PRODUCT MONOGRAPH

PrCOPAXONE®

(glatiramer acetate for injection)
20 mg, single use vials

and

(glatiramer acetate injection)
20 mg / 1 mL, pre-filled syringes
for Subcutaneous Injection

Immunomodulator

TEVA PHARMACEUTICAL
INDUSTRIES LTD.
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Glatiramer acetate injection and glatiramer acetate for injection By:
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
SC	20 mg / 1 mL Prefilled syringes and lyophilized vials	40 mg mannitol in sterile water for injection

INDICATIONS AND CLINICAL USE

Copaxone is indicated for:

- Treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS)
  - To decrease the frequency of clinical exacerbations
  - To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.
- Treatment of patients who have experienced a single demyelinating event, accompanied by abnormal MRI scans and are considered to be at risk of developing Clinically Definite MS (CDMS), after alternative diagnoses are excluded:
  - To delay the onset of definite MS;
  - To decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans).

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established

Geriatrics (> 65 years of age):
COPAXONE® has not been studied in the elderly (> 65 years old).

Pediatrics (< 18 years of age):
The safety and effectiveness of COPAXONE® have not been established in individuals below 18 years of age.

CONTRAINDICATIONS

- COPAXONE® (glatiramer acetate) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS AND PRECAUTIONS

The only recommended route of administration of COPAXONE® (glatiramer acetate) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Cardiovascular

Symptoms of Potentially Cardiac Origin: Approximately 13% of COPAXONE® patients in the multicenter controlled trials (compared to 5% of placebo patients) experienced at least one episode of what was described as transient chest pain (see **ADVERSE REACTIONS: Chest Pain**). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

General

Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate), including a careful review of the **Part III – Consumer Information**. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Localized Adverse Reactions Associated with Subcutaneous Use
At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during clinical trials and postmarketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may 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 areas and sites on a daily basis (see **Part III – Consumer Information**).

Immune

Considerations Involving the Use of a Product Capable of Modifying Immune Responses:
COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all 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 clinical trial of 125 RRMS patients given glatiramer acetate 20 mg 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 almost any foreign substance and, therefore, this risk cannot be excluded.

Carcinogenesis and Mutagenesis
Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see **TOXICOLOGY: Carcinogenicity**). The relevance of these findings for humans is unknown (see **PRECAUTIONS - Considerations Involving the Use of a Product Capable of Modifying Immune Responses**).

Renal
The pharmacokinetics of COPAXONE® in patients with impaired renal function have not been determined.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies (see **TOXICOLOGY: Reproduction and Teratology**). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre- marketing clinical trials with COPAXONE®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE® should only be considered after careful risk/benefit assessment and be used with caution.

Pediatrics (< 18 years of age): The safety and effectiveness of COPAXONE® have not been established in individuals below 18 years of age

Geriatrics (> 65 years of age): COPAXONE® has not been studied in the elderly (> 65 years old).

Monitoring and Laboratory Tests

Data collected pre- and post-market do not suggest the need for routine laboratory monitoring.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the 4 placebo-controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® occurring at an incidence of at least 10% and at least 1.5 times higher than in placebo treated patients were: injection site reactions, vasodilatation, rash, dyspnea and chest pain.

In the placebo-controlled clinical trials approximately 5% discontinued treatment due to an adverse event compared to 1% for placebo treated patients. The adverse events most commonly associated with discontinuation were (in order of descending frequency): injection site reactions, dyspnea, urticaria, vasodilatation and hypersensitivity. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life-threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 14% of Multiple Sclerosis patients exposed to COPAXONE® in the 4 placebo-controlled studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE® compared to 2% for placebo treated patients. An immediate post-injection reaction is a constellation of symptoms occurring immediately after injection that includes at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (individual symptoms are listed separately in Table 1 below). These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one

or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non-immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see **WARNINGS AND PRECAUTIONS, Symptoms of Potentially Cardiac Origin**).

Chest Pain: Approximately 13% of glatiramer acetate patients in the 4 placebo-controlled studies (compared to 5% 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 the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important 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. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see **WARNINGS AND PRECAUTIONS,** Symptoms of Potentially Cardiac Origin).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The adverse reaction data in this section is derived from 4 pivotal, double-blind, placebo-controlled clinical trials which were conducted during premarketing and postmarketing periods in a total of 512 patients treated with glatiramer acetate and 509 patients treated with placebo for up to 36 months. Three trials were conducted in RRMS. The fourth trial was in patients presenting with a first clinical event and MRI features suggestive of MS and included 243 patients treated with glatiramer acetate and 238 patients treated with placebo.

All adverse events were recorded by the clinical investigators, using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into standardized categories using MedDRA dictionary terminology.

The following table lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with glatiramer acetate in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo.

