HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COPAXONE® safely and effectively.
See full prescribing information for COPAXONE.

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

RECENT MAJOR CHANGES

Indications and Usage (1) 2/2009

INDICATIONS AND USAGE

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

DOSAGE AND ADMINISTRATION

- For subcutaneous injection only (2.1)
- Recommended dose: 20 mg/day (2.1)
- Before use, allow the solution to warm to room temperature (2.2)

DOSAGE FORMS AND STRENGTHS

- Prefilled syringe containing 1 mL solution with 20 mg of glatiramer acetate (3)

CONTRAINDICATIONS

Known hypersensitivity to glatiramer acetate or mannitol (4)

WARNINGS AND PRECAUTIONS

- Immediate Post-Injection Reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting (5.1)
- Chest pain, usually transient (5.2)
- Lipoatrophy and skin necrosis may occur. Instruct patient in proper injection technique and to rotate injection sites daily (5.3)
- COPAXONE can modify immune response (5.4)

ADVERSE REACTIONS

- In controlled studies, most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA at 1-800-221-4026 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: [2/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION
COPAXONE (glatiramer acetate injection)

1 INDICATIONS AND USAGE

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

COPAXONE is for subcutaneous use only. Do not administer intravenously. The recommended dose of COPAXONE is 20 mg/day.

2.2 Instructions for Use

Remove one blister that contains the syringe from the COPAXONE prefilled syringes package. Since this product should be refrigerated, let the prefilled syringe stand at room temperature for 20 minutes to allow the solution to warm to room temperature. Inspect the COPAXONE syringe visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution in the syringe should appear clear, colorless to slightly yellow. If particulate matter or discoloration is observed, discard the COPAXONE syringe.

Areas for self-injection include arms, abdomen, hips, and thighs. The prefilled syringe is for single use only. Discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

Single-use prefilled syringe containing 1 mL solution with 20 mg of glatiramer acetate and 40 mg of mannitol.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Immediate Post-Injection Reaction

Approximately 16% of patients exposed to COPAXONE in the 5 placebo-controlled trials compared to 4% of those on placebo experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. The symptoms were generally transient and self-limited and did not require treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.

Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

5.2 Chest Pain

Approximately 13% of COPAXONE patients in the 5 placebo-controlled studies compared to 6% of placebo patients experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection of COPAXONE was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

5.3 Lipoatrophy and Skin Necrosis

At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during the postmarketing experience. Lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites daily.

5.4 Potential Effects on Immune Response

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

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 exposed to daily treatment with the recommended dose. 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, 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

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 clinical practice.

Incidence in Controlled Clinical Trials

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 treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE 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 than with placebo

		GA 20 mg (N=563)	Placebo (N=564)
Blood And Lymphatic System Disorders	Lymphadenopathy	7%	3%
Cardiac Disorders	Palpitations	9%	4%
	Tachycardia	5%	2%
Eye Disorders	Eye Disorder	3%	1%
	Diplopia	3%	2%
Gastrointestinal Disorders	Nausea	15%	11%
	Vomiting	7%	4%
	Dysphagia	2%	1%
General Disorders And Administration Site Conditions	Injection Site Erythema	43%	10%
	Injection Site Pain	40%	20%
	Injection Site Pruritus	27%	4%
	Injection Site Mass	26%	6%
	Asthenia	22%	21%
	Pain	20%	17%
	Injection Site Edema	19%	4%
	Chest Pain	13%	6%
	Injection Site Inflammation	9%	1%
	Edema	8%	2%
	Injection Site Reaction	8%	1%
	Pyrexia	6%	5%
	Injection Site Hypersensitivity	4%	0%
	Local Reaction	3%	1%
	Chills	3%	1%
	Face Edema	3%	1%
	Edema Peripheral	3%	2%
	Injection Site Fibrosis	2%	1%
	Injection Site Atrophy*	2%	0%
Immune System Disorders	Hypersensitivity	3%	2%
Infections And Infestations	Infection	30%	28%
	Influenza	14%	13%
	Rhinitis	7%	5%
	Bronchitis	6%	5%
	Gastroenteritis	6%	4%
	Vaginal Candidiasis	4%	2%
Metabolism And Nutrition Disorders	Weight Increased	3%	1%
Musculoskeletal And Connective Tissue Disorders	Back Pain	12%	10%
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Neoplasm of Skin	2%	1%

