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.

Please see Important Safety Information on Page 5 and accompanying full Prescribing Information.
Doctor Discussion Guide

Helping people with relapsing MS make informed therapy decisions

Whether you are a current COPAXONE® (glatiramer acetate injection) patient or new to COPAXONE® therapy, it’s important to stay informed and take an active role in managing your prescription. Speaking with your doctor is always the first step. Use this guide to help you prepare questions and note your concerns before your appointment.

If you are currently taking COPAXONE®, consider asking the following questions at your next appointment:

How do I ensure my relapsing MS therapy is working as it should?
Notes ______________________________________________________________________________________
____________________________________________________________________________________________

How do I ensure I receive branded COPAXONE® with my next refill?
Notes ______________________________________________________________________________________
____________________________________________________________________________________________

How can I receive refresher injection training for COPAXONE®?
Notes ______________________________________________________________________________________
____________________________________________________________________________________________

If I am prescribed daily COPAXONE® 20 mg, can I switch to 3-times-a-week COPAXONE® 40 mg?
Notes ______________________________________________________________________________________
____________________________________________________________________________________________

Are there tools to help track and manage my COPAXONE® injections?
Notes ______________________________________________________________________________________
____________________________________________________________________________________________

Please see Important Safety Information on Page 5 and accompanying full Prescribing Information.
Doctor Discussion Guide

How do I properly store my COPAXONE® (glatiramer acetate injection) syringes?
Notes

What kind of support am I eligible to receive during my COPAXONE® therapy?
Notes

Use the space below to note your own questions and concerns.

Please see Important Safety Information on Page 5 and accompanying full Prescribing Information.
Doctor Discussion Guide

If you are new to COPAXONE® (glatiramer acetate injection), consider asking the following questions:

☐ How is COPAXONE® administered? What if I have concerns about self-injection?

Notes ______________________________________________________________________________________
____________________________________________________________________________________________

☐ How is COPAXONE® thought to work?

Notes ______________________________________________________________________________________
____________________________________________________________________________________________

☐ How effective is COPAXONE® in reducing relapses?

Notes ______________________________________________________________________________________
____________________________________________________________________________________________

☐ How safe is COPAXONE®?

Notes ______________________________________________________________________________________
____________________________________________________________________________________________

☐ What side effects could I experience?

Notes ______________________________________________________________________________________
____________________________________________________________________________________________

Important tips for new and current patients on COPAXONE® therapy

- Ask your doctor to specify language such as “Dispense as Written” (DAW) or “Brand Medically Necessary” on every COPAXONE® prescription, including refills, to ensure you receive your relapsing MS therapy as prescribed. Language may vary by state.
- Talk to your pharmacist and inspect the packaging to ensure you receive COPAXONE® as prescribed. Please visit COPAXONE.com for help properly identifying Teva’s COPAXONE®.
- Keep a detailed log of your treatment, symptoms, and side effects. Note any questions and concerns you’d like to share with your doctor as they occur.
- The COPAXONE iTracker® 2.0 for iPhone® or Android™ mobile app can help track your injection routine and assist with organizing notes to prepare for doctor appointments.
- Schedule follow-up visits as recommended or needed to manage your relapsing MS.
- Call Teva’s Shared Solutions® at 1-800-887-8100 or visit COPAXONE.com to learn about available support offerings.

Please see Important Safety Information and full Prescribing Information on the following pages.
Doctor Discussion Guide

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 right after or 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 seconds to 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 immediate 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 full Prescribing Information for Teva’s COPAXONE® on the following pages.
COPAXONE (glatiramer acetate injection) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

**Dosage Forms and Strengths**

- COPAXONE 20 mg/mL: administer once per day
  - Schedule depends on the product strength that is selected. The recommended doses are:
    - 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)

**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)

**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.

**Use in Specific Populations**

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

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

Revised: 9/2018
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 RRMS patients given COPAXONE 20 mg per mL, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