Table 1: Controlled Trials: Incidence of Glatiramer Acetate Adverse Reactions ≥2% and More Frequent than Placebo

MedDRA Version 10.0		GA 20 mg (N=512)	Placebo (N=509)
		% of Patients	% of Patients
Blood And Lymphatic System Disorders	Lymphadenopathy	7.2	2.9
Cardiac Disorders	Palpitations	7.6	3.3
	Tachycardia	4.7	1.6
Eye Disorders	Eye Disorder	3.3	1.2
	Diplopia	2.9	1.8
Gastrointestinal Disorders	Nausea	14.5	10.4
	Vomiting	7.4	4.3
	Constipation	7.0	6.3
	Dyspepsia	6.6	6.5
	Dysphagia	2.3	1.2
	Faecal Incontinence	2.3	2.0
General Disorders And Administration Site Conditions	Injection Site Erythema	46.1	10.6
	Injection Site Pain	36.3	17.1
	Injection Site Mass	25.8	5.9
	Injection Site Pruritus	24.4	2.8
	Asthenia	23.8	23.2
	Injection Site Edema	20.9	4.5
	Pain	18.9	16.7
	Chest Pain	12.5	4.9
	Injection Site Inflammation	8.2	1.6
	Injection Site Reaction	8.2	1.4
	Pyrexia	6.4	5.7
	Injection Site Hypersensitivity	4.1	0.0
	Local Reaction	3.7	1.4
	Face Edema	3.3	0.6
	Edema Peripheral	3.3	2.4
	Chills	2.9	0.4
	Injection Site Atrophy*	2.0	0.0
	Injection Site Fibrosis	2.0	0.6
Immune System Disorders	Hypersensitivity	3.3	1.8
Infections And Infestations	Infection	31.8	30.8
	Influenza	15.4	14.5
	Rhinitis	7.4	5.9
	Bronchitis	6.4	5.7
	Gastroenteritis	6.3	4.3
	Vaginal Candidiasis	4.9	2.6
	Otitis Media	3.7	2.9
	Herpes Simplex	2.5	1.8
	Tooth Abscess	2.3	2.2
Metabolism And Nutrition Disorders	Weight Increased	2.9	0.8
	Anorexia	2.3	2.2
Musculoskeletal And Connective Tissue Disorders	Back Pain	13.5	11.2
	Arthralgia	10.4	9.4
	Neck Pain	4.5	3.9

MedDRA Version 10.0		GA 20 mg (N=512)	Placebo (N=509)
		% of Patients	% of Patients
Nervous System Disorders	Headache	30.9	29.1
	Hypertonia	7.8	7.3
	Tremor	4.1	1.8
	Migraine	3.7	2.4
	Syncope	3.1	1.8
Psychiatric Disorders	Depression	13.1	12.0
	Anxiety	11.1	8.8
	Nervousness	2.3	1.0
Renal And Urinary Disorders	Micturition Urgency	5.1	4.3
	Pollakiuria	4.7	4.5
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea	13.3	2.8
	Cough	6.6	5.3
Skin And Subcutaneous Tissue Disorders	Rash	13.7	9.0
	Hyperhidrosis	6.6	4.7
	Pruritus	5.1	4.3
	Ecchymosis	3.5	3.3
	Urticaria	3.1	1.6
	Skin Disorder	2.9	0.8
Vascular Disorders	Vasodilatation	18.0	4.7

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

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 96% of patients were Caucasian. This percentage reflects the higher representation of Caucasian in the MS population, even though it does not reflect the exact world racial distribution among MS patients. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any placebo-controlled trial due to abnormal laboratory findings which were assessed as possibly related to glatiramer acetate.

Other Adverse Events Observed During All Clinical Trials

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), with a subset of patients continuing to 10 years (n=108) and some patients to an average of 13.6 years (n=100) in open-label extensions at a daily dose of 20 mg.

During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having

adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a whole:

Frequent: Injection site edema, injection site atrophy, abscess and injection site hypersensitivity.

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, 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, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Post-Market Adverse Drug Reactions

Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials
Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate) in either ongoing phases of clinical trials or from spontaneous reports, that have been received since market introduction and that may have or not have causal relationship to the drug include the following:

Body as a Whole:
Sepsis, SLE syndrome, hydrocephalus, enlarged abdomen, injection site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection.

Cardiovascular:
Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy, cardiomegaly, arrhythmia, angina pectoris, tachycardia.

Digestive:
Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder.

Hemic and Lymphatic:
Thrombocytopenia, lymphoma-like reaction, acute leukemia.

Metabolic and Nutritional:
Hypercholesteremia.

Musculoskeletal:
Rheumatoid arthritis, generalized spasm.

Nervous:
Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo.

Respiratory:
Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus.

Skin and Appendages:
Herpes simplex, pruritis, rash, urticaria.

Special Senses:
Glaucoma, blindness, visual field defect.

Urogenital:
Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency.

Localized Adverse Reactions Associated with Subcutaneous Use
At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during postmarketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may 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 areas and sites on a daily basis (see **Part III – Consumer Information**).

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. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical–trial did not report any serious or unexpected adverse events thought to be related to treatment.

DOSAGE AND ADMINISTRATION

Dosing Considerations

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

The only recommended route of administration of COPAXONE® (glatiramer acetate) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Recommended Dose and Dosage Adjustment

The recommended dose of COPAXONE® (glatiramer acetate for injection or glatiramer acetate injection) for the treatment of Clinically Isolated Syndrome and Relapsing Remitting MS is a daily injection of 20 mg given subcutaneously.

Administration

Reconstitution:

Single-Use Vials of Lyophilized Powder

To reconstitute lyophilized COPAXONE® for injection, use a sterile syringe and adapter to transfer 1.1 mL of the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter. Use within 8 hours after reconstitution. Withdraw 1.0 mL of the solution into a sterile syringe. Remove the adapter, connect a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include arms, stomach (abdomen), buttocks, and thighs. A vial is suitable for single use only; unused portions should be discarded (see **Part III – Consumer Information - Reconstituted product**). The reconstituted solution should not be left longer than 8 hours at room temperature.

