COPAXONE® (glatiramer acetate injection)

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
COPAXONE is for subcutaneous use only using the prefilled syringe or an optional injection device. Refer to the autoinjector labeling to determine which device to use with COPAXONE and for information regarding instructions for use.

INSTRUCTIONS FOR USE
• 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)

RECENT MAJOR CHANGES
• 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
• Injection: 40 mg/mL in a single-dose, prefilled syringe with a blue plunger

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 (5.1)
• Chest pain, usually transient (5.2)
• Lipoatrophy and skin necrosis may occur. Instruct patients in proper injection technique and to rotate injection sites (5.3)
• COPAXONE can modify immune response (5.4)
• Hepatic Injury: if signs or symptoms of hepatic dysfunction occur, consider discontinuing COPAXONE (5.5)

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 FDA-approved patient labeling. Revised: 4/2022
There is no evidence that COPAXONE does this, but there has not been a systematic evaluation of this risk. Because COPAXONE is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

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

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

5.5 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.

6 ADVERSE REACTIONS

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

- Immediate 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)]
- Hepatic Injury [see Warnings and Precautions (5.5)]

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

* Injection site atrophy comprises terms relating to localized lipoatrophy at injection site.
COPAXONE® (glatiramer acetate injection)

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, hypothyroidism, and hypothyroidism.
- Gastrointestinal:
  - Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.
- Hemic and Lymphatic:
  - Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematema, lymphedema, pancytopenia, and splenomegaly.
- Metabolic and Nutritional:
  - Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, goit, 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, psychotonic depression, and transient stupor.

Respiratory:
- Frequent: Hyperventilation and hay fever.
- Infrequent: Asthma, pneumonia, epistaxis, hyperventilation, and voice alteration.

Skin and Appendages:
- Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.
- Infrequent: Dry skin, skin hyperpotrophy, dermatitis, furunculosis, prurioris, angioneuroda, 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 papanicouloos smear, urinary frequency, and vaginal hemorrhage.
- Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma in situ cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

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 event. 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 a 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

<table>
<thead>
<tr>
<th>COPAXONE® (n=943)</th>
<th>Placebo (n=401)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Erythema</td>
<td>%</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>10</td>
</tr>
<tr>
<td>Injection Site Mass</td>
<td>6</td>
</tr>
<tr>
<td>Injection Site Pruritus</td>
<td>6</td>
</tr>
<tr>
<td>Injection Site Edema</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
</tr>
<tr>
<td>Influenza-like Illness</td>
<td>2</td>
</tr>
<tr>
<td>Injection Site Inflammation</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>2</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory Tract Infection Viral</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
</tr>
</tbody>
</table>

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.

6.3 Hepatic and Biliary Disorders
- Hepatobiliary disorders: cholelithiasis; liver function abnormality; cirrhosis of the liver; hepatocellular carcinoma; hepatitis; hepatic injury [see Warnings and Precautions (5.5)]

6.4 Metabolic and Nutritional Disorders: hypercholesterolemia
- Musculoskeletal System: rheumatoid arthritis; generalized spasm

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
- Risk Summary
- Available human data on the use of COPAXONE in pregnant women are not sufficient to support conclusions about drug-associated risk for major birth defects and miscarriage. Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on embryofetal or offspring development (see Data).

8.2 Lactation
- Data
- There are no adequate and well-controlled studies of COPAXONE in pregnant women. The available postmarketing reports, case series, and small cohort studies do not provide sufficient information to support conclusions about drug-associated risk for major birth defects and miscarriage.

8.3 Pediatric Use
- Available human data on the use of COPAXONE in children and adolescents are not sufficient to determine the safety and effectiveness of COPAXONE in children under 18 years of age.

8.4 Pediatric Use

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 acid 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.
COPAXONE® (glatiramer acetate injection)

**Chemical and Physical Properties**

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is: $(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_{\text{n}}$. 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 solution is approximately 5.5 to 7.0. The biological activity of glatiramer acetate is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS are not fully understood. However, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in vitro systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery. Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally-occurring immune responses. There is no evidence that glatiramer acetate does this, but this has not been systematically evaluated (see Warnings and Precautions (5.4)).

**12.2 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/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.

**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 human lymphocytes. Glatiramer acetate was not mutagenic in other assays.

**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 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 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 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):

**Patients treated with COPAXONE demonstrated fewer new T2 lesions at the last observation (rate ratio 0.47; confidence interval 0.29 to 0.76; p = 0.004).** Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (rate ratio 0.39; confidence interval 0.27 to 0.58; p = 0.001). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.5% 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 0.47; confidence interval 0.29 to 0.76; p = 0.004). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (rate ratio 0.39; confidence interval 0.27 to 0.58; p = 0.001). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.5% in the placebo group and 24.7% in the COPAXONE group.

