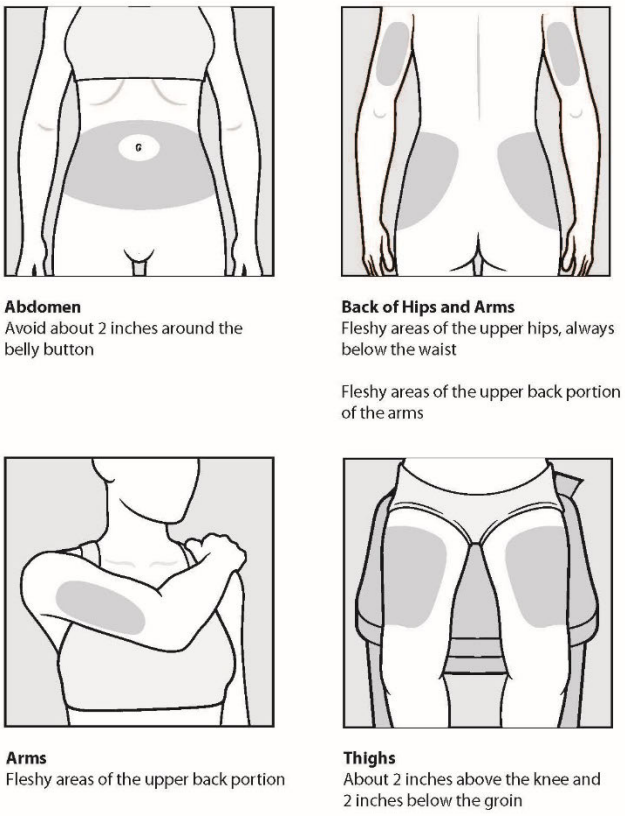


Figure C

- 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.**

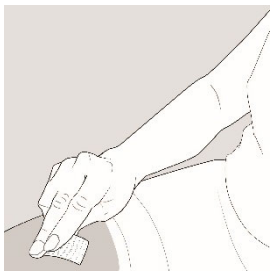


Figure D

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.**

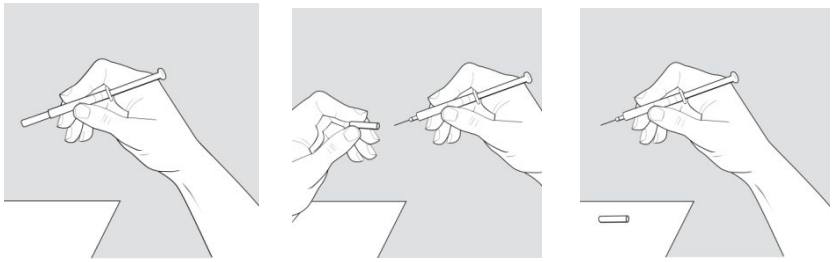


Figure E

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

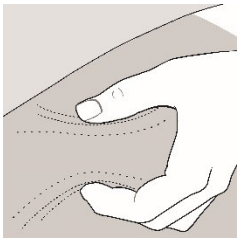


Figure F

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.**

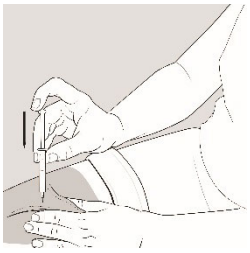


Figure G

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

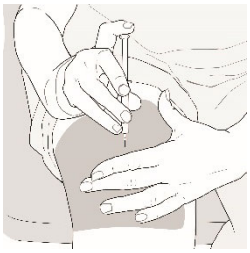


Figure H

Step 10: Give your COPAXONE injection.

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

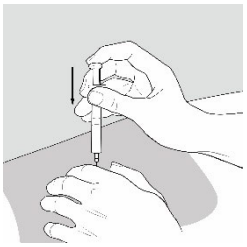


Figure I

Step 11: Remove the needle.

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

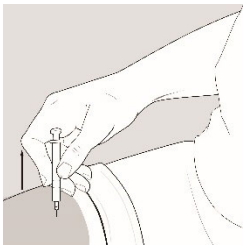


Figure J

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.**

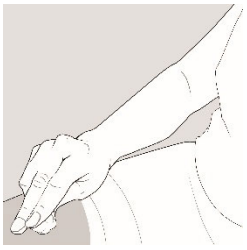


Figure K

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.

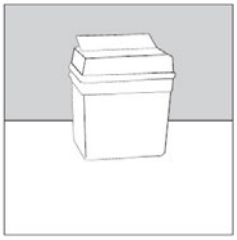


Figure L

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:

020622Orig1s118

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health-Epidemiology Integrated Pregnancy Labeling Review

Date: 12/18/2024 **Date consulted:** 7/22/2024

Reviewers: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM), Office of New Drugs (OND

Cassidi McDaniel, PhD
Division of Epidemiology I (DEPI-I)
Office of Surveillance and Epidemiology (OSE)

Team Leaders: Miriam Dinatale, DO, Maternal Health
DPMH, ORPURM, OND

Catherine Callahan, PhD, MA (Acting)
DEPI-I, OSE

Through: CAPT Sukhminder K. Sandhu, PhD, MPH, MS
Division Director, DEPI-I, OSE

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Neurology 2

Drug: Copaxone (glatiramer acetate injection), for subcutaneous use

NDA: 20622 S-118

Applicant: Teva Pharmaceuticals

Subject: Pregnancy labeling supplement based on Clinical Expert Statement, including interim analysis of pharmacovigilance data titled Annual Analysis Year 4

Approved Indications: 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.

Materials Reviewed:

- Applicant's submission on July 22, 2024
- DN2 consult form for DPMH, July 30, 2024. DARRTS Reference ID 5421640
- DN2 consult form for DEPI-I, July 30, 2024. DARRTS Reference ID 5421638
- [redacted] (b) (4)
- DPMH Maternal Health Copaxone Pregnancy labeling review, NDA 20622, by Wenjie Sun, MD, on October 24, 2022. DARRTS Reference ID 5065768
- DPMH Integrated Pediatrics and Maternal Health Review of Copaxone lactation labeling review, NDA 20622, on March 28, 2022. DARRTS Reference ID 4959522
- DN2 Pregnancy and Lactation Labeling Review by Gerard Boehm, MD, MPH, on November 6, 2019, DARRTS Reference ID 4516428

Consult Question:

DN2 requests DPMH and DEPI-I consultation regarding a labeling supplement in which the applicant proposes changes to the subsection 8.1 Pregnancy.

INTRODUCTION AND BACKGROUND

On July 22, 2024, the applicant (Teva Pharmaceuticals) submitted a Prior Approval Supplement (PAS) for Copaxone (glatiramer acetate injection) under NDA 020622 to update subsection 8.1 of the labeling. The Division of Neurology 2 (DN2) consulted the Division of Pediatrics and Maternal Health (DPMH) and the Division of Epidemiology-I (DEPI-I) on July 30, 2024, to review the applicant's submission and to assist with labeling revisions.

Regulatory History

- Copaxone, glatiramer acetate injection (GA), has been approved for use in the United States since 1996 for the reduction of frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

- On June 28, 2019, Teva submitted a PAS for Copaxone to update labeling to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format. After a review on November 6, 2019, DN2 concluded that available human data on GA use in pregnancy were not sufficient to support conclusions about a drug-associated risk for major birth defects and miscarriage.[1] Copaxone was PLLR converted on December 27, 2019. DPMH was not involved in the PLLR conversion for Copaxone.

[1] DN2 Pregnancy and Lactation Labeling Review by Gerard Boehm, MD. MPH. on November 6, 2019, DARRTS Reference ID 4516428

- On October 21, 2021, the applicant submitted another PAS to the FDA to update lactation labeling based on summary results from the Copaxone in Offsprings of Breastfeeding and treated Reference Member State (RMS) Patients (COBRA) study along with a review of published literature and the applicant's pharmacovigilance database. DPMH was consulted on December 1, 2021, and determined that available data on GA use in lactating females were insufficient to determine if there were any adverse effects on the breastfed infant. However, DPMH recommended editing the labeling under subsection 8.2, Lactation, based on GA's physical characteristics and pharmacokinetics, noting that GA is not expected to be present in milk in clinically relevant amounts, and infant exposure following maternal use is expected to be negligible.

- On July 29, 2022, the applicant submitted a PAS for Copaxone to update subsection 6.1 of labeling based on their review of the available information regarding use of GA in pregnancy and the risk of spontaneous abortion (SAB). The proposed update was triggered by a recent labeling change in the European Union.[2] DPMH reviewed the applicant's submission and their proposed labeling edits for subsection 6.1. In addition, DPMH reviewed the Pregnancy labeling language in subsection 8.1 of approved Copaxone labeling, which states that there are no sufficient data in pregnant women. DPMH proposed the following language under subsection 8.1 Pregnancy Risk Summary.

  (b) (4)

  The applicant did not wish to make any change to subsection 8.1 at that time because "there are no new information that would cause the labeling to be considered inaccurate, false, or misleading." [3] As the result, subsection 8.1 of the labeling was not revised with that submission.

- On July 22, 2024, the applicant submitted a PAS to update subsection 8.1 of Copaxone labeling. The trigger for this submission was to align the labeling with recent changes to Teva's Company Core Safety Information (CCSI), which was revised to reflect that a moderate amount of data on pregnant women indicate no malformations or fetal/neonatal toxicity and that the use of Copaxone may be considered during pregnancy, if necessary.
  - This submission includes data from a report titled Annual Analysis Year 4 (4/1/2019 to 3/31/2023), which was an interim analysis of a study based on the

[2] In a Pharmacovigilance Risk Assessment Committee (PRAC) evaluation of the Periodic Safety Update Report (PSUR), the PRAC concluded that the causal relationship between GA and spontaneous abortion was unlikely. Therefore, product information (PI) for products containing GA were amended in the European Union (EU). Abortion was deleted from the EU summary of product characteristics (SmPC), which triggered a signal evaluation at Teva to determine if the Company Core Safety Information required changes. Teva evaluated its Company Core Safety Information and concluded that a modification to the US Prescribing Information should be made (b) (4)

(b) (4)

[3] Teva's response to FDA Information Request (IR) (sent on 8/30/2022) submitted on 9/9/2022.

applicant's pharmacovigilance data that was conducted as a part of a Risk Management Plan (RMP) to fulfill a commitment to European Medical Agency (EMA). This study was designed to use targeted questionnaires to obtain additional information from cases reported to applicant's safety database to address the question of long-term pregnancy outcomes on the offspring exposed to GA in utero and through lactation.

- DN2 consulted the DPMH and DEPI-I on July 30, 2024, to review the submission and assist with the labeling revision.

For a summary of Copaxone Drug Characteristics and labeling and a discussion of MS and Pregnancy, the reviewer is referred to the previous DPMH review completed in 2022.[4]

REVIEW

DPMH Review of Annual Analysis Year 4 from Teva Global Pharmacovigilance Database (ARISg)

Overview of the Analysis

To fulfill a commitment to the EMA, Teva has been conducting analyses of their pharmacovigilance database, ARISg, annually to address the question of long-term pregnancy outcomes on the offspring exposed to GA in utero and through lactation. In this single-arm study, pregnancy and neonatal outcomes in pregnant women exposed to GA and reported to ARISg were collected via pregnancy questionnaires[5] since April 1, 2019. Questionnaires were sent at 1- and 12-months following delivery.

Both prospective (data acquired prior to outcome or prior to detection of a congenital anomaly at prenatal examination) and retrospective cases (data acquired after pregnancy outcome is known or after the detection of a congenital anomalies (CA) on prenatal test) were included.

Exposure definition: patient has taken GA within 30 days prior to conception and/or during pregnancy.

Primary pregnancy outcome: major anomalies (this is substituted with the term major congenital malformations [MCMs] in this review) in prospective cases exposed to GA. MCMs were identified using European Registry of Congenital Anomalies and Twins (EUROCAT) and

[4] DPMH Maternal Health Copaxone Pregnancy labeling review by Wenjie Sun, MD, on October 24, 2022. DARRTS Reference 5065768

[5] Questions assessed include the following:

1. Womens' baseline characteristics at the time of conception (age, weight, height, body mass index [BMI], and relevant medical history)
2. Concomitant medication use during pregnancy and breastfeeding in pregnant/lactating patients
3. Complications of pregnancy and labor
4. Infant weight and length (height) at birth and during first 12 months (approximately) of life
5. Infant adverse events (AEs), including diseases (need for hospitalization, treatment)
6. Information on infant developmental delay during 1st year of life

Metropolitan Atlanta Congenital Defects Program (MACDP) definitions.[6]

Secondary pregnancy outcomes: preterm birth (PTB, <37 completed weeks), low/very low birth weight (LBW, <2500 g; very LBW, <1500 g), stillbirth, SAB, infant developmental milestones (based on World Health Organization [WHO] standards, and infant survival up to 1 year).

A subset of breastfeeding women with MS exposed to GA were included. Search terms used were:

- Event Preferred Terms (PTs): Exposure via breast milk; Drug exposure via breastmilk; Exposure during breastfeeding; Maternal exposure via breastfeeding
- GA pregnancy questionnaire/s received: Yes

Analysis was performed for two populations:

- all pregnancy cases
- pregnancy cases for which questionnaires were completed (or partially completed)

Pregnancy and neonatal outcomes reported as adverse events (AEs) were assessed for causality based on risk factors described.

DPMH Reviewer Comment:
This reviewer disagrees with the exposure window used in this study. Although the approved labeling does not include an estimated half-life for GA, GA has a short half-life and is unlikely to be present in serum for 4 weeks. This was confirmed in our prior discussions with DN2 and the Clinical Pharmacology Team. Therefore, it is likely the pregestational exposure window defined above may be too wide and could dilute a potential signal.

In this study, it is unclear if chart reviews were performed to verify the pregnancy outcomes, including MCMs. However, the pregnancy questionnaires were sent to both the patients and their health care providers.

Analysis of All Cases

The current submission includes results from the Year 4 report. Teva searched their global pharmacovigilance database[7] (April 1, 2019 to March 31, 2023) to extract eligible patients for the analysis using the following criteria:

- preferred product description (PPD): GA
- latest received date (LRD): April 1, 2019, to March 31, 2023, with an initial received date of June 1, 2018, and onwards (to include only pregnancies that were reported from June 1, 2018, onwards and that had outcomes that fell within the reporting period)
- pregnant: Yes

Interim Analysis Year 4 further stratified the outcome by the dose of GA received (20 mg/mL vs

[6] In case of discrepancy between categorization of congenital anomaly according to MACDP and EUROCAT the more stringent level of categorization was chosen. For example, in the case where MACDP classification was "major" and EUROCAT classification was "minor", the MACDP classification was used.
[7] Medical conditions and comorbidities were extracted using MedDRA Version 26.0.

40 mg/mL),[8] and there were no significant differences between the outcomes reported for these two groups.

A total of 3,875 pregnancy cases were retrieved from the ARISg. After excluding cases due to duplication, paternal exposure, unexposed, or outside the dates[9] (n=361[10] cases), 3,514[11] unique maternally exposed GA cases were included. Among them, 2,242 pregnancies were considered prospective, and 1,272 pregnancies were retrospective. Of the 3,514[10] exposed pregnancies, 2,455[12] (69.85%) had a known outcome at the cut-off date, 558 (15.88%) pregnancies had unknown outcomes, and 501 (14.26%) pregnancies had pending outcomes.

The countries with higher number of pregnancy reports were the U.S. (20.7%), Germany (16.5%), and the United Kingdom (12.9%). See Figure 1 of the Interim Analysis Year 4.

Baseline characteristics
Maternal demographic and baseline characteristics for pregnant women exposed to GA during the analysis period were presented in Interim Analysis Year 4, Table 2.

- The majority of patients (94.97%) reported exposure to GA during the 1st trimester.
- Almost three-quarters of these patients used GA 40 mg/mL (72.19%), whereas the remaining patients used only GA 20 mg/mL (13.24%), both GA 20 mg/mL and 40 mg/mL (1.28%), or an unknown dosage (13.30%).
- The demographic and baseline characteristics were similar in the prospective and retrospective groups, with the exception of a higher percentage of patients taking GA 40 mg/mL (78.28% vs 61.48%), and a lower percentage of patients taking an unknown GA dose in the prospective group (7.58%), compared to the retrospective group (23.35%).
- The indication for GA use was not known in 17.02% of prospective patients, which is

[8] Table 8 of Interim Analysis Year 4
[9] Section 5.1.1. of the 4th Interim Analysis: Of the 3875 cases, 361 pregnancy cases were excluded as follows:
- 237 duplicate pregnancy cases of mother-child linked cases (according to data entry conventions, if a child sustained an adverse event, then both a "mother case" and a "linked child case" for the same pregnancy could be recorded).
- 4 duplicate pregnancy cases of mother-mother linked cases (according to data entry conventions, if twins have 2 different outcomes, then two separate cases could be recorded).
- 88 spouse cases (e.g., paternal exposure during pregnancy).
- 14 mother-child-child linked cases (21cases in total, 7 included).
- 4 mother-mother-child linked cases (6 cases in total, 2 included).
- 3 cases of women who stopped taking GA more than 1 month prior to conception.
- 11 cases that were initially reported before 01 June 2018.

