Teva Pharmaceuticals Safe Needle Collection and Disposal Plan for COPAXONE® (glatiramer acetate injection)

Teva Pharmaceutical Industries Ltd. and Teva Neuroscience, Inc. (collectively “Teva Pharmaceuticals” or “Teva”), respectively the manufacturer and marketer of COPAXONE®, a therapy indicated for the treatment of patients with relapsing forms of multiple sclerosis, are committed to ensuring that MS patients have access to the information they need to keep themselves and their households safe and in compliance with local and state sharps disposal laws.

Teva educates patients regarding the importance of proper needle and syringe disposal through the dissemination of patient communication materials, as well as through Teva’s Shared Solutions®, the patient support program for Teva’s COPAXONE®, which is available to people living with MS, their CarePartners, family members, and anyone who has been touched by MS.

Teva’s Shared Solutions®, through its more than 200 nurses nationwide, provides a variety of services, including 24-hour call center support for anyone with questions about MS, as well as injection support for people taking Teva’s COPAXONE® therapy. Teva’s Shared Solutions® nurses discuss proper needle and syringe disposal with patients over the phone and in person at educational events. In addition, Teva’s Shared Solutions® nurses discuss proper needle and syringe disposal as a key component of patient injection training.

Information about proper sharps disposal is available through a number of key COPAXONE® communications, including:

- COPAXONE® Prescribing Information
- Patient Information Kit
- Patient Starter Kit and Injection Guide
- www.COPAXONE.com

In Teva’s COPAXONE® communications, patients are cautioned against the reuse of needles or syringes and educated about safe disposal procedures. Patients are instructed to:

- Check with their local health department, doctor’s office, or pharmacist for guidance and follow local regulations for disposal
- Dispose of used syringes into a hard-walled plastic container or disposable biohazard sharps container immediately after injection
- Use each COPAXONE® Pre-Filled Syringe for only 1 injection
- Always keep the waste container in an area of the home that is out of the reach of children and pets
- Consider using a needle clip device, which snaps the used needle off the syringe and houses it within a protective compartment
  — Follow local regulations for needle disposal
Patients interested in learning more about proper needle and syringe disposal may contact Teva’s Shared Solutions® toll-free at 1-800-887-8100.

**Use**

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

**Important Safety Information**

Do not take COPAXONE® if you are allergic to glatiramer acetate or mannitol.

Some patients report a short-term reaction within minutes after injecting COPAXONE®. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain, fast heart beat, anxiety, and trouble breathing. These symptoms generally appear within minutes of an injection, last about 15 minutes, and do not require specific treatment. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care. If symptoms become severe, call the emergency phone number in your area. Call your doctor right away if you develop hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site. If any of the above occurs, do not give yourself any more injections until your doctor tells you to begin again.

Chest pain may occur either as part of the post-injection reaction or on its own. This pain should only last a few minutes. You may experience more than one such episode, usually beginning at least one month after starting treatment. Tell your doctor if you experience chest pain that lasts for a long time or feels very intense.

A permanent indentation under the skin (lipoatrophy or, rarely, necrosis) at the injection site may occur, due to local destruction of fat tissue. Be sure to follow proper injection technique and inform your doctor of any skin changes.

The most common side effects of COPAXONE® include redness, pain, swelling, itching, or a lump at the site of injection, flushing, rash, shortness of breath, and chest pain. These are not all of the possible side effects of COPAXONE®. For a complete list, ask your doctor or pharmacist. Tell your doctor about any side effects you have while taking COPAXONE®.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information for Teva’s COPAXONE®.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COPAXONE® safely and effectively. See full prescribing information for COPAXONE.

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

RECENT MAJOR CHANGES
- Warnings and Precautions, Post-Injection Reaction (5.1) 1/2018

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

DOSE 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)

DOSE 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)

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FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
COPAXONE (glatiramer acetate injection) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION
  2.1 Recommended Dose
COPAXONE is for subcutaneous use only. Do not administer intravenously. The dosing schedule depends on the product strength that is selected. The recommended doses are:
- COPAXONE 20 mg/mL: administer once per day
- COPAXONE 40 mg/mL: administer three times per week

COPAXONE 20 mg/mL and COPAXONE 40 mg/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.