Continued		GA 20 mg (N=563)	Placebo (N=564)
Nervous System Disorders	Tremor	4%	2%
	Migraine	4%	2%
	Syncope	3%	2%
	Speech Disorder	2%	1%
Psychiatric Disorders	Anxiety	13%	10%
	Nervousness	2%	1%
Renal And Urinary Disorders	Micturition Urgency	5%	4%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	14%	4%
	Cough	6%	5%
	Laryngospasm	2%	1%
Skin And Subcutaneous Tissue Disorders	Rash	19%	11%
	Hyperhidrosis	7%	5%
	Pruritus	5%	4%
	Urticaria	3%	1%
	Skin Disorder	3%	1%
Vascular Disorders	Vasodilatation	20%	5%

*Injection site atrophy comprises terms relating to localized lipoatrophy at injection site

Adverse reactions which occurred only in 4-5 more subjects in the COPAXONE group than in the placebo group (less than 1% difference), but for which a relationship to COPAXONE could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia (16 x10^9/L), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with COPAXONE were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically relevant age subgroups.

Other Adverse Reactions

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled premarketing studies (n= 979), the role of COPAXONE in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used COPAXONE and reported a reaction divided by the total number of patients exposed to COPAXONE. All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse reactions are defined as those occurring in at least 1/100 patients and *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients.

Body as a Whole:

Frequent: Abscess

Infrequent: Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:

Frequent: Hypertension.

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

Digestive:

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

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

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

Hemic and Lymphatic:

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

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

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

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation and hay fever.

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

Skin and Appendages:

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

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

Special Senses:

Frequent: Visual field defect.

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

Urogenital:

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

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

6.2 Postmarketing Experience

Reports of adverse events occurring under treatment with COPAXONE not mentioned above that have been received since market introduction and may or may not have causal relationship to COPAXONE are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; 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; eructation; 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; convulsion; neuralgia

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

Special Senses: glaucoma; blindness; visual field defect

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/m^2 basis). In rats receiving subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

8.2 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

COPAXONE is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

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

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

CAS - 147245-92-9

COPAXONE is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of COPAXONE 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/m^2 basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in neoplasms was observed.

Glatiramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m^2 basis) no adverse effects were observed on reproductive or developmental parameters.

14 CLINICAL STUDIES

14.1 Relapsing-Remitting Multiple Sclerosis (RRMS)

Evidence supporting the effectiveness of COPAXONE in decreasing the frequency of relapses derives from 3 placebo-controlled trials, all of which used a COPAXONE dose of 20 mg/day.

Study 1 was performed at a single center. Fifty patients were enrolled and randomized to receive daily doses of either COPAXONE, 20 mg subcutaneously, or placebo (COPAXONE: n=25; placebo: n=25). Patients were diagnosed with RRMS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the 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 2 presents the values of the three outcomes described above, as well as several protocol specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

Table 2: Study 1 Efficacy Results

	COPAXONE (N=25)	Placebo (N=25)	P-Value
% Relapse-Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Prestudy	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

Study 2 was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (COPAXONE: n=125; placebo: n=126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. Table 3 presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