COPAXONE® should be reconstituted only with the provided diluent, Sterile Water for Injection.

Vial Size	Volume of Diluent to be Added	Volume to be Injected	Nominal Concentration per mL
2 mL	1.1 mL	1.0 mL	20 mg

For the pre-filled syringe of COPAXONE®, please see the **Part III – Consumer Information - pre-filled syringe** for instructions on the preparation and injection of COPAXONE®.

OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient. The maximum COPAXONE® dose reported in an overdose case is 80 mg glatiramer acetate injection.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

COPAXONE® (glatiramer acetate) is a sterile, lyophilized mixture 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 mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently 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 (EAE), a condition induced in animals that is generally accepted as an experimental 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 the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (see **PRECAUTIONS**).

Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, 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.

STORAGE AND STABILITY

Pre-filled syringes

The pre-filled syringes of COPAXONE® should be refrigerated immediately upon receipt (2° - 8° C). DO NOT FREEZE.

If you cannot have refrigerator storage, pre-filled syringes of COPAXONE® can be stored at room temperature (15° - 30°C) for up to 1 month. Do not store pre-filled syringes at room temperature for longer than 1 month. Note: this drug is light sensitive, do not expose to light when not injecting. Each pre-filled syringe is for single use only.

Single-Use Vials of Lyophilized Powder

Vials of lyophilized COPAXONE® should be stored under refrigeration (2° - 8°C). COPAXONE® may also be stored at room temperature (15° - 30°C) for up to 14 days. The vials of diluent (Sterile Water for Injection) should be stored at room temperature.

Reconstituted solution: The reconstituted solution should not be left longer than 8 hours at room temperature before administration. A vial is suitable for single use only; unused portions should be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pre-filled Syringe

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e. 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection). COPAXONE® (glatiramer acetate injection) is available in packs of 30 single-use 20 mg/1 mL pre-filled glass syringes with 33 alcohol preps (swabs).

Single-Use Vials of Lyophilized Powder

COPAXONE® (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for Injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol, packaged in single use 2 mL amber vials. Each vial of Sterile Water for Injection contains 1.1 mL of Sterile Water for Injection plus a 0.35 mL overage to allow for losses in reconstitution and transfer. COPAXONE® (glatiramer acetate for injection) is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for Injection) for COPAXONE® is supplied in packs of 32 clear vials and is located in the Self Injection Administration Package.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Glatiramer acetate
Chemical name:	Glatiramer acetate is the acetate salt of synthetic polypeptides.
Description:	Glatiramer acetate is prepared by chemically reacting the activated derivatives of four amino acids: L-glutamic acid (L-Glu), L-alanine (L-Ala), L-tyrosine (L-Tyr), and L-lysine (L-Lys) in a specified ratio. The average molar fraction of each amino acid residue are as follows: L-Glu 0.141, L-Ala 0.427, L-Tyr 0.095 and L-Lys 0.338.
Molecular formula and molecular mass:	The average molecular weight of glatiramer acetate is 5,000 to 9,000 daltons. Glatiramer acetate is identified by specific antibodies.
Structural formula:	Poly[L-Glu$^{13\text{-}15}$, L-Ala$^{39\text{-}46}$, L-Tyr$^{8.6\text{-}10}$, L-Lys$^{30\text{-}37}$]$\bullet n CH_3CO_2H$ (n=15-24)
Physical Form:	White to slightly yellowish lyophilized material.
Solubility:	Sparingly soluble in water, insoluble in acetone.
pH:	The pH of a 0.5% w/v solution of glatiramer acetate in water is in the range of 5.5 to 7.0.
Biological Activity:	The biological activity of Copaxone® is determined by its ability to block the induction of EAE in mice.

CLINICAL TRIALS

The efficacy of COPAXONE® (glatiramer acetate) was evaluated in two placebo-controlled trials in patients with Relapsing Remitting MS (RRMS). In a third placebo-controlled study the effects of glatiramer acetate on MRI parameters were assessed. In these studies, a dose of 20 mg/day was used. No other dose or dosing regimen has been studied in placebo-controlled trials of RRMS.

The first trial was a pilot study Trial I (Trial BR-1) which was conducted at a single-center and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial. Fifty patients with RRMS were randomized to receive 20 mg/day glatiramer acetate (n=25) or placebo (n=25) subcutaneously. The protocol- specified primary outcome measure was the proportion of patients who were relapse free during the 2-year duration of the trial, but two additional relevant

outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 2) show that there was a statistically significant effect of glatiramer acetate on number of relapses.

TABLE 2
Trial BR-1: Efficacy Results

Outcome	Trial I[a]		
	Glatiramer acetate 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 pre-study	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

[a]The primary efficacy measure for **Trial I** was the proportion of patients who were relapse free during the 2 year duration of the trial (% **Relapse Free**). Analyses were based on the intent-to-treat population.
* Progression defined as an increase of at least 1 point on the DSS that persists for at least 3 consecutive months.