For subcutaneous use, rotate injection sites with each injection, and avoid injection sites near nerves or blood vessels. 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.

3 DOSAGE FORMS AND STRENGTHS
- Injection: 20 mg/mL in a single-dose prefilled syringe with a white plunger
- Injection: 40 mg/mL in a single-dose prefilled syringe with a blue plunger

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

5 WARNINGS AND PRECAUTIONS
  5.1 Post-Injection Reaction
Approximately 16% of patients exposed to COPAXONE 20 mg/mL in the 5 placebo-controlled trials compared to 4% of those on placebo, and approximately 2% of patients exposed to COPAXONE 40 mg/mL in a placebo-controlled trial compared to none on placebo, experienced a constellation of symptoms that may occur within minutes after injection and included at least two of the following: flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria.

In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. Typically, the symptoms were transient and self-limited and did not require treatment; however, there have been reports of patients with similar symptoms who received emergency medical care. Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

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

5.3 Lipatrophy 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/mL in the 5 placebo-controlled trials compared to none on placebo, and 0.5% of patients exposed to COPAXONE 40 mg/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.

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

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

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This information is for use in the United States of America. Revised: 1/2018
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 RMS patients given COPAXONE 20 mg per mL, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

6 ADVERSE REACTIONS

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

- Post-Injection Reaction [see Warnings and Precautions (5.1)]
- Chest Pain [see Warnings and Precautions (5.2)]
- Lipoatrophy and Skin Necrosis [see Warnings and Precautions (5.3)]
- Potential Effects on Immune Response [see Warnings and Precautions (5.4)]

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

<table>
<thead>
<tr>
<th>Blood And Lymphatic System Disorders</th>
<th>COPAXONE 20 mg/mL (n=563)</th>
<th>Placebo (n=564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Disorder</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>General Disorders And Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>43%</td>
<td>10%</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Injection Site Pruritus</td>
<td>27%</td>
<td>4%</td>
</tr>
<tr>
<td>Injection Site Mass</td>
<td>26%</td>
<td>6%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Pain</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Injection Site Edema</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Injection Site Inflammation</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Edema</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Injection Site Hypersensitivity</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Local Reaction</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Chills</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Face Edema</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*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 exposed to COPAXONE. Data on adverse reactions occurring in the controlled clinical trials of COPAXONE 20 mg per mL were evaluated to analyze 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 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 1/1000 patients.
**COPAXONE® (glatiramer acetate injection)**

**Body as a Whole:**
- **Frequent:** Abcess
- **Infrequent:** Injection site hemotoma, moon face, cellullitis, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosus, lipoma, and photosensitivity reaction.

**Cardiovascular:**
- **Frequent:** Hypertension.
- **Infrequent:** Hypotension, midystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, posterior hypotension, and varicose veins.

**Diet:**
- **Frequent:** Dry mouth, stomatitis, burning sensation on tongue, cholecysitis, 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, hyperthyroïdism, and hypothyroidism.

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

**Hemic and Lymphatic:**
- **Infrequent:** Anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

**Metabolic and Nutritional:**
- **Frequent:** Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanithoma.

**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.

**Respiratory:**
- **Frequent:** Hyperventilation and hay fever.
- **Infrequent:** Asthma, pneumonia, episptaxis, hypoventilation, and voice alteration.

**Special Senses:**
- **Frequent:** Hypertension, mild in intensity.

**Skin and Appendages:**
- **Frequent:** Eczeana, herpex zoster, pubertal rash, skin atrophy, and warts.

**Special Senses:**
- **Frequent:** Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

**Urogenital:**
- **Frequent:** Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicu-

**Vascular Disorders Vasodilatation 3% 0%**

**General Disorders And Administration Site Conditions**

- **Injection Site Erythema**
- **Injection Site Pain**
- **Injection Site Mass**
- **Injection Site Pain**

**Infections And Infestations**

- **Nasopharyngitis**
- **Respiratory Tract Infection**

**Respiratory**, **Thoracic, and Mediastinal Disorders**

- **Dyspnea**
- **Vasodilatation**
- **Nausea**
- **Erythema**
- **Nausea**

**Metabolic and Nutritional Disorders**

- **Weight loss**
- **Alcohol intolerance**
- **Cushing's syndrome**
- **Gout**
- **Abnormal creatinine clearance**