Table 3: Study 2 Efficacy Results

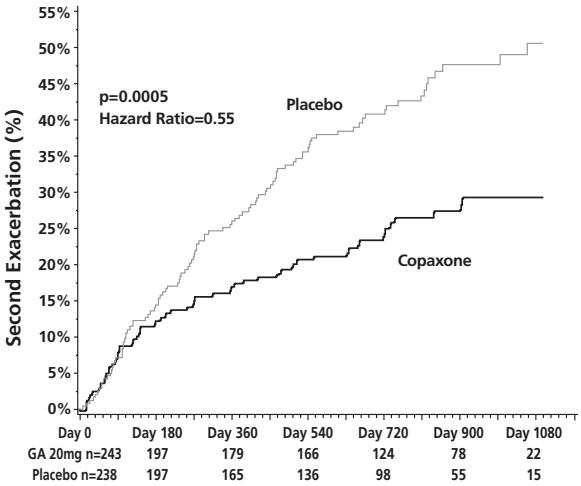
	COPAXONE (N=125)	Placebo (N=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68/2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

In both studies, COPAXONE exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that COPAXONE is considered effective.

In Study 3, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either COPAXONE 20 mg/day (n=243) or placebo (n=238). The primary outcome measure was time to development of a second exacerbation. Patients were followed for up to three years or until they reached the primary endpoint. Secondary outcomes were brain MRI measures, including number of new T2 lesions and T2 lesion volume.

Time to development of a second exacerbation was significantly delayed in patients treated with COPAXONE compared to placebo (Hazard Ratio = 0.55; 95% confidence interval 0.40 to 0.77; Figure 1). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the COPAXONE group.

Figure 1: Time to Second Exacerbation



Patients treated with COPAXONE demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; $p < 0.0001$). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (ratio of 0.89; confidence interval 0.84 to 0.94; $p = 0.0001$).

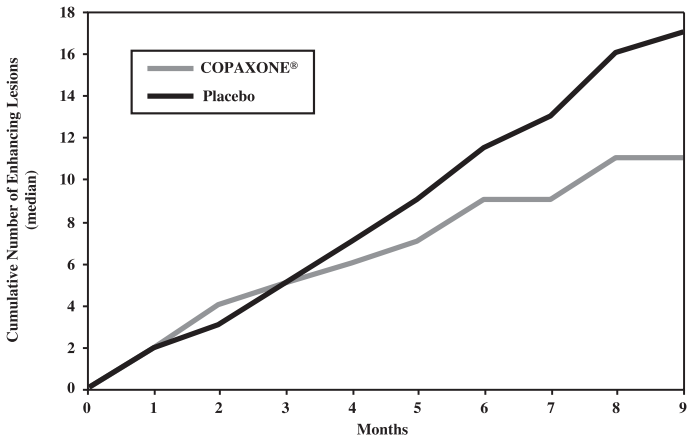
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 4 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 4: Study 4 MRI Results

	COPAXONE (N=119)	Placebo (N=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

Figure 2 displays the results of the primary outcome on a monthly basis.

Figure 2: Median Cumulative Number of Gd-Enhancing Lesions



16 HOW SUPPLIED/STORAGE AND HANDLING

COPAXONE is supplied as a single-use prefilled syringe containing 1 mL of a clear, colorless to slightly yellow, sterile, nonpyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol in cartons of 30 single-use prefilled syringes with 33 alcohol preps (NDC 68546-317-30).

The recommended storage condition for the COPAXONE is refrigeration (2ºC to 8ºC / 36ºF to 46ºF). However, excursions from recommended storage conditions (15ºC to 30ºC / 59ºF to 86ºF) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided. COPAXONE should not be frozen. If a COPAXONE syringe freezes, it should be discarded.

COPAXONE contains no preservative. Do not use if the solution contains any particulate matter.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.7)]

17.1 Pregnancy

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

17.2 Immediate Post-Injection Reaction

Advise patients that COPAXONE may cause various symptoms after injection, include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms 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.

17.3 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 (usually only lasting a few minutes). Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patient should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

17.4 Lipoatrophy and Skin Necrosis at Injection Site

Advise patients that localized lipoatrophy, and rarely, injection site necrosis may occur at injections sites. Instruct patients to follow proper injection technique and to rotate injection areas and sites on a daily basis.