Trial II (01-9001) was a multicenter double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RRMS were randomized to receive 20 mg/day glatiramer acetate (n=125) or placebo (n=126) subcutaneously. Patients were diagnosed with RRMS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair.

Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours).

The protocol-specified primary outcome measure was the mean number of relapses during treatment.

Table 3 shows results of the analysis of primary as well as several secondary outcome measures at two years based on the intent-to-treat population.

TABLE 3
Core (24-month) Double-Blind Study: Effect on Relapse Rate

Outcome	Trial II[a]		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean No of Relapses/2 years[b]	1.19	1.68	0.007*
% Relapse Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Patients Progression Free[c]	98/125 (78%)	95/126 (75%)	0.48
Mean Change in EDSS	-0.05	+0.21	0.023

[a] The primary efficacy measure for **Trial II** was the number of relapses during treatment. Analyses were based on the intent-to-treat population.
[b] Baseline adjusted mean
[c] Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.
* Analysis of Covariance adjusted for baseline EDSS, prior 2-year relapse rate and study centers. ANCOVA or analysis of covariance is a statistical test used to adjust for covariate differences between the treatment and control groups which may confound the true treatment effect when one or more factors are not balanced across treatment groups.

The effects of glatiramer acetate on relapse severity were not evaluated in either trial.

Both studies showed a beneficial effect of glatiramer acetate on relapse rate, and on this basis glatiramer acetate is considered effective.

The third study (9003) was a multi-national, multi-center, MRI-monitored study. A total of 239 patients with RRMS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in Trial II (Study 01-9001) with the additional criteria that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated initially 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 nine months. Other MRI parameters were assessed as secondary endpoints. Table 4 summarizes the results for the parameters monitored during the nine-month double-blind phase for the intent-to-treat cohort. Because the link between MRI findings and the clinical status of patients is contentious, the prognostic value of the following statistically significant findings is unknown.

TABLE 4
Nine-Month Double-Blind Phase: MRI Endpoints - Results

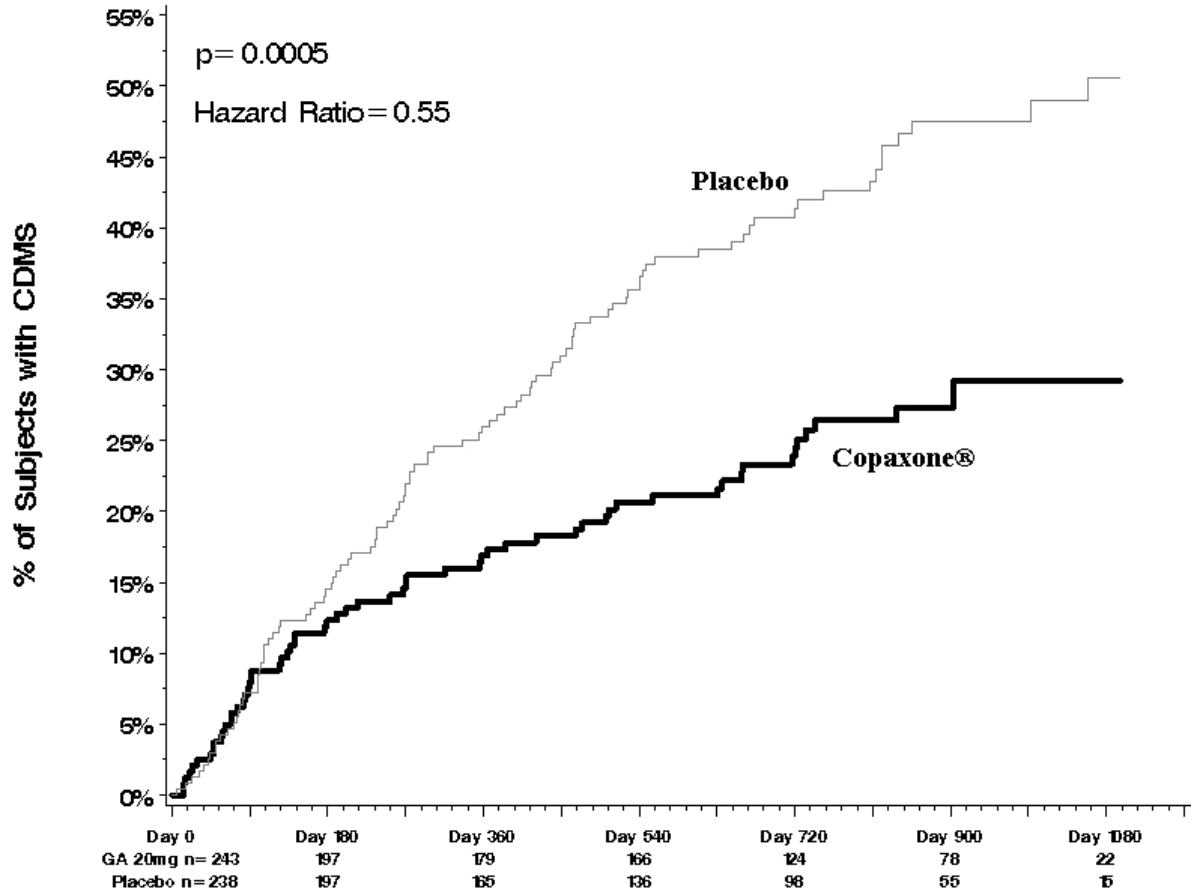
No.	Outcome	Glatiramer Acetate (n=113)	Placebo (n=115)	p-value
Primary Endpoint				
1.	Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	12	17	0.0037
Secondary Endpoints				
2.	Medians of the Cumulative Number of New T1 Gd-Enhancing Lesions	9	14	0.0347
3.	Medians of the Cumulative Number of New T2 Lesions	5	8	0.01
4.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Gd-Enhancing Lesions	-0.309	0	0.0248
5.	Medians of the Cumulative Change from Baseline in volumes (mL) of T2 Lesions	8.852	13.566	0.0229
6.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Hypointense Lesions	1.642	1.829	0.7311
7.	Proportion of T1 Gd-Enhancing Lesion-Free Patients	46.4%	32.2%	0.0653