**Respiratory System:**

- **Chest Pain**
- **Cough**
- **Nosebleed**

**Special Senses**

- **Hypertension**
- **Heart failure**
- **Congestive heart failure**

**Tissue Disorders**

- **Injection Site Hematoma**
- **Injection Site Inflammation**
- **Injection Site Mass**
- **Injection Site Pain**

**Urogenital System:**

- **Hematoma**
- **Nephrosis**
- **Kidney failure**
- **Bladder carcinoma**
- **Urinary frequency**

**Special Senses:**

- **Visual field defect**
- **Nystagmus**
- **Ptosis**
- **Cataract**
- **Corneal ulcer**

**Vascular Disorders**

- **Vasodilatation**
- **Nausea**
- **Dysmenorrhea**
- **Nausea**
- **Vomiting**

**Metabolic and Nutritional Disorders:**

- **Weight loss**
- **Alcohol intolerance**
- **Cushing's syndrome**
- **Gout**

**Respiratory System:**

- **Chest Pain**
- **Cough**
- **Nosebleed**

**Special Senses:**

- **Visual field defect**
- **Nystagmus**
- **Ptosis**
- **Cataract**
- **Corneal ulcer**

No new adverse reactions appeared in subjects treated with COPAXONE 40 mg per mL three times per week in three 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 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: sipsis; SLE syndrome; hydrocephalus; enlarged abdomen; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiac dysrhythmias angiography pectoris.

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; urticaria; cirsitis of the liver; cholelithiasis.

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

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

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

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

Special Senses: glaucoma; blindness

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

**7 DRUG INTERACTIONS**

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

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category B. Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, COPAXONE® should be used during pregnancy only if clearly needed.

Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with interferon beta.
glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

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

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

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

8.5 Geriatric Use
COPAXONE has not been studied in elderly patients.

8.6 Use in Patients with Impaired Renal Function
The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

11 DESCRIPTION
Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine with an average molar ratio of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000. The average molecular weight of the injected material, either intact or partially hydrolyzed, is presumed to enter the systemic circulation intact.

L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

\[ (\text{Glu, Ala, Lys, Tyr}) \cdot xCH_3COOH \]
\[ (\text{C}_6\text{H}_7\text{NO}_2)\cdot x\text{CH}_3\text{COOH} \]
\[ \text{CAS} \cdot 147245-92-9 \]

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day of glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² 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/m² basis). No increase in neoplasms was observed.

Glatiramer acetate was not mutagenic in in vitro (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two separate in vitro chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an in vivo mouse bone marrow micronucleus assay. When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m² basis) no adverse effects were observed on reproductive or developmental parameters.

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

COPAXONE 20 mg per mL per day

Study 1 was performed at a single center. Fifty patients were enrolled and randomized to receive daily doses of either COPAXONE, 20 mg per mL subcutaneously, or placebo (COPAXONE: n=25; placebo: n=25). Patients were diagnosed with RRMS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0—Normal to 10—Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair. Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurologic 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

<table>
<thead>
<tr>
<th>Measure</th>
<th>COPAXONE (n=25)</th>
<th>Placebo (n=25)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Relapse-Free Patients</td>
<td>14/25 (56%)</td>
<td>7/25 (28%)</td>
<td>0.085</td>
</tr>
<tr>
<td>Mean Relapse Frequency</td>
<td>0.62/2 years</td>
<td>2.4/2 years</td>
<td>0.005</td>
</tr>
<tr>
<td>Reduction in Relapse Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared to Prestudy</td>
<td>3.2</td>
<td>1.6</td>
<td>0.025</td>
</tr>
<tr>
<td>Median Time to First Relapse (days)</td>
<td>&gt;700</td>
<td>150</td>
<td>0.03</td>
</tr>
<tr>
<td>% of Progression-Free* Patients</td>
<td>20/25 (80%)</td>
<td>13/25 (52%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Measure</th>
<th>COPAXONE (n=125)</th>
<th>Placebo (n=126)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean No. of Relapses</td>
<td>1.19/2 years</td>
<td>1.68/2 years</td>
<td>0.055</td>
</tr>
<tr>
<td>% Relapse-Free Patients</td>
<td>42/125 (34%)</td>
<td>34/126 (27%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Median Time to First Relapse (days)</td>
<td>287</td>
<td>198</td>
<td>0.23</td>
</tr>
<tr>
<td>% of Progression-Free Patients</td>
<td>98/125 (78%)</td>
<td>95/126 (75%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Mean Change in DSS</td>
<td>-0.05</td>
<td>+0.21</td>
<td>0.023</td>
</tr>
</tbody>
</table>