[10] The applicant reported 361 pregnancy cases in the interim report, but 262 in the Expert Statement. During the assessment of the 4th Annual Interim Pregnancy Report questions were raised by the Reference Member State (RMS) regarding discrepancies between the cases excluded from the 3rd and 4th Annual Interim Reports, classification of congenital anomalies, cases reporting ectopic pregnancies, the number of prospective pregnancy cases with exposure to GA during the first trimester and the number of fetuses reported in these cases (Preliminary Variation Assessment Report dated September 8, 2023). During the preparation of responses, an additional error related to the included cases in the 4th Annual Interim Report was identified and communicated to the RMS. The Clinical Expert Statement reflects all changes resulting from the variation procedure mentioned above and therefore, some numbers are not fully aligned with the 4th Interim Pregnancy Report.
[11] The applicant reported 3,514 pregnancy cases in the interim report but 3,513 pregnancy cases in the Expert Statement. This discrepancy was secondary due to correction of errors related to the interim report.
[12] The applicant reported 2,455 in the interim report (Table 8) but 2,454 in the Expert Statement. This discrepancy was secondary due to correction of errors related to the interim report.

lower than the 36.83% in retrospective patients.

Primary Outcome

Congenital Anomalies (CAs)

3,514[10] exposed pregnancies were included in the overall analysis. Of the pregnancies that had known outcomes (n=2,455), there were 64 cases of CAs among live births (n=52), stillbirths (n=0), pregnancy terminations (n=11), SABs (n=1), and unknown outcomes (n=2).[13]

- 40 cases of MCMs identified (17 prospective, 23 retrospective)
- 12 minor congenital anomalies (8 prospective and 4 retrospective)
- 10 chromosomal/genetic anomalies (5 prospective and 5 retrospective)
- 4 not categorized (4 retrospective)

Primary outcome is MCM in prospective cases of fetus exposed to GA during pregnancy: 17/1211, 1.4%. When limited to the first trimester exposed prospective case only, there are 17 infants with MCMs[14] among 997 fetuses with live birth. The prevalence of MCM was 1.71 per 100 live births. A list of cases and MCMs associated with it can be found below.

1. (b) (6) ventricular septal defect (VSD)
2. VSD
3. club foot
4. congenital optic nerve anomaly, glaucoma
5. hydronephrosis
6. cyst above left eye
7. cryptorchism, hydrocele, exomphalos,
8. congenital heart defect
9. inguinal hernia/congenital renal agenesis
10. cardiac septal defect
11. VSD/macrocephaly/chromosomal mutation,
12. atrioventricular septal defect/congenital heart valve disorder,
13. congenital ureteropelvic junction,
14. congenital lymphatics malformation,
15. acute porphyria, osteochondrodysplasia, lymphatic malformation, congenital heart valve disorder
16. (b) (6): congenital anomaly, no other description given.
17. : congenital cardiovascular anomaly.

The Applicant assessed these cases and concluded that in 12 cases, a potential relation to GA cannot be excluded, 5 were probable, and 7 were possible.

When limited to gestational week 4 to 12 exposure only, there are 14 infants with MCM (excluding case 1, 4, and 17 above) among 752 fetuses with live births (and 0 stillbirths). The prevalence of MCM were 1.86 per 100 live births.

A listing of CAs observed in the prospective and retrospective cases can be found in Appendix A.

[13] Table 3 of the Interim Analysis Year 4.
[14] Section 5.1.3.1.3 and Table 6 of the Interim Analysis Year 4.

DPMH Reviewer Comment:
Among those with first trimester exposure, there are six cases with cardiac defect. The rate of cardiac defect among live births is then calculated as 6/997 or 0.6 per 100 live births. This rate is consistent with background rate of congenital heart disease for the general population (1%).[15]

The rate of MCMs among GA exposed prospective and retrospective cohorts are both less than the rate of MCM reported in the background population (~3%).

Other Pregnancy Outcomes

Other pregnancy outcomes are summarized in the Reviewer's Table 1 and the Applicant's Table 2 below.

Table 1. Pregnancy and Fetal Outcomes in All Cases[16]

Pregnancy and fetal Outcomes	**Prospective**	**Retrospective**	**Total**
Number of Pregnancies with known outcomes	**1,211**	**1,244**	**2,455**
Number of Fetus with Known Results*	1,239	1,273	2,512
Live birth (fetus)	1,138 (91.8%)	996 (78.2%)	2,134 (85.0%)
All Fetal Deaths** (fetus)			
Ectopic	4 (0.3%)	13 (1.3%)	17 (0.7%)
SB	2 (0.2%)	0	2 (0.1%)
SAB	83 (6.7%)	231 (18.1%)	314 (12.5%)
Fetal death with unknown gestation	2	8	10
Pregnancy Terminations (fetus)	10 (0.8%)	25 (2.0%)	35 (1.4%)
Unknown pregnancy outcomes* **	**533**	**25**	**558**
Pending pregnancy outcomes	**498**	**3**	**501**

** Including 2 pairs of triplets and 53 twin cases with known outcome*
***Fetal deaths include ectopic pregnancies, SAB, SB, death of fetus with unknown gestational age.*
****Unknown outcomes: Unknown outcome due to lost to follow-up, consent or contact detail not available.*
The percentage displayed are fetus/all fetus with known results.

DPMH Reviewer Comment:
Although the rate of SABs in the retrospective cases (18.1%) compared to the prospective cases (6.7%) was higher, this may be due to the higher likelihood that patients who experience adverse outcomes are more likely to report the adverse outcome to the company's pharmacovigilance database. Retrospective cases are subject to selection bias and recall bias.

[15] Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019 Apr 1;48(2):455-463.
[16] Reviewers' Table. Data extracted Table 8 of Interim Analysis Year 4. The number of pregnancies with known outcome is discrepant; it is reported to be 2,455 according to the interim report and 2,454 according to revised Expert Statement.

Otherwise, there were no concerns noted regarding the rates of ectopic pregnancies or stillbirths. It is important to note that these data are based on pharmacovigilance data only, and the true incidence of SABs, ectopic pregnancies and stillbirths cannot be estimated from pharmacovigilance data as the number of actual exposures is unknown. Chart verification has not been completed in this study.

Table 2. Characteristics of the Live Birth[17]

Birth characteristics	Prospective	Retrospective	Total
Total live birth pregnancies (mother count), n (%)	1117 (53.47)	972 (46.53)	2089 (100.00)
Single gestations	1091 (97.67)	949 (97.63)	2040 (97.65)
Multiple gestations	26 (2.33)	23 (2.37)	49 (2.35)
Gestational age at the time of birth (weeks)			
Total, n	648	255	903
Mean (SD)	38.61 (2.08)	38.64 (2.28)	38.62 (2.14)
Median (min;max)	39 (23;42)	39 (23;42)	39 (23;42)
Mode of delivery, n (%)			
Vaginal birth	419 (37.51)	328 (33.74)	747 (35.76)
Caesarean section	371 (33.21)	227 (23.35)	598 (28.63)
Unknown	327 (29.27)	417 (42.90)	744 (35.62)
Induction, n (%)	20 (1.79)	18 (1.85)	38 (1.82)
Preterm birth, n (%)	80 (7.16)	59 (6.07)	139 (6.65)
Breastfeeding (whilst on GA), n (%)	260 (23.28)	185 (19.03)	445 (21.30)
Total live birth neonates (foetus count), n (%)	1138 (53.33)	996 (46.67)	2134 (100.00)
Infant gender, n (%)			
Male	526 (46.22)	375 (37.65)	901 (42.22)
Female	459 (40.33)	337 (33.84)	796 (37.30)
Unknown	153 (13.44)	284 (28.51)	437 (20.48)
Infant birth weight (kg)			
Total, n	650	270	920
Mean (SD)	3.24 (0.57)	3.17 (0.70)	3.22 (0.61)
Median (min;max)	3.26 (0.45;5.30)	3.23 (0.67;5.66)	3.25 (0.45;5.66)
Infant birth height (cm)			
Total, n	458	196	654
Mean (SD)	49.62 (3.70)	49.49 (3.94)	49.58 (3.77)

[17] Table 9 of the Interim Analysis Year 4.

Birth characteristics	Prospective	Retrospective	Total
Median (min;max)	50 (20;59)	50 (20.5;58)	50 (20;59)
Adverse foetus/birth outcomes, n (%)			
Low/very low birth weight	55 (4.83)	39 (3.92)	94 (4.40)
Hospitalisation in NICU	55 (4.83)	28 (2.81)	83 (3.89)

Source: Teva Global Pharmacovigilance Database (ARISg).
GA=glatiramer acetate; max=maximum; min=minimum; n=number of patients in the subgroup; NICU=neonatal intensive care unit; SD=standard deviation.
Note: Percentages may not add up to 100 due to rounding.

This table reported 139 cases of Preterm Birth (PTB). There is a discrepancy between 140 cases of PTB reported under the narrative section of the interim report and 139 PTB reported in the Table 9 of the report.
All percentages displayed are among live births only.

The interim report further separated the livebirths into those exposed to either GA 20 mg/mL or 40 mg/mL. Most patients were taking GA at 40 mg/mL. There was a higher percentage of infants with LBW in the 20 mg/mL cohort (prospective cases 6.83%) compared to the 40 mg/mL cohort (4.47%). Similar patterns were seen in NICU admissions (prospective cases 7.35% vs. 4.36%) and PTB (prospective cases 7.59% vs. 5.53%).

445 patients (21.3%) breastfed while taking GA. A higher percentage of patients who were on GA 40 mg/mL breastfed compared to those taking 20 mg/mL (prospective 23.64% vs 18.99%) No other information was reported.

DPMH Reviewer Comment:
This reviewer notes that all but one LBW case were either preterm or had unknown gestational age at birth (Table 48 of the submission). Because the diagnosis of LBW is based on birth weight only and not gestational age, it is likely LBW was secondary to PTB.

It is unclear what contributed to the higher proportion of PTB, LBW, and NICU admission) in the 20 mg/mL cohort compared to 40 mg/mL cohort. This is unlikely due to drug-related effects. If the findings were secondary due to the higher GA dose, one would expect a higher proportion of PTB, LBW, or NICU admission in the 40 mg/mL cohort. This perceived difference might be secondary to the small sample size of the 20 mg/mL cohort.

Infant Adverse Events
Besides the cases with adverse events described above, there were 282 additional reports of infant adverse events (PT) in 195 (120 prospective and 75 retrospective) cases.

The reader is referred to Table 13 of the Interim Analysis for a table of AEs organized by system organ class (SOC) for specific details. Among the 282 PTs reported, the top SOC are listed below.

- 78 events under SOC “Pregnancy, puerperium and perinatal conditions,”
- 53 events under SOC “Infections and infestations,”

- 38 events under SOC "Investigations,"[18]
- 15 events under SOC "Respiratory, thoracic and mediastinal disorders,"
- 14 events under SOC General disorders and administration site conditions," and
- 13 events under SOC "Nervous system disorders."

All other SOCs are represented by 9 or less events. The Applicant did not identify any trends.

DPMH Reviewer Comment:
The way the applicant reported the AEs is different than how AEs normally are reported. The applicant did not report all AEs among all cases.

Infection (53 events, 18.79% of total AE reported) represents the most common AE reported under SOC other than "Pregnancy, puerperium and perinatal conditions". If one AE represents one infant, infections were reported in approximately ~2.5% of infants. Because this study is based on pharmacovigilance data, it is likely there was underreporting of adverse events especially related to infection. Infections are common during the first year of life. In a population-based surveillance study based on the African Neonatal Sepsis Trial (AFRINEST), 13.1% of infants under the age of 2 months had one or more signs of infection reported in their encounters.[19]

Analysis of Pregnancy Cases with Questionnaires

Questionnaires were sent for 1-month post-delivery follow-up and for the 12-month post-delivery follow-up. A total of 759 patients completed at least one follow up questionnaire and were included in this analysis.

- 712 patients (505 prospective and 207 retrospective) completed 1-month questionnaires
- 384 patients (268 prospective and 116 retrospective) completed 12-month questionnaires

The return rate for questionnaires from 4/1/2022 to 3/31/2023 was 49.73%. The countries with the highest number of reports were Germany (23.22%), Canada (14.49%), and Turkey (12.38%).

For a detailed breakdown of results from pregnancy cases with questionnaires, the reader is referred to Appendix B of the review.

DPMH Reviewer Comment:
There were no significant differences between the demographics for those who completed (or partially completed) the questionnaires compared to the patient demographics reported in overall pharmacovigilance database. Pregnancy and infant outcomes, including rates of live births, MCMs and SAB, that were reported in patients who completed questionnaires were similar to the rates reported in the sponsor's pharmacovigilance database. Infant growth was also assessed in patients who completed a questionnaire, and overall infant growth was within the 10 to 90th percentile at 12 months of age. There were more patients with a known mode of delivery in those patients who answered a questionnaire. There was also a higher percentage of infants with LBW and NICU admission in those who completed a questionnaire. Regarding the

[18] According to MedDRA the term "Investigations" refers to laboratory test results, radiologic testing, etc.
[19] Puri D, Nisar YB, Tshefu A, Longombe AL, Esamai F, Marete I, Ayede AI, Adejuyigbe EA, Wammanda RD, Qazi SA, Bahl R. Prevalence of clinical signs of possible serious bacterial infection and mortality associated with them from population-based surveillance of young infants from birth to 2 months of age.

higher percentage of infants who were LBW or had a NICU admission among patients who completed a questionnaire, it is possible that the increased rate of reported adverse outcomes is related to the ability to collect more information when a questionnaire is completed by a patient.

Exposure of GA During Breastfeeding Reported in the Teva Global Pharmacovigilance Database

Overall, 146 women who were administered GA during pregnancy also used GA while breastfeeding their infants in the Year 4 Interim Analysis. See Table 45 of the interim report.

62 mother-infant pairs continued breastfeeding for 4 or more months, 21 mother-infant pairs breastfed for less than 4 months or mixed breast and bottle feeding, 43 mother-infant pairs were still breastfeeding at the time of this report (ongoing), and the duration of breastfeeding is unknown in 20 cases.

Data on weight, length, and gender at birth and at the age of latest assessment (approximately 12 months of age) were available for 55 cases. Five infants were underweight at birth but were in the normal range according to the most recent assessment. Data on infant hospitalization during first 12 months of life were available for 124 cases (125 infants). Among them, 12 cases (14 infants) were hospitalized (due to infection [n=8[20] infants], congenital malformations [n=2], gastrointestinal reflux [n=1], West syndrome[21] [n=1], cyanosis [n=1], dehydration [n=1], prematurity [n=2]).

Additionally, there were 20 additional reports of AEs as follows:

- 10 cases related to infection.
- 3 cases related to milk protein allergy (1 also had Kawasaki)
- 2 eczema cases
- 1 case reported spinal disorder related to an unspecific change in sacral foramen, no surgery was required.
- 1 case of short lingual frenulum, which was corrected by pediatric dentist.
- 1 case reported elevated liver enzymes during the infant's first month of life, which resolved after stopping breastfeeding. It was unclear if the liver enzyme was normal at the beginning of breastfeeding. Co medication not reviewed.
- 1 cases of small fontanelle at 6-month of age, the mother stated her previous child had a similar finding.
- A case of developmental delay (described above, case no. [redacted] (b) (6))

Among the125 mothers who answered a question regarding hospitalization of their infant, 14 mothers noted that their infants (11.2%) were hospitalized.

[20] One twin infant was premature and was hospitalized for rotavirus infection at 12 months of age. Another twin infant was premature and hospitalized for RSV 40 days after birth. Other infants had whooping cough, nasopharyngitis, 2 URIs (twins, not hospitalized for preterm births), viral meningitis, acute bronchitis. See section 5.3.2 of the report.

[21] This case also has VSD but not hospitalized for this reason.

Applicant's Conclusions

The Applicant shared the following conclusions regarding their pharmacovigilance database study:

- "During the cumulative 4-year period of analysis from April 1, 2019, through March 31, 2023, there were 3,514 reported pregnancies.
- The rate of major congenital anomalies in prospective pregnancies is within the reference range as provided by EUROCAT and MACDP population-based databases.
- Adverse pregnancy outcomes in the analysis were found to be within the reference ranges (i.e., SAB, stillbirths, pregnancy terminations).
- The number of preterm deliveries and low birth weight neonates did not exceed the rates found in the reference data.
- No trend towards a specific safety issue in reported child AEs was found in the overall analysis or in the analysis of cases with questionnaires. Infants' growth parameters at the age of approximately 12 months were within the normal ranges for almost all infants by WHO standards (including cases with breastfeeding). There were two reports of developmental issues in infants exposed to GA during pregnancy. In one of the cases the infant was also exposed during breastfeeding. However, proper assessment was limited due to missing data.
- The analysis of pregnancy cases reported during the cumulative 48-month period is aligned with results of the previous 3 annual analyses, preclinical data, postmarketing data, and the well-established benefit-risk profile of GA treatment in MS patients during pregnancy. The benefit-risk profile of GA remains favorable following review of the outlined data.
- The large amount of patient data (1062 prospective pregnancies exposed to GA during the 1st trimester with known outcomes), collected and analyzed without identification of any safety concerns, supports the safety of both 20 mg/mL and 40 mg/mL GA treatment during pregnancy and breastfeeding. Given the totality of evidence (i.e., postmarketing data), and in line with the EMA Guidance (Guideline on risk assessment of medicinal products on human reproduction and lactation from data to labelling; EMA 2008), the MAH considers the benefit-risk balance of GA for use in pregnancy and lactation as positive."