The mean number of relapses in this 9 month study was 0.50 for the COPAXONE® group and 0.77 for the placebo group (p = 0.0077).

A fourth study was a multicenter, randomized, double-blind, placebo-controlled, parallel group study involving 481 patients for up to three years (glatiramer acetate 20 mg/day: n=243; placebo: n=238) was performed in patients with a well-defined, single, unifocal neurological presentation and MRI features suggestive of MS (at least two cerebral lesions on T2-weighted MRI) (sometimes referred to as "clinically isolated syndrome"). The primary outcome measure in the study was the time to conversion to clinically definite MS (CDMS), according to Poser criteria. Secondary outcomes were brain MRI measures including number of new T2 lesions and T2 lesion volume.

Time to conversion to CDMS was significantly delayed in the Glatiramer acetate group corresponding to a risk reduction of 45% (Hazard Ratio = 0.55; 95% CI [0.40; 0.77], p=0.0005) (Figure1).

Figure 1: Time to Conversion to CDMS (ITT Analysis)



Glatiramer acetate prolonged the time to CDMS by 386 (115%) days, from 336 days in the placebo group to 722 days in the glatiramer acetate group (based on the 25th percentile; Kaplan-Meier estimates).

A total of 25% of glatiramer acetate patients, and 43% of placebo patients converted to CDMS in an average duration of treatment of 2.4 years.

The benefit of treatment with glatiramer acetate over placebo was also demonstrated in two secondary MRI-based endpoints. The number of new T2 lesions at last observed value (LOV) was significantly lower ($p<0.0001$) for patients on glatiramer acetate, demonstrating a treatment effect of 58% for glatiramer acetate over placebo (mean number of new T2 lesions at LOV was 0.7 for glatiramer acetate and 1.8 for placebo). Additionally, baseline-adjusted T2 lesion volume at LOV showed a significant reduction ($p=0.0013$) of 13% for glatiramer acetate over placebo (median change in T2 volume from baseline to LOV was 0.7 mL on glatiramer acetate and 1.3 mL on placebo).

Post-hoc subgroup analyses were performed in patients with various baseline characteristics to identify a population at high risk to develop the second attack. For subjects with baseline MRI with at least one T1 Gd-enhancing lesion and 9 or more T2 lesions, conversion to CDMS was evident for 50% of the placebo subjects vs. 28% of the Copaxone subjects in 2.4 years. For subjects with 9 or more T2 lesions at baseline, conversion to CDMS was evident for 45% of the

placebo subjects vs. 26% on Copaxone in 2.4 years. However, the impact of early treatment with Copaxone on the long term evolution of the disease is unknown even in these high-risk subgroups as the study was mainly designed to assess the time to the second event. In any case, treatment should only be considered for patients classified at high risk.

Efficacy data for CIS beyond 3 years are not available.

DETAILED PHARMACOLOGY

Preclinical Studies

Glatiramer acetate is efficacious in suppressing and/or preventing both the clinical and histological manifestations of the most widely accepted animal model of Multiple Sclerosis, EAE. This effect of glatiramer acetate has been demonstrated in a wide variety of species including mice, rats, guinea pigs, rabbits, and primates (rhesus monkeys and baboons).[1-8]

Glatiramer acetate partially cross-reacts with myelin basic protein (MBP) on both the humoral and cellular levels. In addition, it competes with myelin-associated peptides including myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP) for binding to the MHC class II molecules.[9] Glatiramer acetate binds with high affinity to MHC Class II molecules on the surface of antigen presenting cells.[10] *In vitro* studies demonstrate that the affinity of glatiramer acetate is sufficient to competitively displace MBP, MOG and PLP from MHC II.[9] Specificity of glatiramer acetate binding is demonstrated by the observation that anti-MHC II DR antibodies but not anti-MHC I or anti-MHC II DQ antibodies inhibit interaction of glatiramer acetate with MHC II.[9]

Induction of suppressor T-cells has been demonstrated experimentally. T-cell hybridomas established from spleen cells of glatiramer acetate treated animals were shown to adoptively transfer resistance to EAE in untreated animals and to inhibit antigen-specific proliferation and interleukin-2 (IL-2) secretion of an MBP-specific T-cell line.[11] Inhibition of MBP-specific effector T-cells by glatiramer acetate has been demonstrated in several *in vitro* studies. In the presence of antigen presenting cells, glatiramer acetate competitively inhibits proliferation and IL-2 and interferon gamma secretion by human MBP-specific T-cell lines while having no effect on T-cell lines specific for other antigens. Glatiramer acetate alone does not stimulate proliferation,[12,13] IL-2 secretion[12,13] or cytotoxic responses in human MBP-specific T-cells[14.] In addition, glatiramer acetate has been shown to inhibit MBP-specific T-cell cytotoxicity.[14]