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 exacerbation were randomized to receive daily doses of either COPAXONE, 20 mg per mL subcutaneously, or placebo (COPAXONE: n=243; 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.
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

<table>
<thead>
<tr>
<th>COPAXONE 20 mg/mL (n=119)</th>
<th>Placebo (n=120)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medians of the Cumulative Number of T1 Gd-Enhancing Lesions</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

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

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

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

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

What should I tell my doctor before using COPAXONE?
Before you use COPAXONE, tell your doctor if you:
• are pregnant or plan to become pregnant. It is not known if COPAXONE will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if COPAXONE passes into your breast milk. Talk to your doctor about the best way to feed your baby while using COPAXONE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. COPAXONE may affect the way other medicines work, and other medicines may affect how COPAXONE works.

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

How should I use COPAXONE?
• For detailed instructions, see the Instructions for Use at the end of this leaflet for complete information on how to use COPAXONE.
• Your doctor will tell you how much COPAXONE to use and when to use it.
• COPAXONE is given by injection under your skin (subcutaneously).
• Use COPAXONE exactly as your doctor tells you to use it.
• Since every body type is different, talk with your doctor about the injection areas that are best for you.
• You should receive your first dose of COPAXONE with a doctor or nurse present. This might be at your doctor’s office or with a visiting home health nurse who will teach you how to give your COPAXONE injections.

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

If you have symptoms of a post-injection reaction, do not give yourself more injections until a doctor tells you to.
• Chest Pain. You can have chest pain as part of a post-injection reaction or by itself. This type of chest pain usually lasts a few minutes and can begin around 1 month after you start using COPAXONE. Call your doctor right away if you have chest pain while using COPAXONE.

• flushing (vasodilation)
• shortness of breath
• lumps
• rash
• itching
• swelling
• pain

The most common side effects of COPAXONE include:
• skin problems at your injection site including:
  • redness
  • pain
  • swelling
  • itching
  • lumps
• damage to your skin. Damage to the fatty tissue just under your skin’s surface (lipoatrophy) and, rarely, death of your skin tissue (necrosis) can happen when you use COPAXONE. Damage to the fatty tissue under your skin can cause a “dent” at the injection site that may not go away. You can reduce your chance of developing these problems by:
  • following your doctor’s instructions for how to use COPAXONE
  • choosing a different injection area each time you use COPAXONE. See Step 4 in the Instructions for Use, “Choose your injection area”.

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

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

This Patient Information Leaflet summarizes the most important information about COPAXONE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE that is written for health professionals. For more information, go to www.copaxone.com or call 1-800-887-8100.

What are the ingredients in COPAXONE?
Active ingredient: glatiramer acetate
Inactive ingredients: mannitol
COPPL-002
Revised: January 2018
For subcutaneous injection only.

Do not inject COPAXONE in your veins (intravenously).

Do not re-use your COPAXONE prefilled syringes.

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

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

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

Instructions for Using Your COPAXONE 20 mg Prefilled Syringe:

- 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”.

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

Instructions for Using Your COPAXONE 20 mg Prefilled Syringe:

- 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 doctor about the injection areas that are best for you.

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

Step 5: Prepare to give your injection.

- 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.

Figure A

Figure B

Figure C
Step 6: Clean your injection site.
- Clean the injection site using the alcohol wipe and allow your skin to air dry. See 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.

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

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

Step 11: Remove the needle.
After you have injected all of the medicine, pull the needle straight out. See 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.

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.

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