DPMH Conclusion of the Applicant's Pharmacovigilance Database

DPMH did not identify any safety signals in the GA exposed pregnancies within the pharmacovigilance database. The overall rate of MCMs, SABs, PTB, LBW, and infant infections reported through the pharmacovigilance database were not elevated compared to the background population. Although the rate of SABs was higher in retrospectively reported cases compared to the prospectively reported cases, patients with known adverse outcomes are more likely to report their outcomes to a pharmacovigilance database compared to those with normal outcomes.

The pharmacovigilance database has several limitations as follows:

- A significant portion of pregnancies reported in the database have either unknown (n=558) or pending pregnancy outcomes (n=501).
- Pregnancy outcomes were not verified through chart review.
- There is a concern for exposure misclassification as the protocol considers those exposed

to GA to include patients exposed to GA 30 days prior to conception. 30 days prior to conception exceeds the 5 half-lives of the drug. This misclassification may bias the results towards the null.

- Additional limitations of this analysis include selection bias, lack of internal comparator, and inability to control for covariant that may have contributed to the results.

Due to various limitations, DPMH does not recommend including detailed findings from the applicant's pharmacovigilance database in the labeling.

Review of Published Literature

DPMH's Review of Literature

The Applicant did not submit a review of the published literature in this submission, however DPMH recently reviewed GA use during pregnancy in 2022.[22] DPMH concluded the following:

> *"The available human data regarding the use of GA in pregnancy including published prospective and retrospective observational studies and pharmacovigilance reports, have not identified a drug-associated risk of birth defects, miscarriage, and adverse maternal or fetal outcomes. This is consistent with findings in the animal reproduction studies. Additionally, GA has been approved for use since 1996 and it had been previously categorized as pregnancy category B and thus is commonly used for the treatment of MS during pregnancy. Decades of experience has not identified any safety issue related to use of GA during pregnancy."*

DPMH completed an updated search of the published literation from 2022 to present (September 6, 2024) in PubMed, Embase, and review sites.[23] Search terms used were "glatiramer acetate" AND "pregnancy," "glatiramer acetate" AND "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." After excluding studies based on Teva's pharmacovigilance data,[24,25,26] which utilized data from Teva's pharmacovigilance database, the relevant studies which evaluated the effects of GA on pregnancy outcomes are listed below.

- A pharmacovigilance study based on individual case safety reports (ICSRs) retrieved from the European spontaneous reporting system database (EudraVigilance) compared adverse events between natalizumab, alemtuzumab and ocrelizumab vs. glatiramer during pregnancy and lactation.[27] A total of 1,236 ICSRs reporting at least one disease modifying therapy, as a suspected drug were selected. More adverse drug reactions

[22] DPMH Maternal Health Copaxone Pregnancy labeling review, NDA 20622, by Wenjie Sun, MD, on October 24, 2022. DARRTS Reference ID 5065768

[23] Micromedix, ReproTox, Shepard, TERIS

[24] Kaplan S, Dragut CF, Ghimpeteanu A, Current Medical Research and Opinion 2024 40:5 (821-825) Pregnancy and fetal outcomes following paternal exposure to glatiramer acetate. Current Medical Research and Opinion 2024 40:5 (821-825)

[25] Kaplan S, Zeygarnik M, Stern T, Hellwig K. Pregnancy and fetal outcomes following maternal exposure to glatiramer acetate in all three trimesters of pregnancy. Eur J Neurol. 2023 Dec;30(12):3890-3895.

[26] Kaplan S, Zeygarnik M, Stern T. Pregnancy, Fetal, and Infant Outcomes Following Maternal Exposure to Glatiramer Acetate During Pregnancy and Breastfeeding. Drug Saf. 2022 Apr;45(4):345-357.

[27] Sportiello L, Di Napoli R, Balzano N, Mascolo A, Ruggiero R, Di Costanzo L, Monaco D, Maniscalco GT, Capuano A. Disease-Modifying Therapies (DMTs) in Pregnant and Lactating Women with Multiple Sclerosis: Analysis of Real-World Data from EudraVigilance Database. Pharmaceuticals. 2023; 16(11):1566.

(ADRs) unrelated to pregnancy and breastfeeding (n = 1,171; 32.6%) were reported than ADRs specific to pregnancy and breastfeeding (n = 1,093; 30.4%). The most frequently reported unrelated ADR was MS relapse. Alemtuzumab and natalizumab seem to have a lower reporting probability of MS relapse compared to glatiramer (ROR 0.17, 95% CI 0.07–0.45 and ROR 0.34, 95% CI 0.20–0.57). Among pregnancy- and breastfeeding-related ADRs, the most common reported event was spontaneous abortion (n = 321; 8.9%). Natalizumab and ocrelizumab were associated with a higher reporting probability of spontaneous abortion compared to glatiramer (ROR 2.22, 95% CI 1.58–3.12; ROR 2.18, 95% CI 1.34–3.54, respectively), while alemtuzumab had a lower reporting frequency (ROR 0.32, 95% CI 0.17–0.60).

- A study from the Danish Multiple Sclerosis Registry linked with nationwide registries evaluated pregnancy outcomes in disease-modifying therapy (DMT) exposed pregnancies (including GA, interferon [IFN]-β, dimethyl fumarate, and natalizumab), MS unexposed pregnancies, and pregnancies from the general population.[28] This study is reviewed in the next section (i.e., DEPI-I's Literature Search).

DPMH Reviewer Comment:
No new safety signal was identified during this literature review. This reviewer agrees with the conclusion from the prior DPMH review in 2022.

DEPI-I's Literature Search

Methods of DEPI-I's Literature Search

DEPI-I reviewed the list of observational studies identified in previous literature reviews by DN2 in 2019[29] and DPMH in 2022[30] for inclusion in DEPI-I's literature review. To identify articles published since DPMH's literature review in 2022,[31] DEPI-I searched PubMed and Embase databases from January 1, 2022, until September 26, 2024 (the date DEPI-I ran the search) and reviewed the results for comparative observational studies of GA exposure during pregnancy. DEPI-I's search strategy is detailed in Appendix C. The outcomes of interest were pregnancy and infant outcomes, including but not limited to MCMs, preterm birth, low/very low birth weight, stillbirth, SAB, infant developmental milestones, and infant survival up to one year. Studies were required to be published in English language, report original study results, and have a comparator group. Animal studies, case reports, case series, studies analyzing pharmacovigilance databases, qualitative studies, study proposals, descriptive studies, review articles, abstracts/poster presentations, commentaries, clinical guidelines, and letters to the editor or editorials were excluded. DEPI-I reviewed the reference lists of relevant review articles to identify any pertinent original research articles that may have been missed in our search.

[28] Andersen JB, Sellebjerg F, Magyari M. Pregnancy outcomes after early fetal exposure to injectable first-line treatments, dimethyl fumarate, or natalizumab in Danish women with multiple sclerosis. Eur J Neurol. 2023 Jan;30(1):162-171.
[29] Boehm G. Clinical Review for Copaxone (Glatiramer Acetate) Pregnancy and Lactation Labeling Rule Proposal. Nov 6, 2019. Silver Spring (MD): Food and Drug Administration. DARRTS Reference ID: 4516428.
[30] Sun W, Dinatale M, Yao LP. Pregnancy Labeling for Copaxone (Glatiramer Acetate Injection). Oct 24, 2022. Silver Spring (MD): Food and Drug Administration. DARRTS Reference ID: 5065768.
[31] Sun W, Dinatale M, Yao LP. Pregnancy Labeling for Copaxone (Glatiramer Acetate Injection). Oct 24, 2022. Silver Spring (MD): Food and Drug Administration. DARRTS Reference ID: 5065768.

One reviewer screened the titles and abstracts and then screened eligible full texts for inclusion/exclusion. One reviewer assessed the quality of retained studies using the Newcastle-Ottawa Scale (NOS) (Wells et al. 2021). We considered studies with an NOS rating score ≥7 as high-quality (Islam et al. 2016).

Results of DEPI-I's Literature Search

We identified 18 records from PubMed, 124 records from Embase, and 28 records from other sources (DPMH's prior review[32] [n=24], DN2's prior review[33] [n=2], and reverse reference searching [n=2]). After removing duplicates (n=18), there were 152 records for title and abstract review. During title and abstract review, we excluded 127 records due to not studying pregnancy outcomes with GA exposure, not being relevant, or reporting ineligible studies (e.g., pharmacovigilance database study, case series) or article type (e.g., commentary, expert consensus, clinical guidelines, review, conference abstract, statistical analysis plan, not published in English). We retained 25 for further screening during full text review.

DEPI-I shared potentially relevant studies analyzing pharmacovigilance databases (Barbieri et al. 2022, Kaplan et al. 2022, Kaplan et al. 2023, Sportiello et al. 2023) with DPMH for consideration in their literature review. DPMH reviewed Sportiello et al. 2023 in their literature review described above.

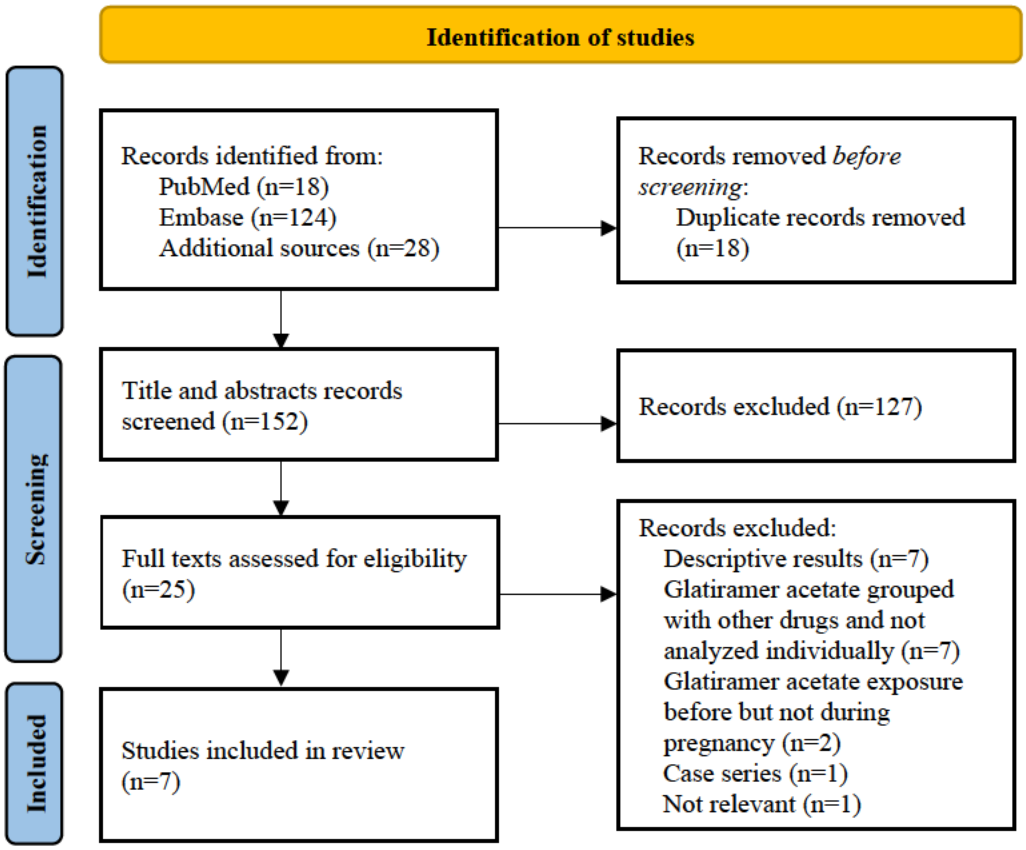
DEPI-I reviewed 25 full texts and retained seven records (**Figure 1**). The reasons for exclusion during full text review were only descriptive results reported (n=7; (Fernández Liguori et al. 2009, Fragoso et al. 2009, Finkelsztejn et al. 2011, Hellwig and Gold 2011, Hellwig et al. 2012, Fragoso et al. 2013a, Sadovnick et al. 2023)), GA grouped with other drugs and not analyzed individually (some of these records reported descriptive results for GA, but inferential analyses were not performed separately for GA) (n=7; (Lu et al. 2012, MacDonald et al. 2019, Thiel et al. 2021, Mainguy et al. 2022, Fink et al. 2023, Moccia et al. 2023, Swital et al. 2024)), GA exposure studied before but not during pregnancy (n=2; (Hradilek et al. 2022, Krysko et al. 2022)), case series[34] (n=1; (Kasatkin et al. 2018) DN2 included this study in their 2019 review, and DPMH reviewed the abstract in 2022), and not relevant (n=1; (Arabipoor et al. 2024)).

[32] Ibid.

[33] Boehm G. Clinical Review for Copaxone (Glatiramer Acetate) Pregnancy and Lactation Labeling Rule Proposal. Nov 6, 2019. Silver Spring (MD): Food and Drug Administration. DARRTS Reference ID: 4516428.

[34] Reviewer classified Kasatkin et al. 2018 as a case series based on details available in the publication (selected 30 cases of pregnancy ending with live births in patients with MS), but the publication did not specify a study design.

Figure 1. Flow Diagram of Literature Review and Screening[35]



Appendix D presents the NOS rating scores for retained studies. Four of the seven retained studies were considered high-quality.

Appendix E summarizes the retained studies. Briefly, all seven retained studies used a cohort design, including four retrospective cohort[36] and three prospective cohort studies. All studies included international populations (Germany [n=2], Italy [n=1], France [n=1], Denmark [n=1], or multiple countries [n=2]). Time periods ranged from 1996 until 2018 (where reported).

In the following sections, we review retained study results by outcome. We present studies in chronological order and only provide details (study design, data source, sample size, exposure definition, and citation) at first mention of comparative results from each study for brevity. Studies often reported results from inferential analyses for some pregnancy outcomes, and only reported descriptive results for other pregnancy outcomes. We only considered a study for a specific pregnancy outcome when the study reported results from inferential analyses for the respective outcome. However, we mention relevant descriptive results in each section below.

[35] Modified from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

[36] Reviewer classified Fragoso et al. 2013b as a retrospective cohort study based on details available in the publication (retrospectively analyzed a database to compare pregnancies exposed vs. unexposed to MS drugs), but the publication did not specify a study design. Reviewer classified Andersen et al. 2023 as a retrospective cohort study based on details available in the publication (retrospectively analyzed Danish registry data to compare pregnancies exposed vs. unexposed to MS drugs), but the publication referred to this as a cross-sectional study.

MCMs

None of the three studies that conducted inferential analyses for MCMs or birth defects observed a statistically significant association with GA exposure during pregnancy. An additional two studies (Giannini et al. 2012 and Fragoso et al. 2013b) only reported descriptive results for MCMs.[37]

- Weber-Schoendorfer et al. 2009 conducted a prospective cohort study of pregnancies enrolled in the Teratology Information Service (TIS), Berlin from 1996-2007, including 31 GA exposed pregnancies (defined as exposure at least during the first trimester), 69 IFN-β exposed pregnancies, 64 unexposed pregnancies with MS, and 1,556 unexposed pregnancies without MS. There were no statistically significant differences in odds of all birth defects (unadjusted odds ratio [OR]: 1.28, 95% CI: 0.14, 5.3) or major birth defects (OR: 4.99, 95% CI: 0.54, 22.19) among GA exposed vs. unexposed pregnancies without MS. Among GA exposed pregnancies, there were two major birth defects (club feet and atrioventricular canal) (Weber-Schoendorfer and Schaefer 2009).
- Herbstritt et al. 2016 conducted a prospective cohort study of pregnancies among women with RRMS enrolled in the German MS and Pregnancy Registry from 2008-2013, including 151 GA exposed (defined as GA administered after the last menstrual period [LMP]) and 95 DMT unexposed pregnancies. GA exposure was not significantly associated with an increased risk of any congenital anomaly (CA) (adjusted odds ratio [aOR]:[38] 0.24, 95% CI: 0.06-1.01) or major CA (aOR: 0.16, 95% CI: 0.03-0.85) compared to DMT unexposed (Herbstritt et al. 2016).
- Andersen et al. 2023 conducted a retrospective cohort study[39] of pregnancies from Danish registries from 1997-2018. The study included DMT exposed pregnancies (required treatment adherence for ≥30 consecutive days prior to LMP, n=1,009, including 141 GA exposed [defined as injection at or after LMP]), MS unexposed pregnancies (n=1,073), and pregnancies from the general population (n=91,112). Three (~3%) GA exposed pregnancies had congenital malformation reported. Comparing GA exposed to MS unexposed pregnancies or the general population, there were no significant differences in odds of MCMs (aOR:[40] 1.07, 95% CI: 0.32-3.65; aOR: 0.76, 95% CI: 0.24-2.34; respectively) (Andersen et al. 2023).