6 ADVERSE REACTIONS

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)]
- Lipomatosis 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, dizziness, urticaria, vasodilatation, and hypersensitivity. The most common adverse reactions were: injection site reactions, vasodilatation, rash, dizziness, 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>Conditions</th>
<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>Lymphadenopathy 7%</td>
<td>3%</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Palpitations 9%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Tachycardia 5%</td>
<td>2%</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Eye Disorder 3%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Diplopia 3%</td>
<td>2%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea 15%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Vomiting 7%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Dysphagia 2%</td>
<td>1%</td>
</tr>
<tr>
<td>General Disorders And Administration Site Conditions</td>
<td>Injection Site Erythema 43%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Pain 40%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Pruritus 27%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Mass 26%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Asthenia 22%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Pain 20%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Edema 19%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Chest Pain 13%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Inflammation 9%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Edema 8%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Reaction 8%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Pyrexia 6%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Injection Site Hypersensitivity 4%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Local Reaction 3%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Chills 3%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Face Edema 3%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Edema Peripheral 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 included in the clinical trials of another drug and may not reflect the rates observed in practice.

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

**Cardiovascular:**

*Frequent:* Hypertension.

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

**Digestive:**

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

**Endocrine:**

*Infrequent:* Goiter, hyperthyroidism, and hypothyroidism.

**Gastrointestinal:**

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

**Hemic and Lympathic:**

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

**Metabolic and Nutritional:**

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

**Musculoskeletal:**

*Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

**Nervous:**

*Frequent:* Ab normal dreams, emotional lability, and stupor.

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

**Respiratory:**

*Frequent:* Hyperventilation and hay fever.

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

**Skin and Appendages:**

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

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

**Special Senses:**

*Frequent:* Visual field defect.

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

**Urogenital:**

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

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

**COPAXONE 40 mg per mL three times per week**

Among 943 patients treated with COPAXONE 40 mg per mL three times per week in a blinded, placebo-controlled trial, approximately 3% of the subjects discontinued treatment because of an adverse reaction. The most common adverse reactions were injection site reactions, which were also the most common cause of discontinuation. Table 2 lists signs and symptoms that occurred in at least 2% of patients treated with COPAXONE 40 mg per mL in the blinded, placebo-controlled trial. These signs and symptoms were numerically more common in patients treated with COPAXONE 40 mg per mL than in patients treated with placebo. Adverse reactions were usually mild in intensity.

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

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

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

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

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

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

**Metabolic and Nutritional Disorders:** hypercholesterolemia

**Musculoskeletal System:** rheumatoid arthritis; generalized spasm

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

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

**Special Senses:** glaucoma; blindness

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

**7 DRUG INTERACTIONS**

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

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category B.

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

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/m² basis). In rats receiving subcutaneous glatiramer acetate at...
doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

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

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

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

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

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

11 DESCRIPTION
Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies. Chemical alterations to the protein, for example, by reduction of L-glutamic acid propeptide, yield no evidence that 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
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 increase 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 vivo chromosome 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.
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 0.69; confidence interval 0.64 to 0.84; 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>Medians of the Cumulative Number of T1 Gd-Enhancing Lesions</th>
<th>COPAXONE 20 mg/mL (n=119)</th>
<th>Placebo (n=120)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPAXONE</td>
<td>GA 20 mg/mL</td>
<td>Placebo</td>
<td>0.0030</td>
</tr>
<tr>
<td>197</td>
<td>197</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>179</td>
<td>166</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>166</td>
<td>136</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>136</td>
<td>98</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>55</td>
<td>15</td>
<td></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 received any interferon-beta for at least 2 months prior to screening. Baseline EDSS scores ranged from 0 to 5.5 with a median of 2.5. Neurological evaluations were performed at baseline, every three months, and at unscheduled visits for suspected relapse or early termination. MRI was performed at baseline, months 6 and 12, or early termination. A total of 91% of those assigned to COPAXONE and 93% of those assigned to placebo completed treatment at 12 months.

The primary outcome measure was the total number of confirmed relapses (persistence of neurological symptoms for at least 48 hours confirmed on examination with objective signs). The effect of COPAXONE on several magnetic resonance imaging (MRI) variables, including number of new or enlarging T2 lesions and number of enhancing lesions on T1-weighted images, was also measured at months 6 and 12. Table 6 presents the results for the intent-to-treat population.