17.5 Instructions for Use

Instruct patients to read the COPAXONE Patient Information leaflet carefully. 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 on a daily basis. Caution patients against the reuse of needles or syringes. Instruct patients in safe disposal procedures.

17.6 Storage Conditions

Advise patients that the recommended storage condition for COPAXONE is refrigeration (36-46ºF /2-8ºC), although COPAXONE can be stored at room temperature (59-86ºF /15-30ºC) for up to one month. COPAXONE should not be exposed to higher temperatures or intense light.

17.7 FDA-Approved Patient Labeling

Read this information carefully before you use COPAXONE. Read the information you get when you refill your COPAXONE prescriptions because there may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What is COPAXONE?

COPAXONE (co-PAX-own) is a medicine you inject to treat Relapsing-Remitting Multiple Sclerosis. Although COPAXONE is not a cure; patients treated with COPAXONE have fewer relapses.

Who should not use COPAXONE?

- Do not use COPAXONE if you are allergic to glatiramer acetate or mannitol.

What are the possible side effects of COPAXONE?

- **Call your doctor right away if you develop any of the following symptoms: hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site.** Do not give yourself any more injections until your doctor tells you to begin again.
- The most common side effects of COPAXONE are redness, pain, swelling, itching, or a lump at the injection site. These reactions are usually mild and seldom require medical care.
- Some patients report a short-term reaction right after injecting COPAXONE. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes after an injection, last a few minutes, and then go away by themselves without further problems.
- A permanent depression under the skin at the injection site may occur, due to a local destruction of fat tissue.
- **If symptoms become severe, call the emergency phone number in your area.** Do not give yourself any more injections until your doctor tells you to begin again.

These are not all 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.

Information for pregnant and nursing women

- COPAXONE has not been studied in pregnant women. Talk to your doctor about the risks and benefits of COPAXONE if you are pregnant or planning a pregnancy.
- It is not known if COPAXONE passes into breastmilk. Talk to your baby's doctor about the risks and benefits of breastfeeding while using COPAXONE.

How should I use COPAXONE?

- The recommended dose of COPAXONE for the treatment of Relapsing-Remitting Multiple Sclerosis is 20 mg once a day injected subcutaneously (in the fatty layer under the skin).
- Look at the medicine in the prefilled syringe. If the medicine is cloudy or has particles in it, do not use it. Instead, call Shared Solutions® at 1-800-887-8100 for assistance.
- Have a friend or relative with you if you need help, especially when you first start giving yourself injections.
- Each prefilled syringe should be used for only one injection. Do not reuse the prefilled syringe. After use, throw it away properly.
- Do not change the dose or dosing schedule or stop taking the medicine without talking with your doctor.

How do I inject COPAXONE?

There are 3 basic steps for injecting COPAXONE prefilled syringes:

1. Gather the materials.
2. Choose the injection site.
3. Give yourself the injection.

<u>Step 1</u>: Gather the materials

1. First, place each of the items you will need on a clean, flat surface in a well-lit area:
   - 1 blister pack with COPAXONE Prefilled Syringe
     Remove only 1 blister pack from the COPAXONE Prefilled Syringe carton. Keep all unused syringes in the Prefilled Syringe carton and store them in the refrigerator.
   - Alcohol prep (wipe)
   - Dry cotton ball (not supplied)
2. Let the blister pack with the syringe inside warm up to room temperature for 20 minutes.
3. To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.

4. There may be small air bubbles in the syringe. To avoid loss of medicine when using COPAXONE prefilled syringes, do not expel (or do not attempt to expel) the air bubble from the syringe before injecting the medicine.

Step 2: Choose the injection site

- There are 7 possible injection areas on your body: arms, thighs, hips and lower stomach area (abdomen) (See Figure 1).