**Table 5: Study 4 MRI Results**

**Table 3: Study I Efficacy Results**

**Table 4: Study 2 Efficacy Results**

* 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=120; placebo: n=131) 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:

**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 42.5% 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 0.47; confidence interval 0.29 to 0.76; p = 0.004). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (rate ratio 0.39; confidence interval 0.27 to 0.58; p = 0.001). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.5% in the placebo group and 24.7% in the COPAXONE group.
COPAXONE® (glatiramer acetate injection)

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: Study 5 Efficacy and MRI Results

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>COPAXONE 40 mg/mL (n=943)</th>
<th>Placebo (n=461)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of confirmed relapses during the 12-month placebo-controlled phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean Estimates</td>
<td>0.331</td>
<td>0.505</td>
<td>&lt;0.0001</td>
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<tr>
<td>Relative risk reduction</td>
<td>34%</td>
<td>50%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI Endpoints</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of new or enlarging T2 lesions at Months 6 and 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean Estimates</td>
<td>3.650</td>
<td>5.592</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean Estimates</td>
<td>0.905</td>
<td>1.639</td>
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<tr>
<td>Relative risk reduction</td>
<td>45%</td>
<td>63%</td>
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</tbody>
</table>

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).

An optional autoinjector is available by prescription separately (see Dosage and Administration [2.2]). Ensure TEVA’s COPAXONE is used with a compatible autoinjector if an optional autoinjector is prescribed (see Patient Counseling Information [7]). 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 (Patient Information and Instructions for Use).

Optional Autoinjector

Advise patients with new or existing glatiramer acetate prescriptions to consult their pharmacist or healthcare provider about using an optional prescribed compatible autoinjector device. Advise patients that not all optional prescribed autoinjectors are compatible with all glatiramer acetate products and using an autoinjector that is not compatible may increase the risk for medication errors, such as missing a dose or administration of a partial dose.

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

Immediate Post-Injection Reaction

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

Chest Pain

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

Lipoatrophy and Skin Necrosis at Injection Site

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

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 [5.5]).

Pregnancy

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

Lactation

Advise patients that COPAXONE is distributed in breast milk. Instruct patients that if they are breastfeeding or plan to breastfeed while taking COPAXONE they should inform their physician (see Use in Specific Populations [8.1]).

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.

Patient Information

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

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

What is COPAXONE?

COPAXONE is 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.

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, but any amount is expected to be low if it does. 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.

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.
- COPAXONE can be given using a prefilled syringe or an optional autoinjector that your healthcare provider may prescribe separately for use with COPAXONE.
- If you use an autoinjector to give COPAXONE:
  1. Check with your healthcare provider when you fill or refill your medicine. Make sure the autoinjector you have is the right one for your COPAXONE. Not all optional autoinjectors can be used with all glatiramer acetate products. If you use the wrong autoinjector, you might not get enough medicine from your dose.
  2. Read your autoinjector 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. Call your doctor right away if you have any of these immediate post-injection reaction symptoms including:
  1. redness to your cheeks or other parts of the body (flushing)
  2. chest pain
  3. fast heart beat
  4. anxiety
  5. breathing problems or tightness in your throat
  6. swelling, rash, hives, or itching
- If you have symptoms of an immediate 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 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 doctor right away if you have chest pain while using COPAXONE.
- **Damage to your skin.** Damage to the fatty tissue just under your skin's surface (lipoatrophy) and, rarely, death of your skin tissue (necrosis) can happen when you use COPAXONE. Damage to the fatty tissue under your skin can cause a "dent" at the injection site that may not go away. You can reduce your chance of developing these problems by:
  1. following your doctor's instructions for how to use COPAXONE
  2. 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:
  1. nausea
  2. loss of appetite
  3. tiredness
  4. dark colored urine and pale stools
  5. yellowing of your skin or the white part of your eye
  6. bleeding more easily than normal
  7. confusion
  8. sleepiness
- The most common side effects of COPAXONE include:
  1. skin problems at your injection site including:
    1. redness
    2. pain
    3. swelling
    4. itching
    5. lumps
  2. rash
  3. shortness of breath
  4. flushing (vasodilation)

Tell your doctor if you have any side effect that bothers you or that does not go away.
- These are not all the possible side effects of COPAXONE. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

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

For subcutaneous injection only.
- Do not inject COPAXONE in your veins (intravenously).
- Do not re-use your COPAXONE prefilled syringes.
- Do not share your COPAXONE prefilled syringes with another person. You may give another person an infection or get an infection from them.
- You should receive your first dose of COPAXONE with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will show you how to give your own injections.
- COPAXONE comes in either a 20 mg Prefilled Syringe with needle attached or a 40 mg Prefilled Syringe with needle attached. How often a dose is given depends on the product strength that is prescribed. Your doctor will prescribe the correct dose for you.

If you plan to use COPAXONE with an autoinjector that was prescribed separately by your healthcare provider for use with COPAXONE, ask your doctor or pharmacist for Patient Instructions for Use for your device.

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.]

- 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.]

- 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.

**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.

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.

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

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