[37] In Giannini et al. 2012, GA exposed pregnancies had no malformations. In Fragoso et al. 2013b, GA exposed pregnancies had one bone malformation, which the medical team considered as "non-drug-related."
[38] It was unclear which confounders were adjusted for. The study considered the following as confounders if associated with both the exposure and outcome ($p<0.2$): Age at conception, disease duration, body mass index (BMI), smoking during pregnancy, relapse during pregnancy, steroid use during any trimester of pregnancy due to MS relapses, steroid use during first trimester, and gestational week of cohort entry.
[39] Reviewer classified Andersen et al. 2023 as a retrospective cohort study based on details available in the publication (retrospectively analyzed Danish registry data to compare pregnancies exposed vs. unexposed to MS drugs), but the publication referred to this as a cross-sectional study.
[40] Adjusted for prior abortion, maternal age at LMP, educational level, prior caesarean section, calendar year of birth.

SAB

None of the six studies that conducted inferential analyses for SAB observed a statistically significant association with GA exposure during pregnancy. One additional study (Fragoso et al. 2013b) only reported descriptive results for SAB.[41]

- In Weber-Schoendorfer et al. 2009, there was no statistically significant difference in odds of SAB (unadjusted OR: 0.39, 95% CI: 0.01-2.48) among GA exposed vs. unexposed pregnancies without MS. IFN-β1b exposed pregnancies (n=21) had significantly higher SAB prevalence than GA exposed pregnancies (27.8% vs. 3.9%, p=0.03).
- Giannini et al. 2012 conducted a prospective cohort study of pregnancies among MS patients from 21 Italian MS Centers from 2002-2008, including 17 GA exposed pregnancies (defined as discontinued GA less than four weeks from conception), 88 IFN-β exposed pregnancies, and 318 MS unexposed pregnancies (defined as discontinued DMT at least 4 weeks from conception or never treated with DMTs). SAB occurred in 5.9% (n=1) of GA exposed, 7.9% (n=7) of IFN-β exposed, and 6.3% (n=20) of unexposed. GA exposure was not significantly associated with SAB (aOR:[42] 0.44, 95% CI: 0.04, 4.51; publication did not specify the comparator group used) (Giannini et al. 2012).
- In Herbstritt et al. 2016, GA exposure was not significantly associated with an increased risk of SAB (aOR:[43] 0.93, 95% CI: 0.30-2.85) compared to DMT unexposed.
- Nguyen et al. 2019 conducted a retrospective cohort study of pregnancies among women with RRMS aged 15-45 years enrolled in the MSBase Registry from 2005-2016. Comparing DMT unexposed (n=886), FDA pregnancy category B (i.e., GA n=137; no exposure definition provided), or FDA pregnancy category C & D (i.e., IFN-β n=350, natalizumab n=104, rituximab n=2, fingolimod n=21, dimethyl fumarate n=17, azathioprine n=4), there was no significant difference for SAB (p=0.90). GA exposed pregnancies had the same percentage of SAB (6% vs. 6%) compared to DMT unexposed (p-value not reported) (Nguyen et al. 2019).
- Tillaut et al. 2022 conducted a retrospective cohort study of pregnancies among women with MS aged 15-49 years in the French national health insurance database from 2010-2015. The study included DMT exposed pregnancies (defined as at least one DMT received ≤14 days before or during pregnancy, n=2,569, including 610 GA exposed), those unexposed during pregnancy and stopped DMT in the year prior to conception (n=1,696), and those unexposed during pregnancy or in the year prior to conception (n=3,868). The probability of SAB among GA exposed pregnancies (adjusted

[41] In Fragoso et al. 2013b, GA exposed had 2 SAB (obstetricians in charge of case considered "non-drug-related").
[42] Adjusted for age at conception; educational level; disease duration, Expanded Disability Status Scale (EDSS); previous pregnancies and abortions; smoking, alcohol, and substance exposure during pregnancy; gestational age; caesarean delivery; and infant gender.
[43] It was unclear which confounders were adjusted for. The study considered the following as confounders if associated with both the exposure and outcome (p<0.2): Age at conception, disease duration, BMI, smoking during pregnancy, relapse during pregnancy, steroid use during any trimester of pregnancy due to MS relapses, steroid use during first trimester, and gestational week of cohort entry.

probability:[44] 0.040, 95% CI: 0.024-0.056) was similar to both unexposed cohorts (those unexposed during pregnancy and stopped DMT in the year prior to conception adjusted probability: 0.049, 95% CI: 0.038-0.059; those unexposed during pregnancy or in the year prior to conception adjusted probability: 0.041, 95% CI: 0.034-0.047) (Tillaut et al. 2022).

- In Andersen et al. 2023, among the 141 GA exposed pregnancies, 22 (15.6%) ended in SAB. Comparing GA exposed vs. MS unexposed pregnancies or the general population, there was no significant difference in odds of SAB (aOR:[45] 1.41, 95% CI: 0.85-2.38; aOR: 1.52, 95% CI: 0.97-2.37; respectively).

Stillbirth

The one study that conducted inferential analyses for stillbirth did not observe a statistically significant association with GA exposure during pregnancy. An additional two studies (Giannini et al. 2012 and Andersen et al. 2023) reported no stillbirths among GA exposed pregnancies.[46]

- In Tillaut et al. 2022, the probability of stillbirth among GA exposed pregnancies (adjusted probability:[47] 0.001, 95% CI: 0.000-0.002) was similar to both unexposed cohorts (those unexposed during pregnancy and stopped DMT in the year prior to conception adjusted probability: 0.004, 95% CI: 0.001-0.007; those unexposed during pregnancy or in the year prior to conception adjusted probability: 0.004, 95% CI: 0.002-0.006).

Preterm Delivery

None of the five studies that conducted inferential analyses for preterm delivery observed a statistically significant association with GA exposure during pregnancy. One additional study (Fragoso et al. 2013b) only reported descriptive results for preterm delivery.[48]

- In Weber-Schoendorfer et al. 2009, there was no statistically significant difference in odds of preterm births (unadjusted OR: 0.59, 95% CI: 0.01, 3.74) among GA exposed vs. unexposed pregnancies without MS.
- In Giannini et al. 2012, there was no significant difference in preterm delivery between GA exposed and MS unexposed (25% [n=4] vs. 20.1% [n=58], p>0.735).
- In Herbstritt et al. 2016, GA exposure was not significantly associated with an increased risk of preterm birth (aOR:[49] 0.53, 95% CI: 0.21-1.31) compared to DMT unexposed.

[44] Adjusted for year of pregnancy outcome, rank of pregnancy, mean age at pregnancy outcome, health insurance scheme, mean Charlson comorbidity index, and FDep social deprivation index in 2013.
[45] Adjusted for prior abortion, maternal age at LMP, educational level, prior caesarean section, calendar year of birth.
[46] In Giannini et al. 2012, GA exposed pregnancies had no stillbirths. In Andersen et al. 2023, inferential analysis of stillbirth was not possible among the GA exposed cohort due to no events.
[47] Adjusted for year of pregnancy outcome, rank of pregnancy, mean age at pregnancy outcome, health insurance scheme, mean Charlson comorbidity index, and FDep social deprivation index in 2013.
[48] In Fragoso et al. 2013b, GA exposed had one premature delivery (considered "possibly drug-related;" "patient had 3 previous illegally provoked abortions, under precarious conditions of medical care").
[49] It was unclear which confounders were adjusted for. The study considered the following as confounders if associated with both the exposure and outcome (p<0.2): Age at conception, disease duration, BMI, smoking during

- In Nguyen et al. 2019, comparing DMT unexposed, FDA pregnancy category B (i.e., GA), or FDA pregnancy category C & D, there was no significant difference for preterm deliveries (p=0.14). GA exposed pregnancies had similar percentages of preterm birth (17% vs. 20%) compared to DMT unexposed (p-value not reported; no statistically significant differences noted for GA).
- In Andersen et al. 2023, among the 141 GA exposed pregnancies, eight (8.8%) pregnancies ended in preterm birth. Comparing GA exposed vs. MS unexposed pregnancies or the general population, there was no significant difference in odds of preterm birth (aOR:[50] 1.28, 95% CI: 0.51-3.17; aOR: 1.30, 95% CI: 0.58-2.95; respectively).

Small for gestational age (SGA), Birth Weight, and Birth Length

Two of the four studies that conducted inferential analyses for SGA, birth weight, or birth length observed a statistically significant association with GA exposure during pregnancy. One additional study (Weber-Schoendorfer et al. 2009) only reported descriptive results for birth weight.[51]

- In Giannini et al. 2012, there were no significant differences in mean birth weight and length in GA exposed vs. MS unexposed (p=0.751).
- Fragoso et al. 2013b conducted a retrospective cohort study[52] of pregnancies after MS diagnosis from a database (data submitted by doctors from Brazil, United Kingdom, Mexico, and Argentina). The study included 41 GA exposed (defined as at least eight weeks of continuous exposure to DMT at start of pregnancy), 17 IFN exposed, and 89 unexposed (defined as no DMT exposure for at least three months prior to pregnancy) pregnancies. Birth weight was not significantly different in GA exposed vs. unexposed (p=0.09); 19% (n=7 of 37) GA exposed pregnancies had low birth weight (<2500 g). GA exposed had significantly different birth height than unexposed (mean=47.0 ± 5.8 vs. 49.3 ± 2.1 cm; p=0.001). Birth height was similar among GA exposed and IFN exposed (mean=47.2 ± 2.9 cm), and the article noted these birth heights were within normal range (Fragoso et al. 2013b).
- In Herbstritt et al. 2016, there were no differences in mean birth weight (p=0.56) or length (p=0.64) between GA exposed vs. DMT unexposed.
- In Andersen et al. 2023, SGA occurred in 8.8% (n=8) pregnancies exposed to GA, 4.4% (n=31) of pregnancies exposed to any DMT, 3.4% (n=28) pregnancies among women with MS unexposed to DMTs, and 3.0% (n=1,965) pregnancies from the general

pregnancy, relapse during pregnancy, steroid use during any trimester of pregnancy due to MS relapses, steroid use during first trimester, and gestational week of cohort entry.

[50] Adjusted for prior abortion, maternal age at LMP, educational level, prior caesarean section, calendar year of birth.

[51] Weber-Schoendorfer et al. 2009: Mean birth weights of term newborns were 3233 g for IFN-β exposed, 3479 g for GA exposed, 3328 g for MS unexposed, and 3467 g for non-MS unexposed. Although inferential analyses were not reported for GA exposure, birth weights were adjusted for maternal age, gestational age at delivery, smoking, sex of the newborn, and exposure to glucocorticoids.

[52] Reviewer classified Fragoso et al. 2013b as a retrospective cohort study based on details available in the publication (retrospectively analyzed a database to compare pregnancies exposed vs. unexposed to MS drugs), but the publication did not specify a study design.

population. GA exposed pregnancies had significantly higher odds of SGA compared to the MS unexposed cohort (aOR:[53] 3.59, 95% CI: 1.44-8.95) or the general population (aOR: 3.25, 95% CI: 1.59-6.62).

Other Pregnancy or Infant Outcomes

None of the four studies that conducted inferential analyses for other pregnancy or infant outcomes (not covered under the prior sections) observed a statistically significant association with GA exposure during pregnancy. An additional two studies (Giannini et al. 2012 and Fragoso et al. 2013b) reported descriptive results for other pregnancy or infant outcomes.[54]

- In Herbstritt et al. 2016, GA exposure was not significantly associated with an increased risk of cesarean section (aOR:[55] 1.63, 95% CI: 0.83-3.22) compared to DMT unexposed. In the GA exposed cohort, there were no fetal deaths or elective abortions; there was one ectopic pregnancy (0.7%) and one early neonatal death (0.7%).
- In Nguyen et al. 2019, comparing DMT unexposed, FDA pregnancy category B (i.e., GA), or FDA pregnancy category C & D, there were no significant differences for term deliveries (p=0.50). Pregnancies exposed to FDA pregnancy category C & D were more likely to have induced abortions compared to pregnancies unexposed to DMTs or exposed to FDA pregnancy category B (i.e., GA) (p=0.01). GA exposed pregnancies had similar percentages of term deliveries (53% vs. 57%), induced abortion (4% vs. 3%), and unknown pregnancy outcome (20% vs. 14%, p=0.073) compared to DMT unexposed (other p-values not reported; no statistically significant differences noted for GA).
- In Tillaut et al. 2022, the adjusted probabilities[56] among GA exposed pregnancies were similar to both unexposed cohorts (all 95% CIs overlapped) for live birth (0.798, 95% CI: 0.765-0.832), elective abortion (0.135, 95% CI: 0.107-0.163), therapeutic abortion (0.011, 95% CI: 0.002-0.019), ectopic pregnancy (0.003, 95% CI: 0.000-0.007), and others (hydatidiform mole or other abnormal product of pregnancy; 0.012, 95% CI: 0.003-0.021). GA exposed pregnancies had significantly higher adjusted probability of live birth than natalizumab (0.595, 95% CI: 0.537-0.653) or other DMT exposed pregnancies (0.344, 95% CI: 0.271-0.416). GA exposed pregnancies had significantly lower adjusted probability of elective abortion than natalizumab (0.332, 95% CI: 0.277-0.387) or other DMT exposed pregnancies (0.590, 95% CI: 0.514-0.665). In the two

[53] Adjusted for prior abortion, maternal age at LMP, educational level, prior caesarean section, calendar year of birth.

[54] Giannini et al. 2012: Cesarean delivery was observed in 43.8% (n=7) of GA exposed, 44.7% (n=34) of IFN-β exposed, and 45.1% (n=130) of MS unexposed. GA exposed pregnancies had no major complications, voluntary abortions, or extra-uterine pregnancies. Maternal complications occurred in 25% (n=4) of GA exposed and 15% (n=28) MS unexposed pregnancies. Fragoso et al. 2013b: GA exposed and unexposed pregnancies had obstetric (29.2% vs. 28.0%) and neonatal (19.5% vs. 11.2%) complications. Specifically, GA exposed had three induced abortions (none related to fetal abnormalities) and one neonatal death (considered "non-drug-related"). Average Apgar scores were similar in all groups (≥9).

[55] It was unclear which confounders were adjusted for. The study considered the following as confounders if associated with both the exposure and outcome (p<0.2): Age at conception, disease duration, BMI, smoking during pregnancy, relapse during pregnancy, steroid use during any trimester of pregnancy due to MS relapses, steroid use during first trimester, gestational week of cohort entry, and preterm birth (for cesarean section only).

[56] Adjusted for year of pregnancy outcome, rank of pregnancy, mean age at pregnancy outcome, health insurance scheme, mean Charlson comorbidity index, and FDep social deprivation index in 2013.

sensitivity analyses modifying the DMT exposure definition,[57] GA exposed pregnancies (sensitivity analysis 1: 0.161, 95% CI: 0.127-0.195; sensitivity analysis 2: 0.139, 95% CI: 0.111-0.168) had significantly higher adjusted probability of elective abortion than those unexposed during pregnancy and stopped DMT in the year prior to conception (sensitivity analysis 1: 0.100, 95% CI: 0.086-0.113; sensitivity analysis 2: 0.090, 95% CI: 0.074-0.105) but similar probability to those unexposed during pregnancy or in the year prior to conception (sensitivity analysis 1: 0.143, 95% CI: 0.131-0.154; sensitivity analysis 2: 0.142, 95% CI: 0.131-0.154).

- In Andersen et al. 2023, among the 141 GA exposed pregnancies, 26 (18.4%) ended in elective abortion, and 91 (64.5%) pregnancies resulted in live births. It is unclear why the live birth rate for the GA cohort is less than all other cohorts (IFN-β n=633, 72.7%; natalizumab n=177, 69.5%; unexposed n=1,073, 77.2%; general population n=91,112, 70.2%), except dimethyl fumarate (n=58, 58.6%). Comparing GA exposed vs. MS unexposed pregnancies or the general population, there was no significant difference in odds of any adverse event (≥1 MCM, SAB, preterm birth, stillbirth, SGA, or low Apgar score) (aOR:[58] 1.32, 95% CI: 0.85-2.04; aOR: 1.42, 95% CI: 0.97-2.08; respectively). Adjusted analyses of low Apgar scores and placenta complications were not possible among the GA exposed cohort due to low/no events. There were no significant findings for deliver mode (spontaneous delivery, acute cesarean section, etc.) among GA exposed vs. MS unexposed pregnancies or the general population (p≥0.05).