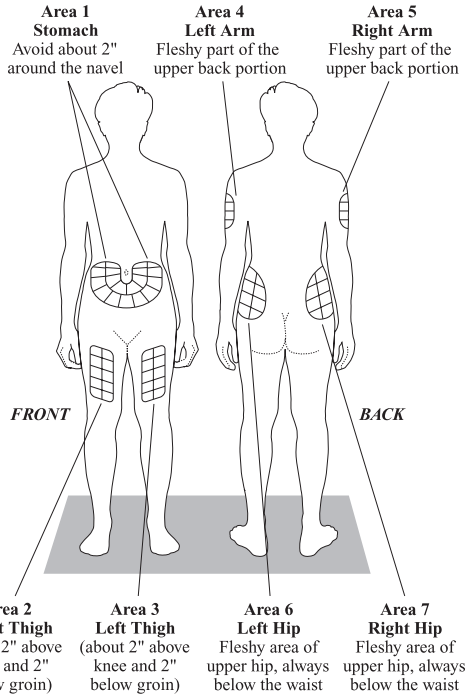
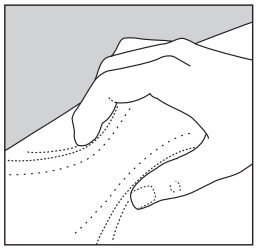


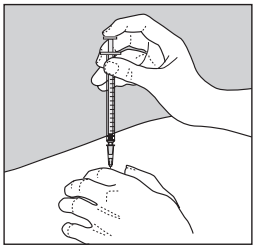
Figure 1

- Each day, pick a different injection area from one of the 7 areas. **Do not inject in the same area more than once a week**.
- Within each injection area there are multiple injection sites. Have a plan for rotating your injection sites. Keep a record of your injection sites, so you know where you have injected.
- There are some sites in your body that may be hard to reach for self-injection (like the back of your arm), and you may need help.
- Do not inject in sites where skin depression has occurred, because further injections in these sites may make the depression deeper.

Step 3: Give yourself the injection

1. Remove the syringe from its protective blister pack by peeling back the paper label. Before use, look at the liquid in the syringe. If it is cloudy or contains any particles, do not use it and call Shared Solutions® at 1-800-887-8100 for assistance. If the liquid is clear, place the syringe on the clean, flat surface.
2. Choose an injection site on your body. Clean the injection site with a new alcohol prep and let the site air dry to reduce stinging.
3. Pick up the syringe as you would a pencil. Remove the needle shield from the needle.
4. With your other hand, pinch about a 2-inch fold of skin between your thumb and index finger (See Figure 2).
5. Insert the needle at a 90-degree angle (straight in), resting the heel of your hand against your body. When the needle is all the way in release the fold of skin (See Figure 3).





6. To inject the medicine, hold the syringe steady and push down the plunger.
7. When you have injected all of the medicine, pull the needle straight out.
8. Press a dry cotton ball on the injection site for a few seconds. **Do not rub the injection site**.
9. Throw away the syringe in a safe hard-walled plastic container.

What is the proper use and disposal of prefilled syringes?

Each prefilled syringe should be used for only 1 injection. Throw away all used prefilled syringes in a hard-walled plastic container, such as an empty liquid laundry detergent bottle. Keep the container closed tightly and out of the reach of children. When the container is full, check with your doctor, pharmacist, or nurse about proper disposal, as laws vary from state to state.

How should I store COPAXONE prefilled syringes?

Keep the COPAXONE prefilled syringe carton in the refrigerator, out of the reach of children.

The COPAXONE package should be refrigerated at 36-46ºF (2-8ºC). You can store it at room temperature, 59-86ºF (15-30ºC), for up to one month. Do not store COPAXONE at room temperature for longer than one month. **Do not freeze COPAXONE**. If a COPAXONE prefilled syringe freezes, throw it away in a proper container.

COPAXONE is light sensitive. Protect it from light when not injecting. Do not use the prefilled syringe if the solution contains particles or is cloudy.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. 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 condition you have. It may harm them.

This 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. Also, you can call Shared Solutions® for any questions about COPAXONE and its use. The phone number for Shared Solutions® is 1-800-887-8100.

U.S. Patent Nos. 5981589, 6054430, 6342476, 6362161, 6620847, 6939539, 7199098.

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