Table 6: Study 5 Efficacy and MRI Results

<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>Adjusted Mean Estimates</td>
<td>0.331</td>
<td>0.505</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>34%</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI Endpoints</th>
<th>Adjusted Mean Estimates</th>
<th>Relative risk reduction</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of new or enlarging T2 lesions at Months 6 and 12</td>
<td>3.650</td>
<td>35%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12</td>
<td>0.905</td>
<td>45%</td>
<td>1.639</td>
</tr>
</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 plunger, in individual blister packages supplied in 30-count cartons (NDC 68546-317-30).
• 40 mg per mL in a single-dose, prefilled syringe with a blue plunger, in individual blister packages supplied in 12-count cartons (NDC 68546-325-12).

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

17 PATIENT COUNSELING INFORMATION

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

Immediate Post-Injection Reaction

Advisors 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.

Instruct 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

Advisors 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

Advisors 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.

Pregnancy

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

Instructions for Use

Instruct patients to read the COPAXONE Patient Information leaflet carefully.

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

Storage Conditions

Advisors 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.

Marketed by: Teva Neuroscience, Inc., Overland Park, KS 66211
Distributed by: Teva Pharmaceuticals USA, Inc., North Wales, PA 19454
Product of Israel
COP-003
COPAXONE® (glatiramer acetate injection)

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

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

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

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

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

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

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

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

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

What are the possible side effects of COPAXONE?
COPAXONE may cause serious side effects, including:
• 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:
  ◦ 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 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.

COPAXONE® (glatiramer acetate injection)

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

The most common side effects of COPAXONE include:
• skin problems at your injection site including:
  ◦ redness
  ◦ pain
  ◦ swelling
  ◦ itching
  ◦ lumps
  ◦ rash
  ◦ shortness of breath
  ◦ flushing (vasodilation)

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

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

COPPL-003
Revised: September 2018
Instructions for Use

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

For subcutaneous injection only.
Do not inject COPAXONE® in your veins (intravenously).
Do not re-use your COPAXONE® prefilled syringes.
Do not share your COPAXONE® prefilled syringes with another person.
You may give another person an infection or get an infection from them.
You should receive your first dose of COPAXONE® with a doctor or nurse present.
This might be at your doctor’s office or with a visiting home health nurse who will show you how to give your own injections.

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

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

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

How do I inject COPAXONE®?

Step 1: Gather the supplies you will need to inject COPAXONE®. See Figure A.
• 1 blister pack with a COPAXONE® Prefilled Syringe with needle attached
• Alcohol wipe (not supplied)
• Dry cotton ball (not supplied)
• A place to record your injections, like a notebook (not supplied)
• Sharps disposal container (not supplied). See Step 13 below, “Dispose of your needles and syringes”.

Figure A

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

Figure B

Step 3: Look closely at your COPAXONE® prefilled syringe.
• The possible injection areas on your body include (See Figure C):
  ◦ your stomach area (abdomen) around the belly button
  ◦ the back of your upper arms
  ◦ upper hips (below your waist)
  ◦ your thighs (above your knees)

Figure C

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.

Step 6: 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 7: 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 8: 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 9: 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 10: 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 11: 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 12: 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 13: “Dispose of your needles and syringes.”
• Dispose of your needles and syringes.
• 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.”

Instructions for Using Your COPAXONE® 20 mg Prefilled Syringe:
• Do not inject COPAXONE® in areas where the skin has scarring or “dents”.
• There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.
• Do not inject in sites where the skin has scarring or “dents”.
• Using scarred or dented skin for your injections may make your skin worse.

Instructions for Using Your COPAXONE® 40 mg Prefilled Syringe:
• Do not inject COPAXONE® in areas where the skin has scarring or “dents”.
• There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.
• Do not inject in sites where the skin has scarring or “dents”.
• Using scarred or dented skin for your injections may make your skin worse.
Step 6: Clean your injection site.
- Clean the injection site using the alcohol wipe and allow your skin to air dry. See Figure D.

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.