DEPI-I Reviewer Comments:
The currently available evidence remains limited in study quality and the number of comparative observational studies reporting results from inferential analyses for a specific pregnancy outcome. Data from seven cohort studies reviewed did not report potential associations between in utero GA exposure and MCMs, SAB, stillbirth, preterm delivery, and other pregnancy or infant outcomes. Data for SGA (when also considering studies of birth weight) and birth length were inconsistent and scarce.

Only one retained study (Andersen et al. 2023) evaluated SGA as an outcome. Andersen et al. 2023 reported statistically significantly higher odds of SGA among GA exposed pregnancies compared to MS unexposed pregnancies (aOR: 3.59, 95% CI: 1.44-8.95) or pregnancies from the general population (aOR: 3.25, 95% CI: 1.59-6.62). These findings should be interpreted cautiously. The wide confidence intervals, likely due to limited sample size of GA exposed pregnancies, are not informative. Anderson et al. 2023 was designed to compare outcomes among a composite DMT exposed cohort vs. control cohorts; additionally, they investigated comparisons for numerous individual DMT exposures and pregnancy outcomes. They did not adjust for multiple comparisons, which could have increased the chance of identifying false positive results (Li et al. 2017). The SGA prevalence of 8.8% reported among GA exposed pregnancies in Anderson et al.'s study falls within the range of prevalence estimates (4.6% to 15.3%) from 12 European prospective cohorts (Ruiz et al. 2015), although differences in data collection and SGA outcome definitions limit meaningful comparison. Among the remaining

[57] Sensitivity analysis 1 only included exposures during pregnancy and removed the ≤14 days before conception. Sensitivity analysis 2 included exposures during the 28 days before conception or during pregnancy.
[58] Adjusted for prior abortion, maternal age at LMP, educational level, prior caesarean section, calendar year of birth.

three studies (Giannini et al. 2012, Fragoso et al. 2013b, Herbstritt et al. 2016) evaluating birth weight and length, none reported a statistically significant difference for birth weight, but one (Fragoso et al. 2013b; a low-quality study) reported statistically significantly smaller length in GA exposed compared to unexposed pregnancies. The mean birth length (47.0 ± 5.8 cm) among GA exposed pregnancies in Fragoso et al.'s study is similar to the 10th percentile birth length from WHO growth charts[59] (~47.5 cm for boys and ~47 cm for girls).

Various study limitations should be acknowledged when interpreting study findings:

- ***Limited sample size**: Most cohort studies had limited sample size of GA exposed pregnancies to sufficiently power the studies. Herbstritt et al. 2016 was the only study to report a power calculation, which indicated adequate sample size of GA exposed pregnancies (n=151) "to detect a three-fold increase in major CAs (assuming 4%; power 80%, two-sided p=0.05)." Among retained cohort studies, Tillaut et al. 2022 had the largest sample of 610 GA exposed pregnancies, while remaining studies had smaller sample sizes (≤151 GA exposed pregnancies). Some studies attempted to increase statistical power by including a large control group (Weber-Schoendorfer et al. 2009) or combining various DMTs into one exposure group (Andersen et al. 2023). For the purposes of this review, we limited to analyses of GA exposure only, which were likely underpowered to evaluate associations between GA exposure during pregnancy and risk of adverse pregnancy and infant outcomes.*
- ***Short duration of exposure during pregnancy**: Retained studies included pregnancies with short duration of GA exposure during pregnancy, typically early in pregnancy. Many women were only exposed to GA during the first trimester of pregnancy (86.1% and 98.0% of GA exposed pregnancies in Tillaut et al. 2022 and Herbstritt et al. 2016, respectively). When available in publications, the median duration of GA exposure during pregnancy ranged from 29 (IQR: 5-42) days (Nguyen et al. 2019, data from 2011-2016) up to 7.7 (IQR: 4.5-12) weeks (Andersen et al. 2023). Fragoso et al. 2013b reported a longer exposure duration for any MS drug (included GA, IFN-β, immunoglobulin, and oral corticosteroids; mean: 18.4 ± 13.2 [range: 8-40] weeks), but they did not report exposure duration separately for GA. Thus, these studies are insufficient to inform safety of GA exposure throughout or in the later stages of pregnancy, including all other outcomes other than MCMs, such as minor birth defects, preterm delivery, SGA, etc. (Organization of Teratology Information Specialists (OTIS) 2023).*
- ***Confounding**: Confounding is a limitation because three studies did not adjust for any potential confounders. Four of the seven studies adjusted for confounders in inferential analyses, but findings from observational cohort studies remain susceptible to residual confounding when potential confounders are not adjusted for (e.g., MS severity, corticosteroid treatment for MS relapses during pregnancy (Rodriguez et al. 2019), comorbidities, or lifestyle factors, such as smoking, alcohol, or substance use during pregnancy).*
- ***Selection bias**: Some of the cohort studies are susceptible to selection bias. For example, Weber-Schoendorfer et al. 2009 enrolled patients based on contacts for teratogen risk*

[59] WHO Growth Chart: Birth to 24 months: Boys: Length-for-Age and Weight-for-Age Percentiles, accessed Nov 5, 2024. Available from: https://www.cdc.gov/growthcharts/data/who/GrChrt_Boys_24LW_100611.pdf. WHO Growth Chart: Birth to 24 months: Girls: Length-for-Age and Weight-for-Age Percentiles, accessed Nov 5, 2024. Available from: https://www.cdc.gov/growthcharts/data/who/GrChrt_Girls_24LW_9210.pdf.

assessment, Herbstritt et al. 2016 enrolled patients volunteering to participate in a registry, and Nguyen et al. 2019 included patients from an MS registry, where the authors acknowledged possible selective reporting of pregnancy data. The impact of selection bias may differ across the retained studies. Findings from Weber-Schoendorfer et al. 2009 would be expected to be biased towards the null if controls contacting the teratogen service had exposures associated with adverse pregnancy or infant outcomes. Weber-Schoendorfer et al. 2009 included an MS-control group not exposed to GA, IFN-β, or known teratogens (31% were exposed to glucocorticoids for MS relapse, and 14% were exposed to immunoglobulins); they also included a non-MS control group counseled about "exposures known to be nonteratogenic." Findings from Nguyen et al. 2019 would be expected to be biased away from the null if follow-up adverse pregnancy outcomes were more likely to be reported among exposed than unexposed pregnancies. Selection bias was minimal in studies using administrative data sources.

- ***Exposure misclassification**: Exposure misclassification is a limitation of the cohort studies; this misclassification would be expected to be nondifferential by exposure cohorts and bias findings towards the null. Studies that used administrative dispensing data cannot confirm if or when patients actually took the medication. Studies used various exposure definitions. For instance, Giannini et al. 2012 classified people who discontinued GA within four weeks before conception as exposed, while Tillaut et al. 2022 classified people dispensed GA within 14 days before or during pregnancy as exposed. Other studies required GA exposure at the start of pregnancy, during the first trimester, or anytime during pregnancy.*
- ***External validity**: The cohort studies only included populations outside the United States. Potential differences in prescribing and continuation of GA during pregnancy may limit generalizability of findings to U.S. populations. However, in the absence of data from U.S. populations, findings from non-U.S. populations are informative for labeling.*
- ***MCM outcome definitions**: Studies used different methods to collect and define MCMs. Weber-Schoendorfer et al. 2009 collected birth defects through questionnaires "mailed to the patient or her physician and/or the pediatrician," and they classified birth defects following (Merks et al. 2003) and the National Birth Defects Prevention Study (NBDPS) (Rasmussen et al. 2003). In contrast, Andersen et al. 2023 and Herbstritt et al. 2016 identified congenital malformations from registry data and classified congenital malformations using the EUROCAT definition. Herbstritt et al. 2016 also verified medical problems by contacting the treating pediatrician. Differences in collection and classification of MCMs could limit the comparability of findings across studies.*
- ***Underestimating SAB**: Underestimation of SAB is a limitation for many of the cohort studies. SABs could be underestimated due to enrollment of women during pregnancy (Herbstritt et al. 2016), lack of reporting to databases like the MSBase (Nguyen et al. 2019), administrative data not capturing SABs that do not necessitate healthcare (Tillaut et al. 2022), or data only being available from hospitalized registrations (Andersen et al. 2023).*

A strength of all the cohort studies was the use of a comparator cohort of pregnancies among women with MS not exposed to medications to treat MS. This comparator cohort allows for analyses comparing pregnancy outcomes among GA exposed vs. unexposed pregnancies while controlling for potential confounding from the underlying disease, but these analyses would not control for differences in severity of disease. Although some consider MS to not be associated

with adverse pregnancy outcomes (Wang et al. 2023), a recent systematic review of 15 observational studies reported increased risk of adverse pregnancy outcomes among women with versus without MS (Rahmati et al. 2024). Disease activity or severity may also impact risk of adverse pregnancy outcomes (Bove and Houtchens 2022). Findings may be susceptible to confounding by MS activity or severity, which would be expected to bias findings away from the null if untreated patients had less severe disease than treated patients.

Available data from observational studies are limited and susceptible to limitations. DEPI-I considers the evidence from the seven cohort studies alone as insufficient to rule out a potential risk. However, in the present review or DPMH's 2022 review,[60] DPMH also reviewed data from the applicant's pharmacovigilance database and the literature (e.g., other pharmacovigilance databases, case series, and descriptive studies), so labeling recommendations should consider data from all these relevant sources. FDA Draft Guidance[61] suggests providing risk statements based on all relevant human data, animal data, and/or the drug's pharmacology under the Risk Summary heading of the Pregnancy subsection. Given this guidance and the lack of safety signals identified in the cohort studies reviewed, DEPI-I recommends including available data from observational studies and methodological limitations in Copaxone labeling. DEPI-I did not review results from pharmacovigilance databases, case series, or descriptive studies and defers to DPMH for conclusions and recommendations from these data sources.

DISCUSSION/CONCLUSIONS

DPMH last reviewed GA use during pregnancy in 2022. DPMH and DEPI-I teams did not identify any new safety signals in this review. DPMH and DEPI-I teams agree that the labeling should be updated to reflect the current experience with GA use during pregnancy.

DPMH and DEPI-I do not recommend any postmarketing requirements (PMR) for pregnancy safety studies at the current time.

LABELING RECOMMENDATIONS

DPMH and DEPI-I teams propose labeling updates, which are similar to previous labeling recommendations for subsection 8.1 in 2022. DPMH and DEPI-I refer to the final NDA action for final labeling.

DPMH and DEPI-I Proposed Pregnancy and Lactation Labeling

(b) (4)

[redacted]

[60] Sun W, Dinatale M, Yao LP. Pregnancy Labeling for Copaxone (Glatiramer Acetate Injection). Oct 24, 2022. Silver Spring (MD): Food and Drug Administration. DARRTS Reference ID: 5065768.

[61] Draft Guidance for Industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*. Jul 2020. Silver Spring, MD: Food and Drug Administration. Available at: https://www.fda.gov/media/90160/download. Accessed Nov 13, 2024.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

References

Andersen JB, Sellebjerg F and Magyari M, 2023, Pregnancy outcomes after early fetal exposure to injectable first-line treatments, dimethyl fumarate, or natalizumab in Danish women with multiple sclerosis, Eur J Neurol, 30(1):162-171.

Arabipoor A, Moini A, Nabavi SM, Mohiti S, Mashayekhi M and Zolfaghari Z, 2024, Evaluation of ovarian reserve and the assisted reproductive technology (ART) cycles' outcome as well as the relapse rate within one year after ART in women with multiple sclerosis: a case-control study, J Ovarian Res, 17(1):165.

Barbieri MA, Sorbara EE, Battaglia A, Cicala G, Rizzo V, Spina E and Cutroneo PM, 2022, Adverse Drug Reactions with Drugs Used in Multiple Sclerosis: An Analysis from the Italian Pharmacovigilance Database, Frontiers in Pharmacology, 13.

Bove RM and Houtchens MK, 2022, Pregnancy Management in Multiple Sclerosis and Other Demyelinating Diseases, Continuum (Minneap Minn), 28(1):12-33.

Fernández Liguori N, Klajn D, Acion L, Cáceres F, Calle A, Carrá A, Cristiano E, Deri N, Garcea O, Jaureguiberry A, Onaha P, Patrucco L, Riccio P, Rotta Escalante R, Saladino M, Sinay V, Tarulla A and Villa A, 2009, Epidemiological characteristics of pregnancy, delivery, and birth outcome in women with multiple sclerosis in Argentina (EMEMAR study), Mult Scler, 15(5):555-562.

Fink K, Gorczyca A, Alping P, Englund S, Farmand S, Langer-Gould AM, Piehl F, McKay K, Frisell T and Razaz N, 2023, Multiple sclerosis, disease-modifying drugs and risk for adverse perinatal and pregnancy outcomes: Results from a population-based cohort study, Multiple Sclerosis Journal, 29(6):731-740.

Finkelsztejn A, Fragoso YD, Ferreira ML, Lana-Peixoto MA, Alves-Leon SV, Gomes S, Damasceno BP, Mendes MF, Salgado PR, Correa EC, Comini-Frota ER, Diniz DS, Gama PD, Kaimen-Maciel DR, Morales RR, Arruda WO, Grzesiuk AK, Khouri JM, Lopes JS, Rocha CF, Domingues R, Gonçalves MV, Lorenti MA, Parolin MK, Siquineli F, Tosta ED, Brooks JB, Gallina AS, Melges LD and Ruocco HH, 2011, The Brazilian database on pregnancy in multiple sclerosis, Clin Neurol Neurosurg, 113(4):277-280.

Fragoso YD, Adoni T, Alves-Leon SV, Azambuja ND, Jr., Barreira AA, Brooks JB, Carneiro DS, Carvalho MJ, Claudino R, Comini-Frota ER, Domingues RB, Finkelzstejn A, Gama PD, Giacomo MC, Gomes S, Goncalves MV, Grzesiuk AK, Kaimen-Maciel DR, Mendes MF, Morales NM, Morales RR, Muniz A, Papais-Alvarenga RM, Parolin MK, Ribeiro SB, Ruocco HH, Siquineli F and Tosta ED, 2013a, Long-term effects of exposure to disease-modifying drugs in the offspring of mothers with multiple sclerosis: a retrospective chart review, CNS Drugs, 27(11):955-961.

Fragoso YD, Boggild M, Macias-Islas MA, Carra A, Schaerer KD, Aguayo A, de Almeida SM, Alvarenga MP, Alvarenga RM, Alves-Leon SV, Arruda WO, Brooks JB, Comini-Frota ER, Ferreira ML, Finkelsztejn A, Finkelsztejn JM, de Freitas LD, Gallina AS, da Gama PD, Georgetto S, Giacomo MC, Gomes S, Gonçalves MV, Grzesiuk AK, Kaimen-Maciel DR, Lopes J, Lourenco GA, Malfetano FR, Morales NM, Morales Rde R, Oliveira CL, Onaha P, Patroclo C, Ribeiro SB, Ribeiro TA, Salminen HJ, Santoro P, Seefeld M, Soares PV, Tarulla A and Vasconcelos CC, 2013b, The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis, Clin Neurol Neurosurg, 115(2):154-159.

Fragoso YD, Finkelsztejn A, Comini-Frota ER, da Gama PD, Grzesiuk AK, Khouri JM, Alves-Leon SV, Morales Rde R, Lana-Peixoto MA and Rocha CF, 2009, Pregnancy and multiple sclerosis: the initial results from a Brazilian database, Arq Neuropsiquiatr, 67(3a):657-660.

Giannini M, Portaccio E, Ghezzi A, Hakiki B, Pastò L, Razzolini L, Piscolla E, De Giglio L, Pozzilli C, Paolicelli D, Trojano M, Marrosu MG, Patti F, La Mantia L, Mancardi G, Solaro C, Totaro R, Tola MR, De Luca G, Lugaresi A, Moiola L, Martinelli V, Comi G and Amato MP, 2012, Pregnancy and fetal outcomes after Glatiramer Acetate exposure in patients with multiple sclerosis: a prospective observational multicentric study, BMC Neurol, 12:124.