Attempts have been made to characterize bioavailability using subcutaneously administered ^{125}I-Glatiramer acetate in animals. Serum samples were qualitatively analyzed by HPLC to estimate the proportion of intact glatiramer acetate and glatiramer acetate-related peptide fragments over time. The HPLC elution pattern was consistent with that for glatiramer acetate three minutes after injection. By 15 minutes, the elution pattern shifted to two distinct smaller species and free iodide. It is unclear if the smaller species represented ^{125}I-Glatiramer acetate metabolites or other unrelated species iodinated as a result of iodide exchange. These studies have not been repeated in man.

Other *in vitro* and *in vivo* studies in animals demonstrate that ^{125}I-Glatiramer acetate is rapidly degraded at the site of injection. Tissue homogenate studies suggest this may also be true in

man. Due to the possibility of de-iodination, iodide exchange and incorporation of amino acids from glatiramer acetate into other peptides, results from these studies with ^{125}I-Glatiramer acetate must be cautiously interpreted.

TOXICOLOGY

Acute Toxicity

Glatiramer acetate was well tolerated following a single subcutaneous injection at a dose of 400 mg/kg in the rat. No toxic effects were noted.

After I.V. administration of 200 mg/kg in the rat, severe morbidities with about 10% mortalities were recorded. At 40 mg/kg, no mortalities occurred and only transient tremor was noted in one animal.

Long-Term Toxicity (Subchronic and Chronic)

Toxicity and reproductive studies were performed with glatiramer acetate involving 560 rats treated for up to 6 months, 68 rabbits treated for up to 2 weeks, 23 dogs treated for up to 3 months and 32 monkeys treated for up to 1 year. The several deaths that occurred (5 rats in the 6-month study, 2 rats in the 4-week study, 1 rat in the segment III reproduction study and 1 monkey in the 1-year study) were judged as incidental and unrelated to treatment.

Chronic and subchronic daily subcutaneous injections were systemically well tolerated at doses of up to 30 mg/kg/day for periods extending for up to 6 months in the rat and up to one year in the monkey.

In aging male rats (at the end of the life-span carcinogenicity study), there was a small increase in the incidence of glomerulonephritis. The NOAEL for this finding was 7.5 mg/kg/day.

At doses of 30 mg/kg and above some findings such as slight reduction in body weight gain, and occasional minor changes in blood chemistry and hematological parameters were noted. These findings were noted in some studies and not in others, and were without any clinical sequelae. No remarkable findings were noted in ophthalmoscopic or in EKG evaluations. In monkeys treated with 30 mg/kg/day there were some evidence for over immune stimulations such as an increase in the titer of antinuclear antibodies, an increase in the incidence of germinal centers in the bone marrow and of minor chronic focal fibrosing arterial lesions. The association of these findings to treatment is uncertain and the NOAEL for these findings was set to 10 mg/kg/day.

Based on these findings, the NOAEL for the systemic effects of glatiramer acetate in chronic studies is considered to be 7.5 mg/kg.

Local lesions at the injection sites were consistently observed in all studies and were dose related. At doses of 30 mg/kg/day and above in the rat and the monkey, injection site reactions were clinically significant and poorly tolerated.

Carcinogenicity

Two life-span carcinogenicity studies with glatiramer acetate, one in mice and one in rats, were completed. Results from the two carcinogenicity studies do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously to rats and mice, at dose levels of up to 60 mg/kg/day.

In the two-year carcinogenicity study in the mouse, repeated administration of doses up to 60 mg/kg/day, showed no evidence for systemic carcinogenicity. In males of the high dose group (60 mg/kg/day), but not in females, there was an increased incidence of fibrosarcomas at the injection sites. These rapidly growing sarcomas, consisting of spindle or fusiform cells with local invasion but no metastasis, were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a two-year carcinogenicity study in rats, subcutaneous administration of glatiramer acetate at a dose of 30 mg/kg/day was associated with an increased incidence of benign adrenal pheochromocytomas in males only. This effect was not seen at 15 mg/kg/day and was within the historical control values for the testing laboratory.

Mutagenicity

Glatiramer acetate showed a marginal and inconsistent effect on structural chromosomal aberrations in cultured human lymphocytes. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given 140 mg/kg, equivalent to approximately 60% of the LD_{50}/kg, i.p. Glatiramer acetate, with or without metabolic activation, did not induce point mutations in four strains of *Salmonella typhimurium*, two strains of *Escherichia coli*, or mouse lymphoma L5178Y cell cultures.

Reproduction and Teratology

In fertility and reproduction studies in rats, glatiramer acetate at doses up to 36 mg/kg/day had no adverse effects on reproductive parameters.

Embryofetal development toxicity studies have been performed in rats and rabbits at doses up to approximately 37.5 mg/kg and have revealed no evidence of impaired development of the fetus due to glatiramer acetate.

Peri post natal development toxicity studies did not reveal any effect on the development and reproductive performances of pups born to female rats that were dosed until weaning of the pups with glatiramer acetate at doses up to 36 mg/kg.

Antigenicity Studies

Studies to assess anaphylaxis in sensitized guinea pigs and mice showed that glatiramer acetate elicited IgG activity but very low or no IgE activity.

Cardiac Study

In a dog study, a pharmacological effect of intravenous glatiramer acetate, i.e. reduction of blood pressure, was achieved at a dose of 6.0 mg/kg (10-times the human therapeutic dose on a mg/m^2 basis) but not at a 2-fold lower dose. This was not associated with a decrease in coronary artery blood flow or ischemic change on ECG.

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PART III: CONSUMER INFORMATION

COPAXONE® (glatiramer acetate injection)
pre-filled syringe

This leaflet is part III of a three-part "Product Monograph" published when COPAXONE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COPAXONE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
COPAXONE® (glatiramer acetate injection) 20 mg/1 mL pre-filled glass syringe is used to treat patients with Relapsing Remitting Multiple Sclerosis, or patients who have experienced one episode of neurological symptoms likely to be a first sign of multiple sclerosis.

Multiple Sclerosis (MS) is thought to be an autoimmune disease that causes inflammation in small areas of the central nervous system (brain or spinal cord). Autoimmune means the body's immune system attacks its own cells. This inflammation causes damage to the myelin that covers the nerve fibers and ensures they work properly. The loss of myelin (or *demyelization*) eventually leads to neurological symptoms. In the Relapsing Remitting form of MS, symptomatic flare-ups (called *relapses*) are followed by periods when the symptoms go away completely or partly (called *remissions*).

Although it is not a cure, patients treated with COPAXONE® experience fewer relapses.

What it does:
COPAXONE is a mixture of peptides (or small proteins) that resemble a protein in myelin. COPAXONE is thought to work by modifying the immune processes that are believed to cause MS.

When it should not be used:
Do NOT take COPAXONE if you had an allergic reaction to glatiramer or mannitol.

What the medicinal ingredient is:
Glatiramer acetate

What the nonmedicinal ingredients are:
40 mg mannitol in sterile water for injection

What dosage forms it comes in:
Single-use 20 mg/1 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution.

WARNINGS AND PRECAUTIONS

Before you begin using COPAXONE®, make sure you understand all the information provided about its possible benefits and risks. If you do not understand any of the information provided in this section, contact your doctor for further clarification. You may also contact Shared Solutions® by calling 1-800-283-0034 or at www.sharedsolutions.ca and info@sharedsolutions.ca.

- COPAXONE® is not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are using this medication.

- Inform your physician if you are nursing.

- Do not change the dose or dosing schedule without consulting your physician.

- Do not stop using the drug without consulting your physician.

Post-Injection Reaction: Some patients have reported a transient, self-limited reaction immediately after injecting COPAXONE® (Post-Injection Reaction, see ***Side Effects and what to do about them***).

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor if you are taking any other prescription or non-prescription medicines. This includes any vitamin or mineral supplements, or herbal products.

PROPER USE OF THIS MEDICATION

The first time you use COPAXONE® you will be given full instructions and should be supervised by a doctor or nurse.

Instructions for the preparation and injection of COPAXONE® pre-filled syringe

Step 1: Gathering the materials

First, assemble one of each of the items you will need on a clean, flat surface in a well-lit area.

- One blister with COPAXONE® pre-filled syringe*
- Alcohol prep (wipe).

- Dry cotton ball (not supplied).

* Remove only one blister with pre-filled syringe at a time from the COPAXONE® pre-filled syringe package. Keep all unused syringes in the refrigerator.

To ensure that the solution has warmed up to room temperature, allow the unopened blister containing the syringe to stand at room temperature for at least 20 minutes.

Prior to injection, to prevent infection, wash and dry your hands. Do not touch your hair or skin, unnecessarily, after washing your hands.

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

Step 2: Choosing the site for injection

- There are seven possible areas on your body for injection: back of the upper arms (2 areas), front and outside of thighs (2 areas), upper buttocks/rear hips (2 areas) and stomach (abdomen) (See figure-1).

- Each day of the week you should pick one of the seven areas, and from within that area, pick an injection site. Pick each injection area only once per week.

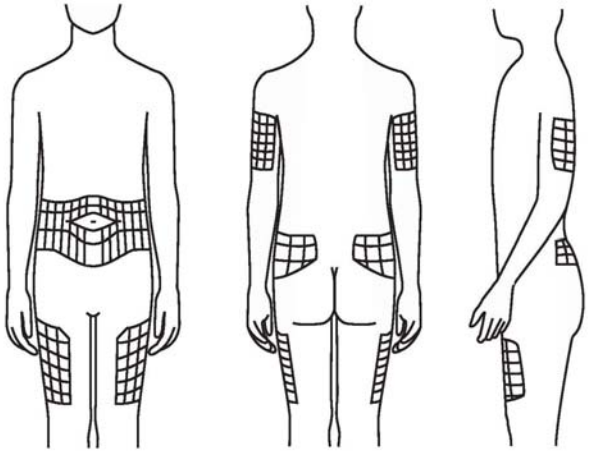
- Within each of the seven injection areas there are multiple injection sites. Rotate the injection sites within an area. **Choose a different injection site each time**. **Please note:** do not inject in any area that is painful or discoloured or where you feel firm knots or lumps.

- It is recommended to have a planned rotating injection site schedule and to note it in a daily planner.