Hellwig K and Gold R, 2011, Glatiramer acetate and interferon-beta throughout gestation and postpartum in women with multiple sclerosis, J Neurol, 258(3):502-503.
Hellwig K, Haghikia A, Rockhoff M and Gold R, 2012, Multiple sclerosis and pregnancy: experience from a nationwide database in Germany, Ther Adv Neurol Disord, 5(5):247-253.
Herbstritt S, Langer-Gould A, Rockhoff M, Haghikia A, Queisser-Wahrendorf A, Gold R and Hellwig K, 2016, Glatiramer acetate during early pregnancy: A prospective cohort study, Mult Scler, 22(6):810-816.
Hradilek P, Meluzinova E, Zapletalova O, Hanulikova P, Horakova D, Woznicova I, Pavliska L, Stetkarova I, Valis M, Stourac P, Adamkova J, Ampapa R, Vachova M and Mares J, 2022, Is pregnancy in MS patients safe and what is its impact on MS course? Real World evidence of 1533 pregnancies in Czech Republic, Multiple Sclerosis and Related Disorders, 59.
Islam MM, Iqbal U, Walther B, Atique S, Dubey NK, Nguyen PA, Poly TN, Masud JH, Li YJ and Shabbir SA, 2016, Benzodiazepine Use and Risk of Dementia in the Elderly Population: A Systematic Review and Meta-Analysis, Neuroepidemiology, 47(3-4):181-191.
Kaplan S, Zeygarnik M and Stern T, 2022, Pregnancy, Fetal, and Infant Outcomes Following Maternal Exposure to Glatiramer Acetate During Pregnancy and Breastfeeding, Drug Saf, 45(4):345-357.
Kaplan S, Zeygarnik M, Stern T and Hellwig K, 2023, Pregnancy and fetal outcomes following maternal exposure to glatiramer acetate in all three trimesters of pregnancy, Eur J Neurol, 30(12):3890-3895.
Kasatkin DS, Spirin NN, Vinogradova TV and Shitova AS, 2018, Effects of the Treatment of Mothers with Multiple Sclerosis Using Disease-Modifying Drugs on Child Development, Neuroscience and Behavioral Physiology, 48(7):864-869.
Krysko KM, Anderson A, Singh J, McPolin K, Rutatangwa A, Rowles W, Sadovnick AD, Houtchens MK and Bove R, 2022, Risk factors for peripartum depression in women with multiple sclerosis, Multiple Sclerosis Journal, 28(6):970-979.
Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, Devereaux PJ and Thabane L, 2017, An introduction to multiplicity issues in clinical trials: the what, why, when and how, Int J Epidemiol, 46(2):746-755.
Lu E, Dahlgren L, Sadovnick A, Sayao A, Synnes A and Tremlett H, 2012, Perinatal outcomes in women with multiple sclerosis exposed to disease-modifying drugs, Mult Scler, 18(4):460-467.
MacDonald SC, McElrath TF and Hernández-Díaz S, 2019, Use and safety of disease-modifying therapy in pregnant women with multiple sclerosis, Pharmacoepidemiol Drug Saf, 28(4):556-560.
Mainguy M, Tillaut H, Degremont A, Le Page E, Mainguy C, Duros S, Polard E and Leray E, 2022, Assessing the Risk of Relapse Requiring Corticosteroids After In Vitro Fertilization in Women With Multiple Sclerosis, Neurology, 99(17):E1916-E1925.
Merks JH, van Karnebeek CD, Caron HN and Hennekam RC, 2003, Phenotypic abnormalities: terminology and classification, Am J Med Genet A, 123a(3):211-230.
Moccia M, Affinito G, Fumo MG, Giordana R, Di Gennaro M, Mercogliano M, Carotenuto A, Petracca M, Lanzillo R, Triassi M, Brescia Morra V and Palladino R, 2023, Fertility, pregnancy and childbirth in women with multiple sclerosis: A population-based study from 2018 to 2020, Journal of Neurology, Neurosurgery and Psychiatry, 94(9):689-697.
Nguyen AL, Havrdova EK, Horakova D, Izquierdo G, Kalincik T, van der Walt A, Terzi M, Alroughani R, Duquette P, Girard M, Prat A, Boz C, Sola P, Ferraro D, Lugaresi A, Lechner-Scott J, Barnett M, Grand'Maison F, Grammond P, Ramo-Tello C, Turkoglu R, McCombe P, Pucci E, Trojano M, Granella F, Spitaleri D, Van Pesch V, Soysal A, Oreja-Guevara C, Verheul F, Vucic S, Hodgkinson S, Slee M, Ampapa R, Prevost J, Menoyo JLS, Skibina O, Solaro C, Olascoaga J, Shaw C, Madsen KG, Naidoo K, Hyde R, Butzkueven H and Jokubaitis V, 2019, Incidence of pregnancy and disease-modifying therapy exposure trends in women with multiple sclerosis: A contemporary cohort study, Mult Scler Relat Disord, 28:235-243.
Organization of Teratology Information Specialists (OTIS), 2023, Mother To Baby | Fact Sheets [Internet]. Brentwood (TN): OTIS; 1994-. Critical Periods of Development,, accessed Nov 18, 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK582659/.

Rahmati S, Galavi Z, Kavyani B, Arshadi H, Geerts J and Sharifi H, 2024, Maternal and neonatal outcomes in pregnant women with multiple sclerosis disease: A systematic review and meta-analysis, Midwifery, 134:104004.
Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM and Moore CA, 2003, Guidelines for case classification for the National Birth Defects Prevention Study, Birth Defects Res A Clin Mol Teratol, 67(3):193-201.
Rodriguez A, Wang Y, Ali Khan A, Cartwright R, Gissler M and Järvelin MR, 2019, Antenatal corticosteroid therapy (ACT) and size at birth: A population-based analysis using the Finnish Medical Birth Register, PLoS Med, 16(2):e1002746.
Ruiz M, Goldblatt P, Morrison J, Kukla L, Švancara J, Riitta-Järvelin M, Taanila A, Saurel-Cubizolles MJ, Lioret S, Bakoula C, Veltsista A, Porta D, Forastiere F, van Eijsden M, Vrijkotte TG, Eggesbø M, White RA, Barros H, Correia S, Vrijheid M, Torrent M, Rebagliato M, Larrañaga I, Ludvigsson J, Olsen Faresjö Å, Hryhorczuk D, Antipkin Y, Marmot M and Pikhart H, 2015, Mother's education and the risk of preterm and small for gestational age birth: a DRIVERS meta-analysis of 12 European cohorts, J Epidemiol Community Health, 69(9):826-833.
Sadovnick D, Criscuoli M, Yee I, Carruthers R, Schabas A, Devonshire V and Smyth P, 2023, The Canadian Multiple Sclerosis Pregnancy Study: First-trimester miscarriages in women with multiple sclerosis, Multiple Sclerosis Journal, 29(3):407-414.
Sportiello L, Di Napoli R, Balzano N, Mascolo A, Ruggiero R, Di Costanzo L, Monaco D, Maniscalco GT and Capuano A, 2023, Disease-Modifying Therapies (DMTs) in Pregnant and Lactating Women with Multiple Sclerosis: Analysis of Real-World Data from EudraVigilance Database, Pharmaceuticals, 16(11).
Swital M, Drouin J, Miranda S, Bakchine S, Botton J and Dray-Spira R, 2024, Use of multiple sclerosis disease-modifying therapies during pregnancy in France: Nationwide study between 2010 and 2021, Mult Scler, 30(2):227-237.
Thiel S, Ciplea AI, Gold R and Hellwig K, 2021, The German Multiple Sclerosis and Pregnancy Registry: rationale, objective, design, and first results, Ther Adv Neurol Disord, 14:17562864211054956.
Tillaut H, Degrémont A, Kerbrat S, Roux J, Le Page E, Mainguy C, Duros S, Polard E and Leray E, 2022, Pregnancy in women with multiple sclerosis in France from 2010 to 2015: Incidence, outcomes, and exposure to disease-modifying therapies, Mult Scler, 28(5):778-789.
Wang Y, Wang J and Feng J, 2023, Multiple sclerosis and pregnancy: Pathogenesis, influencing factors, and treatment options, Autoimmun Rev, 22(11):103449.
Weber-Schoendorfer C and Schaefer C, 2009, Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study, Mult Scler, 15(9):1037-1042.
Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P, 2021, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, accessed Oct 17, 2024. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

APPENDIX A. Congenital Anomalies in All Cases

Table A1. Congenital Anomalies in All Prospective Cases[62]

MedDRA HLT	Event PT name	Event PT count	Categorisation of CA
Anterior and posterior chamber disorders congenital	Developmental glaucoma	1	Major
Autosomal chromosomal abnormalities	Trisomy 18	2	Chromosomal/genetic
	Trisomy 21	1	Chromosomal/genetic
Cardiac disorders congenital NEC	Heart disease congenital	1	Major
Cardiac septal defects congenital	Cardiac septal defect	1	Major
	Atrioventricular septal defect	1	Major
	Ventricular septal defect	3	Major
Cardiac valve disorders congenital	Congenital heart valve disorder	2	Major
Cardiovascular disorders congenital NEC	Congenital cardiovascular anomaly	1	Major

[62] Table 4 of the Interim Analysis Year 4

MedDRA HLT	Event PT name	Event PT count	Categorisation of CA
Chromosomal abnormalities NEC	Chromosomal mutation	1	Chromosomal/genetic
	Cytogenetic abnormality	1	Chromosomal/genetic
	Foetal chromosome abnormality	1	Chromosomal/genetic
Congenital disorders NEC	Congenital anomaly	1	Major
Endocrine disorders congenital NEC	Congenital hyperinsulinaemic hypoglycaemia	1	Not categorised by both EUROCAT and MACDP
Eyelid disorders congenital	Congenital eyelid malformation	1	Major
Gastrointestinal tract disorders congenital NEC	Congenital inguinal hernia	1	Major
	Exomphalos	1	Major
Inborn errors of porphyrin metabolism	Porphyria acute	1	Chromosomal/genetic
Lymphatic system disorders congenital	Lymphatic malformation	2	Major
Male reproductive tract disorders congenital	Cryptorchism	1	Major
	Hydrocele	2	Minor
Musculoskeletal and connective tissue disorders of limbs congenital	Talipes	1	Major
	Clinodactyly	1	Minor
Musculoskeletal and connective tissue disorders of skull congenital	Macrocephaly	1	Major
Non-site specific cartilage disorders congenital	Osteochondrodysplasia	1	Chromosomal/genetic
Optic nerve and optic disc disorders congenital	Congenital optic nerve anomaly	1	Major
Persistent foetal circulation disorders	Patent ductus arteriosus	1	Minor
Renal and urinary tract disorders congenital NEC	Congenital hydronephrosis	1	Major
	Congenital ureteropelvic junction obstruction	1	Major
Renal disorders congenital	Renal aplasia	1	Major
Tongue disorders congenital	Ankyloglossia congenital	5	Minor
Total number of events		**41**	

Source: Teva Global Pharmacovigilance Database (ARISg).
CA=congenital anomaly; EUROCAT=European Registry of Congenital Anomalies and Twins; HLT=high level term; MACDP= Metropolitan Atlanta Congenital Defects Program; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term.

Table A2. Congenital Anomalies in All Retrospective Cases[63]

MedDRA HLT	Event PT name	Event PT count	Categorisation of CA
Autosomal chromosomal abnormalities	Trisomy 21	5	Chromosomal/genetic
Arterial disorders congenital	Pulmonary artery atresia	1	Major
Cardiac septal defects congenital	Ventricular septal defect	2	Major
	Atrioventricular septal defect	1	Major
	Atrial septal defect	2	Minor
		1	Major
Central nervous system disorders congenital NEC	Spina bifida	1	Major
Congenital disorders NEC	Foetal malformation	1	Not categorised by both EUROCAT and MACDP
Ear disorders congenital NEC	Congenital anomaly of inner ear	1	Major
External ear disorders congenital	Anomaly of external ear congenital	1	Minor
Gastric disorders congenital	Pyloric stenosis	1	Major
Great vessel disorders congenital	Congenital aortic anomaly	1	Major
	Transposition of the great vessels	1	Major
Hearing disorders congenital	Deafness congenital	1	Major
Male reproductive tract disorders congenital	Hypospadias	1	Major
	Hydrocele	1	Minor
Multiple cardiac abnormalities congenital	Fallot's tetralogy	1	Major
	Polydactyly	4	Major
	Adactyly	1	Major

[63] Table 5 of the Interim Analysis Year 4

MedDRA HLT	Event PT name	Event PT count	Categorisation of CA
Musculoskeletal and connective tissue disorders of limbs congenital	Congenital musculoskeletal disorder of limbs	1	Major
	Syndactyly	1	Major
	Amniotic band syndrome	1	Major
Musculoskeletal and connective tissue disorders of face, neck and jaw congenital	Gnathoschisis	1	Major
Musculoskeletal and connective tissue disorders of skull congenital	Microcephaly	1	Major
Musculoskeletal disorders congenital NEC	Otospondylomegaepiphyseal dysplasia	1	Major
Non-site specific cartilage disorders congenital	Osteochondrodysplasia	1	Chromosomal/genetic
Non-site specific muscle disorders congenital	Kinematic imbalances due to suboccipital strain	1	Not categorised by both EUROCAT and MACDP
Oral cavity disorders congenital NEC	Labial tie	2	Minor
Palate disorders congenital	Cleft lip and palate	2	Major
Pancreatic disorders congenital	Congenital pancreatic anomaly	1	Major
Persistent foetal circulation disorders	Patent ductus arteriosus	1	Not categorised by both EUROCAT and MACDP
Renal and urinary tract disorders congenital NEC	Congenital urinary tract obstruction	1	Major
Renal disorders congenital	Congenital pyelocaliectasis	1	Major
	Renal aplasia	1	Major
	Pelvic kidney	1	Major
Skin and subcutaneous tissue disorders congenital NEC	Congenital skin disorder	1	Minor
	Congenital skin dimples	1	Not categorised by both EUROCAT and MACDP
Thyroid disorders congenital	Congenital hypothyroidism	1	Not categorised by both EUROCAT and MACDP
Tongue disorders congenital	Ankyloglossia congenital	3	Minor
Total number of events		**52**	

Source: Teva Global Pharmacovigilance Database (ARISg).

CA=congenital anomaly; EUROCAT=European Registry of Congenital Anomalies and Twins; HLT=high level term; MACDP= Metropolitan Atlanta Congenital Defects Program; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term.

APPENDIX B. Analysis of Pregnancy Cases with Questionnaires

Questionnaires were sent for 1-month post-delivery follow-up and for the 12-month post-delivery follow-up. The return rate for questionnaires was 49.73%.[64] A total of 759 patients completed at least one follow up questionnaires and were therefore included in this analysis.

- 712 (505 prospective and 207 retrospective) completed 1-month questionnaires
- 384 (268 prospective and 116 retrospective) completed 12-month questionnaires

The countries with highest number of reports were Germany (23.22%), Canada (14.49%), and Turkey (12.38%).

Demographic Characteristics

Overall, the mean maternal age was 31.90 (SD±4.50) years, and the median maternal age was 32 (19;49) years. The mean maternal pre-pregnancy BMI was 24.74 (SD±5.50) kg, median was 23.34 (16.53;54.05). 84.98% were on 40mg/mL dose. The distribution of demographics between prospective and retrospective cases are similar. There were more cases of GA use due to MS indication in the retrospective cohort (82.43%) than the prospective cohort (72.41%); the prospective cohort had more GA use due to relapsing-remitting MS (20.33%) than the retrospective cohort (11.26%). There were more prospective cases (28.95%) that used GA throughout pregnancy than the retrospective cohort (17.96%).

Primary outcome

Congenital Anomalies

There were 14 MCM among 492 prospective fetuses[65] with 1st trimester exposure to GA.[66] The rate of MCM is 2.84 per 100 live births. Among the 14 MCM, top three SOC involved included cardiovascular abnormalities (n=5), genitourinary abnormalities (n=4) and lymphatic abnormalities (n=2).

The MCMs were categorized based on both EUROCAT and MACDP definitions as per protocol (and see Table 26 of the Interim Analysis). The rate of MCM is comparable to the background rate based on EUROCAT definition, 2.00 per 100 births and the MACDP definition, 3 per 100 live births.

The rate of congenital heart defects is approximately 1%, which is consistent with the background rate in the general population.[67]

[64] 833 unique cases (not duplicated) with initially received date of June 1, 2018 to March 31, 2023, and latest received date was April 1, 1011 to March 31, 2023 were included in the analysis. 440 cases did not give consent or they were lost to follow up. 393 gave consent for the study. Overall, 561 questionnaire were sent (1 month, 12 month, or both), 279 questionnaire were received.

[65] There were 523 fetus (prospective) that had an exposed during pregnancy. The rate of MCM is 2.68 per births.

(b) (6)

[redacted]

[67] Liu Y, et al. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. International Journal of Epidemiology, 2019, 455–463

Other Pregnancy Outcomes

Live Births, Spontaneous Abortions, Stillbirths, Pregnancy Terminations

The findings of secondary outcomes are summarized in the table below.

Table 2. Pregnancy Outcomes in GA Exposed Women Who Completed Questionnaires[68]

Pregnancy Outcomes	**Prospective**	**Retrospective**	**Total**
Number of Pregnancies completed Questionnaires	531	220	759
Number of Fetus with Known Results [69]	552	228	780
Live birth (fetus)	523 (94.75 %)	189 (82.9%)	712 (91.3%)
All Fetal Deaths[70] (fetus)			
Ectopic	1 (0.18%)	2 (0.88%)	3 (0.38%)
SB	0	0	0
SAB	26 (4.71%)	33 (14.47%)	59 (7.5%)
Fetal death with unknown gestation	0	0	0
Pregnancy Terminations (fetus)	2 (0.36%)	4 (1.76%)	6 (0.76%)

The Applicant also conducted an analysis to compare the fetal outcomes of those exposed to GA at 20 mg/mL versus 40 mg/mL. There are a higher number of live births in the prospective 40 mg/mL (95.14%) than 20 mg/mL (92.31%) group, and lower rates of SAB in 40 mg/mL (4.44%) compared to the 20 mg/mL (6.15%) group. There are fewer patients in the 20 mg/mL (n=94) compared to the 40 mg/mL (n=645) group.

Reviewers' comments:
Higher doses of GA did not impact pregnancy outcome adversely. This finding is consistent with the finding in the overall analysis.

Characteristics of Live Births including Preterm Births, Low Birth Weights, and NICU Admissions

[68] Reviewers' Table with data extracted from Table 17 of the Interim Analysis Year 4
[69] Including 1 case with triplets (live births) and 19 twin cases with known outcome (16 pairs with both live birth; 1 pair with both spontaneous abortion; 2 pairs
with live birth and spontaneous abortion).
[70] Fetal deaths include ectopic pregnancies, SAB, SB, death of fetus with unknown gestational age.

Table 3. Characteristics of Live Births[71]

Birth characteristics	Prospective	Retrospective	Total
Total live birth pregnancies (mother count), n (%)	512 (73.78)	182 (26.22)	694 (100.00)
Single gestations	499 (97.46)	176 (96.70)	675 (97.26)
Multiple gestations	13 (2.54)	6 (3.30)	19 (2.74)
Gestational age at the time of birth (weeks)			
Total, n	489	170	659
Mean (SD)	38.72 (1.92)	38.87 (2.23)	38.76 (2.00)
Median (min;max)	39 (24;42)	39 (23;42)	39 (23;42)
Mode of delivery, n (%)			
Vaginal birth	266 (51.95)	114 (62.64)	380 (54.76)
Caesarean section	212 (41.41)	61 (33.52)	273 (39.34)
Unknown	34 (6.64)	7 (3.85)	41 (5.91)
Induction, n (%)	9 (1.76)	8 (4.40)	17 (2.45)
Preterm birth, n (%)	50 (9.77)	16 (8.79)	66 (9.51)
Breastfeeding (whilst on GA), n (%)	155 (30.27)	59 (32.42)	214 (30.84)
Total live birth neonates (foetus count), n (%)	523 (73.46)	189 (26.54)	712 (100.00)
Infant gender, n (%)			
Male	280 (53.54)	86 (45.50)	366 (51.40)
Female	220 (42.07)	99 (52.38)	319 (44.80)
Unknown	23 (4.40)	4 (2.12)	27 (3.79)
Infant birth weight (kg)			

Birth characteristics	Prospective	Retrospective	Total
Total, n	481	171	652
Mean (SD)	4.24 (0.55)	3.21 (0.64)	3.23 (0.58)
Median (min; max)	3.25 (0.45; 5.3)	3.25 (0.67; 5.66)	3.25 (0.45; 5.3)
Infant birth height (cm)			
Total, n	458	196	654
Mean (SD)	49.62 (3.70)	49.49 (3.94)	49.58 (3.77)
Median (min;max)	50 (20;59)	50 (20.5;58)	50 (20;59)
Adverse foetus/birth outcomes, n (%)			
Low/very low birth weight	38 (7.27)	21 (11.11)	59 (8.29)
Hospitalisation in NICU	45 (8.60)	19 (10.05)	64 (8.99)

Source: Teva Global Pharmacovigilance Database (ARISg).
GA=glatiramer acetate; max=maximum; min=minimum; n=number of patients in the subgroup; NICU=neonatal intensive care unit; SD=standard deviation.
Note: Percentages may not add up to 100 due to rounding.

It is unclear if this is a typo since the median is far from the mean and the spread is similar to the All-Case table, if the actual number should be 3.24.

[71] Table 18 of Interim Analysis Year 4

The Applicant also conducted an analysis to compare the fetal outcomes of those exposed to GA at 20 mg/mL versus 40 mg/mL, the results are similar between the groups. Overall, there were fewer patients in the 20 mg/mL (n=82) group compared with 40 mg/dL (n=593) group. Therefore, there was a higher percentage of LBW infants and NICU admissions in the prospective cohort taking GA 20 mg/mL (n=5, 8.33% and n=10, 16.67%, respectively) compared to GA 40 mg/mL(n=31, 6.89% and n=49, 10.89%).

Infant Adverse Events
After excluding maternal events, there are 194 infant events by SOC. This can be found in Table 21 of the Interim Analysis. The top SOCs listed are as follows.

- 46 events (23.71%) represent SOC "Pregnancy, puerperium and perinatal conditions",
- 41 events (21.13%) represent SOC "Infections and infestations",
- 23 events (11.86%) represent SOC "Investigations",
- 12 events (6.19%) represent SOC “Respiratory, thoracic and mediastinal disorders”
- 10 events (5.15%) represent SOC “Nervous system disorders”

All other SOCs are presented by 8 (4.12%) events or less. The Applicant did not identify any trends.

Child Development
According to the 12-month questionnaires, the following data were collected.[72]

- Weight and Height
    - Information on weight was collected in 237 infants who had mean weight of 10.11 (SD±1.48) kg and median weight of 10.00 (6.95; 15.50) kg.
    - Information on height was collected in 206 infants who had a mean height of 77.15 (SD±5.01) cm and median height of 76.35 (62; 97) cm.
    - 21 infants were overweight (≥98th percentile) and 5 infants were under weight (<2nd percentile).

    DPMH Reviewer Comment: Both mean and median weight and height are within 10-90 percentile for 12 months of age.
- 348 cases reported hospitalization status, 25 cases or 26 infants (7.18%) were hospitalized.
    - 17 cases (18 infant) were hospitalized due to an infection. The rate of hospitalization was 4.89%, which was lower than the rate of

[72] Table 22 of the Interim Analysis Year 4

hospitalization reported in the general background.[73,74,75,76,77] The Applicant also compared the rate to COBRA study which was published by Ciplea et al, 2022. This study of breastfed infants exposed and unexposed to GA from the German MS Pregnancy Registry did not show a difference between the rate of hospitalization in the two cohorts.

DPMH Reviewer Comment: The majority of hospitalizations were related to infection. This reviewer agrees that this percentage of hospitalized patients is not increased from the background rate. DPMH has previously reviewed the COBRA study and concluded that the data were insufficient to identify any adverse effects on the breastfed infant. See DPMH review on March 28, 2022, DARRTS Reference ID 4959522.

- There were 282 questions answered about organ system abnormalities in infants; there were 11 reports of infants (3.90%) with an organ system abnormality.
    - 2 reported developmental issues
        - Case no. (b) (6): the child was exposed to GA before pregnancy and during the first trimester. The gynecologist reported unusual development in gross motor skills (sitting and rolling over without help), fine motor skills (picking up small objects between thumb and index finger), speech, perception/emotional and social skills (react to simple demands, recognizing familiar persons). No additional information was collected (co-medications) to assess

[73] "During 2003, the US national infectious disease hospitalization rate was 7010.8 hospitalizations per 100,000 live births, or approximately 7 infectious disease hospitalization for every 100 infants." Yorita KL, Holman RC, Sejvar JJ, Steiner CA, Schonberger LB. Infectious disease hospitalizations among infants in the United States. Pediatrics 2008;121(2):244-52.

[74] "From 2000 to 2012, the rate of infectious disease hospitalizations in infants <1 year old decreased from approximately 700 to approximately 500 per 10,000 US children (approximately 5%-7%)" Goto T, Tsugawa Y, Mansbach JM, Camargo CA Jr, Hasegawa K. Trends in infectious disease hospitalizations in US children, 2000 to 2012. Pediatr Infect Dis J 2016;35(6):e158-63.

[75] "The frequency of infectious disease-related hospitalization in infants <1 year old was 3,074 (95% CI, 2,472-3,724) per 100,000 children (approximately 3%) in 2011, based on the Nationwide Emergency Department Sample." Hasegawa K, Tsugawa Y, Cohen A, Camargo CA Jr. Infectious disease-related emergency department visits among children in the United States. Pediatr Infect Dis J 2015;34(7):681-5.

[76] "The mean annual crude infectious disease hospitalization rate in infants <1 year old was 5,561.9 (95% CI 5,355.2- 5,768.7) per 100,000 population (5.6%) from 2001 to 2014 in the US calculated by using the National (Nationwide) Inpatient Sample." Kennedy JL, Haberling DL, Huang CC, Lessa FC, Lucero DE, Daskalakis DC, et al. Infectious disease hospitalizations: United States, 2001 to 2014. Chest 2019;156(2):255-68.

[77] "Based on the abovementioned studies, infectious disease hospitalization rate in infants <1 year old ranged from 3 to7% in the US. Higher rates were reported in New Zealand. From 2005 to 2011, there were 69,902 infectious disease admissions for 46,657 children <2 years old in New Zealand." Seibt S, Gilchrist CA, Reed PW, Best EJ, Harnden A, Camargo CA Jr, et al. Hospital readmissions with acute infectious diseases in New Zealand children < 2 years of age. BMCPediatr 2018;18(1):98.

causal effect of GA or what the specific developmental issue was.

- Case no. [redacted] (b) (6): the child was exposed to GA before pregnancy and during the first trimester. Co-medical conditions included hypothyroidism. Labor was complicated with premature rupture of membrane (delivery at 38 weeks), secondary uterine inertia, obstructed labor in the expulsion stage, beginning chorioamnionitis and ventouse extraction from middle of pelvis. The child was admitted to the NICU after birth due to adaption disorder and for continuous positive airway pressure. At the 12=month questionnaire, the mother reported the child had an enlarged right side of its body to include the right hand, foot, arm leg, and tongue with positive development and partial normalization. No other data were provided. The child was breastfed, but there was no GA exposure during lactation.

- 6 cases involved area/organ system abnormalities (cardiac septal defect, cardiac murmur, skin dimples, ankyloglossia congenital, congenital ureteropelvic junction obstruction)
- 1 case reported juvenile idiopathic arthritis; there was family history of this condition.
- 1 reported case of West syndrome and hypotonia.
- 1 reported case of hemangioma.

APPENDIX C. DEPI-I's Literature Search Strategy

Parameter	Details
Date of search	September 26, 2024
Database	PubMed and Embase
Search terms	("copaxone" OR "glatiramer") AND ("pregnancy" or "prenatal" or "in utero")
Years included in search	2022-2024
Language	English
Species	Human

Source: Reviewer generated.

APPEARS THIS WAY ON ORIGINAL.

APPENDIX D. Quality Rating of Cohort Studies Retained in DEPI-I's Literature Search: The Newcastle-Ottawa Scale, Listed in Chronological Order[a]

Study (Author, Year)	Selection 1) Representativeness of the exposed cohort 2) Selection of the non-exposed cohort 3) Ascertainment of exposure 4) Demonstration that outcome of interest was not present at start of study	Comparability 1) Comparability of cohorts on the basis of the design or analysis	Outcome 1) Assessment of outcome 2) Was follow-up long enough for outcomes to occur 3) Adequacy of follow up of cohorts
	One star may be allocated for each numbered item, except comparability that can be allocated two stars.		
Weber-Schoendorfer et al. 2009	★★★		★
Giannini et al. 2012	★★★★	★★	★★
Fragoso et al. 2013b	★★		★★
Herbstritt et al. 2016	★★★★	★★	★★★
Nguyen et al. 2019	★★★		★
Tillaut et al. 2022	★★★★	★★	★★★
Andersen et al. 2023	★★★★	★★	★★★

Source: Reviewer generated.

[a] Ratings for Selection, Comparability, and Outcome were applied from Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P, 2021, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, accessed Oct 17, 2024. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

APPENDIX E. Evidence Table Summarizing Studies Retained in DEPI-I's Literature Search, Listed in Chronological Order

Author, Year	Study Design	Population	Exposure	Outcome(s)	Covariate Adjustment	Results (Risk Estimates + Confidence Intervals)	Comment
Weber-Schoendorfer et al. 2009	Prospective cohort	Pregnancies enrolled in the Teratology Information Service (TIS), Berlin from 1996-2007	Exposure at least during the first trimester • Glatiramer acetate (GA): n=31 • Interferon (IFN)-β: n=69 • Multiple sclerosis (MS) unexposed to GA or IFN: n=64 • Non-MS unexposed: n=1,556	Major birth defects, spontaneous abortion (SAB), stillbirth (results not reported), preterm delivery (<37 weeks), gestational age at delivery (results not reported), and birth weight	Odds ratios (ORs) were not adjusted for covariates. Birth weights were adjusted for maternal age, gestational age at delivery, smoking, sex of the newborn, and exposure to glucocorticoids.	There were no statistically significant differences in odds of SAB (OR: 0.39, 95% confidence interval [CI]: 0.01-2.48), preterm births (OR: 0.59, 95% CI: 0.01, 3.74), all birth defects (OR: 1.28, 95% CI: 0.14, 5.3), or major birth defects (OR: 4.99, 95% CI: 0.54, 22.19) among GA exposed vs. non-MS unexposed pregnancies. IFN-β1b exposed pregnancies had significantly higher SAB prevalence than GA exposed pregnancies (27.8% vs. 3.9%, p=0.03). Mean birth weights of term newborns were 3233 g for IFN-β exposed, 3479 g for GA exposed, 3328 g for MS unexposed, and 3467 g for non-MS unexposed. Among GA exposed pregnancies, there were two major birth defects (club feet and atrioventricular canal).	Wide CI due to small sample size of GA exposed pregnancies; ORs were unadjusted and prone to confounding; glucocorticoids and immunoglobulins used more frequently in MS unexposed (31% and 14%) vs. GA (9.7% and 0%) or IFN-β (11.6% and 1.5%) exposed, respectively; potential selection bias due to patients enrolling in TIS for risk assessment; median GA exposure duration during pregnancy (DP) was 6.9 weeks, only 25% continued GA longer than gestational week 7
Giannini et al. 2012	Prospective cohort	MS patients from 21 Italian MS Centers with pregnancy from 2002-2008	Exposure defined as discontinued disease-modifying therapy (DMT) <4 weeks from conception • GA exposed pregnancies: n=17 • IFN-β exposed pregnancies: n=88	SAB, birth weight, birth length, preterm birth (<37 weeks), and cesarean delivery	Age at conception; educational level; disease duration, Expanded Disability Status Scale (EDSS); previous pregnancies and abortions; smoking, alcohol, and substance	SAB occurred in 5.9% (n=1) of GA exposed, 7.9% (n=7) of IFN-β exposed, and 6.3% (n=20) of unexposed. GA exposure was not significantly associated with SAB (adjusted odds ratio [aOR]: 0.44, 95% CI: 0.04, 4.51; publication did not specify the comparator group used). There was no significant difference in preterm delivery between GA exposed (25%, n=4) and unexposed (20.1%, n=58) (p>0.735).	Small sample size of GA exposed pregnancies; recall bias because data were collected up to 6 months after delivery; exposure misclassification (exposure definition may have misclassified pregnancies not exposed as exposed); potential selection bias due to study enrollment; 40 MS unexposed pregnancies

Author, Year	Study Design	Population	Exposure	Outcome(s)	Covariate Adjustment	Results (Risk Estimates + Confidence Intervals)	Comment
			• MS unexposed pregnancies: n=318 (discontinued DMT ≥4 weeks from conception or never treated with DMTs)		exposure DP; gestational age; caesarean delivery; and infant gender	There were no significant differences in mean birth weight and length in GA exposed vs. unexposed (p=0.751). Cesarean delivery was observed in 43.8% (n=7) of GA exposed, 44.7% (n=34) of IFN-β exposed, and 45.1% (n=130) of unexposed. GA exposed pregnancies had no major complications, malformations, stillbirths, voluntary abortions, or extra-uterine pregnancies. Maternal complications occurred in 25% (n=4) of GA exposed and 15% (n=28) unexposed pregnancies.	received glucocorticoids vs. no exposed pregnancies; mean GA exposure duration DP was 4.9 ± 2.8 (range: 2-12) weeks
Fragoso et al. 2013b	Retrospective cohort (determined by reviewer; not specified by authors)	Pregnancies after MS diagnosis from a database studying DMT exposure DP (data submitted by doctors from Brazil, United Kingdom, Mexico, and Argentina)	≥8 weeks continuous exposure to DMT at start of pregnancy • GA exposed: n=41 • IFN exposed: n=17 • Unexposed (no DMT exposure for ≥3 months prior to pregnancy): n=89	Obstetric complications, neonatal complications, birth weight and height, Apgar score	No covariates adjusted for.	GA exposed and unexposed pregnancies had obstetric (29.2% vs. 28.0%) and neonatal (19.5% vs. 11.2%) complications Specifically, GA exposed had 2 SAB (obstetricians in charge of case considered "non-drug-related") and 3 induced abortions (none related to fetal abnormalities), 1 premature delivery (considered "possibly drug-related;" "patient had 3 previous illegally provoked abortions, under precarious conditions of medical care"), 1 neonatal death (considered "non-drug-related"), and one bone malformation (considered "non-drug-related"). Birth weight was not significantly different in GA exposed vs. unexposed (p=0.09); 19% (n=7 of 37) GA exposed pregnancies had low birth weight (<2500 g). GA exposed had significantly smaller birth height than unexposed (47.0 ± 5.8 vs. 49.3 ± 2.1 cm; p=0.001).	Small sample size; cases may not be representative of pregnancies in MS population; confounding, higher baseline EDSS in exposed vs. unexposed; inferential analyses only reported for birth weight and height, while other results were descriptive; mean follow-up <50 months after delivery, so longer follow-up is needed for certain neonatal risks (e.g., neurodevelopment); mean exposure duration DP (any DMT) was 18.4 ± 13.2 (range: 8-40) weeks

Author, Year	Study Design	Population	Exposure	Outcome(s)	Covariate Adjustment	Results (Risk Estimates + Confidence Intervals)	Comment
						Average Apgar scores were similar in all groups (≥9).	
Herbstritt et al. 2016	Prospective cohort	Pregnancies among women with relapsing remitting MS (RRMS) enrolled in the German MS and Pregnancy Registry from 2008-2013	• GA exposed (administered after the last menstrual period [LMP]): n=151 • DMT unexposed: n=95	Congenital anomalies (CAs), major CA, SAB, fetal death, early neonatal death, preterm birth, elective abortion, ectopic pregnancies, cesarean section, and birth weight and length	Age at conception, disease duration, body mass index (BMI), smoking DP, relapse DP, steroid use DP (any trimester) due to MS relapses, steroid use during first trimester, gestational week of cohort entry, and preterm birth (for cesarean section only)	GA exposure was not significantly associated with an increased risk of SAB (aOR: 0.93, 95% CI: 0.30-2.85), any CA (aOR: 0.24, 95% CI: 0.06-1.01), major CA (aOR: 0.16, 95% CI: 0.03-0.85), preterm birth (aOR: 0.53, 95% CI: 0.21-1.31), or cesarean section (aOR: 1.63, 95% CI: 0.83-3.22) compared to DMT unexposed. There were no differences in mean birth weight (p=0.56) or length (p=0.64) between GA exposed vs. DMT unexposed. In the GA exposed cohort, there were no fetal deaths or elective abortions, and there was 1 ectopic pregnancy (0.7%) and 1 early neonatal death (0.7%).	Limited sample size; most (n=148) women stopped GA during first trimester (median GA exposure duration DP: 31.0 [range: 0-154] days); potential confounding (unclear which confounders were adjusted for, more relapses and corticosteroids used in unexposed pregnancies vs. GA exposed); potential selection bias due to voluntary registry enrollment; enrollments later in pregnancy may already have diagnosed CAs; SABs may be underestimated due to enrollment during pregnancy; powered to detect 3-fold increase in major CAs
Nguyen et al. 2019	Retrospective cohort	Pregnancies among women with RRMS aged 15-45 years enrolled in the MSBase Registry from 2005-2016	• DMT exposed ○ "FDA pregnancy category B:" GA n=137 ○ "FDA pregnancy category C & D:" IFN-β n=350, natalizumab	Term deliveries, preterm deliveries (<37 weeks), SAB, induced abortions, and unknown outcomes (not reported, lost to follow-up,	No covariates adjusted for in comparisons of pregnancy outcomes by exposure.	Comparing DMT unexposed, FDA pregnancy category B, or FDA pregnancy category C & D, there were no significant differences for term deliveries (p=0.50), preterm deliveries (p=0.14), or SAB (p=0.90). Pregnancies exposed to FDA pregnancy category C & D were more likely to have induced abortions compared to pregnancies unexposed to DMTs or	Limited sample size of GA exposed pregnancies; potential underreporting (MSBase does not mandate reporting of pregnancy data); potential selection bias of pregnancy data reported and detection bias due to more closely following exposed pregnancies;

Author, Year	Study Design	Population	Exposure	Outcome(s)	Covariate Adjustment	Results (Risk Estimates + Confidence Intervals)	Comment
			n=104, rituximab n=2, fingolimod n=21, dimethyl fumarate n=17, azathioprine n=4 • DMT unexposed: n=886	or ongoing pregnancy at data extract)		exposed to FDA pregnancy category B (i.e., GA) (p=0.01). GA exposed pregnancies had similar percentages of term deliveries (53% vs. 57%), preterm birth (17% vs. 20%), SAB (6% vs. 6%), induced abortion (4% vs. 3%), and unknown pregnancy outcome (20% vs. 14%, p=0.073) compared to DMT unexposed (other p-values not reported; no statistically significant differences noted for GA).	median time on GA DP was 52 (IQR: 18-101) days from 2005-2010 and 29 (IQR: 5-42) days from 2011-2016; only 14 GA exposed pregnancies continued therapy throughout pregnancy
Tillaut et al. 2022	Population-based retrospective cohort	Pregnancies among women with MS aged 15-49 years in the French national health insurance database from 2010-2015	• DMT exposed (≥1 DMT received ≤14 days before or DP): n=2,569, including: ○ GA n=610 ○ IFN-β n=1,421 ○ Natalizumab n=304 ○ Other DMTs (fingolimod n=101, dimethyl fumarate n=51, azathioprine n=33, teriflunomide n=13, mycophenolate mofetil n=4, methotrexate n=1) ○ ≥1 DMT n=31 • Unexposed DP and stopped DMT in the	Livebirth; stillbirth (gestational age ≥22 weeks); elective, therapeutic, or spontaneous abortion, ectopic pregnancy; or others (hydatidiform mole or other abnormal product of pregnancy)	Year of pregnancy outcome, rank of pregnancy, mean age at pregnancy outcome, health insurance scheme, mean Charlson comorbidity index, and FDep social deprivation index in 2013	The probabilities of all pregnancy outcomes in the GA exposed were similar to both unexposed cohorts (all 95% CIs overlapped). GA exposed adjusted probabilities: • Live birth: 0.798, 95% CI: 0.765-0.832 • Stillbirth: 0.001, 95% CI: 0.000-0.002 • Elective abortion: 0.135, 95% CI: 0.107-0.163 • Therapeutic abortion: 0.011, 95% CI: 0.002-0.019 • SAB: 0.040, 95% CI: 0.024-0.056 • Ectopic: 0.003, 95% CI: 0.000-0.007 • Other: 0.012, 95% CI: 0.003-0.021 GA exposed pregnancies had significantly higher adjusted probability of live birth than natalizumab (0.595, 95% CI: 0.537-0.653) or other DMT (0.344, 95% CI: 0.271-0.416) exposed pregnancies. GA exposed pregnancies had significantly lower adjusted probability of elective abortion than natalizumab (0.332, 95% CI: 0.277-0.387) or other DMT (0.590, 95% CI: 0.514-0.665) exposed pregnancies.	Administrative claims data cannot capture outcomes not resulting in healthcare (e.g., early SAB); exposure misclassification; 86.1% of GA exposed pregnancies only had reimbursement during the first trimester; residual confounding (lifestyle factors not adjusted for); in the two sensitivity analyses (SA) modifying the DMT exposure definition, GA exposed pregnancies (SA1: 0.161, 95% CI: 0.127-0.195; SA2: 0.139, 95% CI: 0.111-0.168) had significantly higher adjusted probability of elective abortion than those unexposed DP and stopped DMT in the year prior to conception (SA1: 0.100, 95% CI: 0.086-

Author, Year	Study Design	Population	Exposure	Outcome(s)	Covariate Adjustment	Results (Risk Estimates + Confidence Intervals)	Comment
			year prior to conception: n=1,696 • Unexposed DP or in the year prior to conception: n=3,868				0.113; SA2: 0.090, 95% CI: 0.074-0.105) but similar probability to those unexposed DP or in the year prior to conception (SA1: 0.143, 95% CI: 0.131-0.154; SA2: 0.142, 95% CI: 0.131-0.154)
Andersen et al. 2023	Population-based retrospective cohort (determined by reviewer; authors specified as cross-sectional)	Pregnancies resulting in abortion, live birth, or stillbirth captured in the Danish registries from 1997-2018; identified pregnancies in women with MS and a random sample of 5% of Danish general population	• DMT exposed (required treatment adherence for ≥30 consecutive days prior to LMP): n=1,009, including: ○ GA exposed (injection at or after LMP) n=141 ○ IFN-β n=633 ○ Dimethyl fumarate n=58 ○ Natalizumab n=177 • MS unexposed to DMTs: n=1,073 • General population: n=91,112	Stillbirth, MCMs, small for gestational age (SGA), preterm birth (<37 weeks), SAB, placenta complication, low Apgar score (<7), and any adverse event (≥1 MCM, SAB, preterm birth, stillbirth, SGA, or low Apgar score), and delivery mode (spontaneous delivery, acute cesarean section, etc.)	Prior abortion, maternal age at LMP, educational level, prior caesarean section, and calendar year of birth	GA exposed pregnancies had significantly higher odds of SGA vs. MS unexposed cohort (aOR: 3.59, 95% CI: 1.44-8.95) or the general population (aOR: 3.25, 95% CI: 1.59-6.62). Comparing GA exposed vs. MS unexposed pregnancies or the general population, there were no significant differences in odds of MCMs (aOR: 1.07, 95% CI: 0.32-3.65; aOR: 0.76, 95% CI: 0.24-2.34), preterm birth (aOR: 1.28, 95% CI: 0.51-3.17; aOR: 1.30, 95% CI: 0.58-2.95), SAB (aOR: 1.41, 95% CI: 0.85-2.38; aOR: 1.52, 95% CI: 0.97-2.37), or any adverse event (aOR: 1.32, 95% CI: 0.85-2.04; aOR: 1.42, 95% CI: 0.97-2.08). Adjusted analyses of stillbirth, low Apgar scores, and placenta complications were not possible among GA exposed cohort due to low/no events. There were no significant findings for deliver mode among GA exposed vs. MS unexposed pregnancies or the general population (p≥0.05).	Wide confidence intervals, likely due to limited sample size of GA exposed pregnancies; potential confounding due to not adjusting for corticosteroid use DP or lifestyle factors; SAB may be underestimated because the study only included hospitalized registrations; sensitivity analyses confirmed robustness of main analyses for the DMT exposed cohort but not for GA exposure; median GA exposure during pregnancies resulting in live births was 7.7 (IQR: 4.5-12) weeks

Source: Reviewer generated from review of observational studies from the literature.

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/

WENJIE SUN
12/18/2024 12:55:38 PM

CASSIDI C MCDANIEL
12/18/2024 01:25:38 PM

MIRIAM C DINATALE
12/18/2024 01:51:41 PM

CATHERINE L CALLAHAN
12/18/2024 02:01:23 PM

SUKHMINDER K SANDHU
12/18/2024 02:03:51 PM

LYNNE P YAO
12/20/2024 11:33:18 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761262Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 020622/S-118

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-118

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

DATE OF SUBMISSION: July 22, 2024

DATE OF RECEIPT: July 22, 2024

This supplemental application proposes changes to the Prescribing Information, Section 8.1 (Pregnancy) and corresponding patient labeling to align with recent changes to Teva's Company Core Safety Information (CCSI), which was revised to reflect that a moderate amount of data on pregnant women indicate no malformative or fetal/neonatal toxicity and that the use of Copaxone may be considered during pregnancy, if necessary.

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 September 20, 2024, in accordance with 21 CFR: 314.101(a).

If the application is filed, the goal date will be January 22, 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

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/

KRISTEN J HASLAM
08/28/2024 01:03:02 PM

U.S. FOOD & DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**	
TO: CDER Division of Pediatric and Maternal Health *(please check appropriate box(es))* ☐ Pediatric Team ☑ Maternal Health Team			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Kristen Haslam, RPM, Division of Neurology 2, 240-402-4246	
DATE OF CONSULT 07/30/2024	IND NO.	NDA 020622	TYPE OF SUBMISSION Labeling Supplement S-118	DATE OF SUBMISSION 07/22/2024
NAME OF DRUG Copaxone (glatiramer acetate injection)	NAME OF FIRM Teva		DRUG CLASS	INDICATION(S) Multiple Sclerosis
Goal Date 12/22/2024	**DPMH will work with you to establish a suitable due date for the completed consult. Please check one of the three boxes.**			
	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☑ Routine (1 – 10 months)
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from DPMH team leaders.				

REASON FOR REQUEST (check all that apply)

Pediatrics:	Maternal Health Team:
☐ Labeling Review – non-PLLR ☐ Safety Labeling Supplement ☐ 505(b)(2)/ANDA Pediatric Labeling ☐ Industry Meeting Attendance (PDUFA or BSUFA) ☐ Other Industry Meeting Attendance ☐ BPCA-Related Questions or Documents for Review ☐ PREA-Related Questions or Documents for Review ☐ PeRC Preparation Assistance/iPSP Review ☐ SPA ☐ 30-day IND Review ☐ Other Protocol Review ☐ Tracked Safety Issue ☐ Advisory Committee Preparation ☐ Assistance with Guidance development ☐ Assistance with Citizen Petition Response ☐ Medical Necessity Determination ☐ Off-Patent BPCA/409i Related Questions ☐ Other (please explain):	☐ Labeling Review – PLLR ☒ Labeling Review – non-PLLR ☐ Industry Meeting Attendance Pregnancy Exposure Registry (protocol or report) ☐ 30-day IND Review ☐ Evaluation of possible safety signal ☐ Risk Management – Pregnancy Prevention and Planning ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ Guidance development ☐ Advisory Committee Preparation ☐ Citizen Petition ☐ Other (please explain):

Link to electronic submission (if available): EDR Location: \\CDSESUB1\evsprod\NDA020622\0691	Materials to be reviewed:

(1) Please briefly describe the submission:

This submission is for a prior approval labeling supplement proposing changes to the pregnancy section (Section 8.1) of the US Prescribing Information and corresponding patient labeling to align with recent changes to Teva's Company Core Safety Information (CCSI) (provided in the submission as a 1,044 page document), which was revised to reflect that a moderate amount of data on pregnant women indicate no malformative or fetal/neonatal toxicity and that the use of Copaxone may be considered during pregnancy, if necessary.
The sponsor included the USPI, PI, and IFU in the labeling file.
DN2 has also consulted DEPI for review and comments. We have not consulted DB7. Please advise if their review is requested.

Goal dates:
Filing Date: 9/20/24
Action Date: 01/22/24

(2) Describe the reason for your consult. Include specific questions:
Please review and provide comments.

(3) Meeting dates requiring DPMH presence:
DN2 will schedule a labeling team meeting once all reviewers have been assigned. The meeting will be scheduled in December 2024.

(4) Please list any prior Pediatric or Maternal Health consults for this product by date within the last 3 years that may be relevant to this consult (DARRTS Reference ID # if known): None

Review team:
Project Manager: Kristen Haslam
Clinical reviewer & Team Leader: Daniela PimentelMaldonado/ Laura Baldassari
Other: Associate Director of Safety: Alice Hughes
Associate Director of Labeling: Tracy Peters
Consulted Divisions: DEPI

PRINTED NAME or SIGNATURE OF REQUESTOR:
Kristen Haslam

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/

KRISTEN J HASLAM
07/30/2024 12:10:43 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE for DEPI-I			Kristen Haslam, DN2, Kristen.haslam@fda.hhs.gov	
DATE 07/30/2024	IND NO.	NDA NO. 020622	TYPE OF DOCUMENT Labeling Prior Approval Supplement S-118	DATE OF DOCUMENT 07/22/2024
NAME OF DRUG Copaxone (glatiramer acetate injection)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 12/22/2024
NAME OF FIRM: Teva				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ■ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DN2 requests DEPI-I's review of the following submission: EDR Location: \\CDSESUB1\evsprod\NDA020622\0691

This submission is for a prior approval labeling supplement proposing changes to the pregnancy section (Section 8.1) of the US Prescribing Information and corresponding patient labeling to align with recent changes to Teva's Company Core Safety Information (CCSI) (provided in the submission as a 1,044 page document), which was revised to reflect that a moderate amount of data on pregnant women indicate no malformative or fetal/neonatal toxicity and that the use of Copaxone may be considered during pregnancy, if necessary.

The sponsor included the USPI, PI, and IFU in the labeling file.

Please review and provide comments.

DN2 has also consulted DPMH for review and comments. We have not consulted DB7. Please advise if their review is requested.

Please provide a reviewer assignment as soon as possible. DN2 will schedule a labeling team meeting once all reviewers have been assigned. The meeting will be scheduled in December 2024.

Goal dates:
Filing Date: 9/20/24
Action Date: 01/22/24

Review Team:
DN2 Clinical: Daniela Pimentel Maldonado and Laura Baldassari
Associate Director of Safety: Alice Hughes
Associate Director of Labeling: Tracy Peters
DPMH: Pending Assignment
DEPI: Pending Assignment

SIGNATURE OF REQUESTER Kristen Haslam	METHOD OF DELIVERY (Check all that apply) ■ EMAIL ■ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/

KRISTEN J HASLAM
07/30/2024 12:09:15 PM