- There are some areas on your body that may be difficult for self-injection (like the back of the arm), and you may require assistance.

- Do not inject sites where skin depression has occurred because further injections in these sites may make the depression deeper.

Arms Administer the injection in the upper back portion of the arm.	**Stomach** Administer the injection leaving 5 cm (2") around the navel



Buttocks Administer the injection in the upper outer rear quadrant.	**Thighs** Administer the injection in the front and outer part of the thigh, 5 cm (2") above the knee and 5 cm (2") below the groin.

Figure 1

Step 3: Injection

1. Remove the syringe from its protective blister by peeling back the paper label. Place the syringe on a clean, flat surface.

2. Choose an injection site on your body. Clean the injection site with a fresh alcohol prep and let it air dry for 60 seconds to reduce any stinging.

3. Using the hand you write with, pick up the syringe as you would a pencil. Remove the needle cap from the needle.

4. With your other hand, pinch about a 5 centimeter (2 inch) fold of skin between your thumb and index finger (See figure-2).

5. Insert the needle at a perpendicular angle (90^{o}), 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).

Figure 2

Figure 3

6. To inject the medication, hold the syringe steady and push down on the plunger. The injection should take just a few seconds.

7. Pull the needle straight out.

8. Press a dry cotton ball on the injection site for few seconds.

9. Discard the syringe and the needle cap in a safe hard-walled plastic container.

10. Make sure that the rest of the unused syringes are kept in the refrigerator.

How do I reach the upper back portions of my arms?

For these two injection areas, it is not possible to pinch_5 centimeters (2 inches) of skin with one hand and inject yourself with the other hand. Ask your nurse for instructions on how to use these areas.

- **If you experience dizziness, skin eruptions with irritation, sweating, chest pain, difficulty in breathing, or other uncomfortable changes in your general health, call your physician immediately. Make no more injections until the physician tells you to begin again.**

- **If symptoms become severe, call the appropriate emergency phone number in your area. Make no more injections until the physician tells you to begin again. Be sure to inform your physician about any side effects.**

Proper use of used pre-filled syringes:
Each pre-filled syringe should be used for only one injection. Discard all used pre-filled syringes in a hard-walled plastic container, such as a liquid laundry detergent bottle. Keep the cover of this container closed tight and out of the reach of children. When the container is full, check with your physician, pharmacist or nurse about proper disposal, as local laws may vary.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most commonly observed adverse reactions associated with the use of COPAXONE® are redness, pain, inflammation, itching, or a lump at the site of injection. These reactions are usually mild and seldom require professional treatment. A permanent depression under the skin at the injection site may also occur, due to a destruction of fat tissue at that site.

Some patients have reported a transient, self-limited reaction immediately after injecting COPAXONE® (Post-Injection Reaction). Symptoms associated with this reaction could include flushing, chest pain/chest tightness, heart palpitations, anxiety, difficulty in breathing, constriction of the throat and urticaria. These symptoms occurred rarely, generally appeared within minutes of an injection, lasted approximately 15 minutes, and resolved without further problems. These symptoms may occur at the beginning of treatment or several months after you started treatment with COPAXONE®. You may also experience these symptoms in more than one occasion.

After you inject COPAXONE®, if you experience hives, skin eruption with irritation, dizziness, sweating, chest pain, difficulty in breathing, severe pain at the injection site or other uncomfortable changes in your general health, **call your physician immediately**. Discontinue your injections until your physician tells you to begin again.

If symptoms become severe, **call the appropriate emergency phone number in your area**. Discontinue your injections until your physician tells you to begin again. Be sure to inform your physician about any side effects.

This is not a complete list of side effects. For any unexpected effects while taking COPAXONE®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep the COPAXONE® package in a safe place, out of the reach of children

The COPAXONE® package should be refrigerated immediately upon receipt (2° - 8° C). DO NOT FREEZE. If you cannot have refrigerator storage, pre-filled syringes of COPAXONE® can be stored at room temperature (15° - 30° C) for up to 1 month. Do not store pre-filled syringes of COPAXONE® at room temperature for longer than 1 month.

Note: this drug is light sensitive, do not expose to light when not injecting. Do not use if it contains particles.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.copaxone.ca
or by contacting the sponsor, Teva Neuroscience, at:
1-800-283-0034

This leaflet was prepared by Teva Neuroscience

Last revised: <MON DD, YYYY>.

PART III: CONSUMER INFORMATION

COPAXONE® (glatiramer acetate for injection)
Product for Reconstitution

This leaflet is part III of a three-part "Product Monograph" published when COPAXONE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COPAXONE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
COPAXONE® (glatiramer acetate injection) 20 mg/1 mL pre-filled glass syringe is used to treat patients with Relapsing Remitting Multiple Sclerosis, or patients who have experienced one episode of neurological symptoms likely to be a first sign of multiple sclerosis.

Multiple Sclerosis (MS) is thought to be an autoimmune disease that causes inflammation in small areas of the central nervous system (brain or spinal cord). Autoimmune means the body's immune system attacks its own cells. This inflammation causes damage to the myelin that covers the nerve fibers and ensures they work properly. The loss of myelin (or *demyelination*) eventually leads to neurological symptoms. In the Relapsing Remitting form of MS, symptomatic flare-ups (called *relapses*) are followed by periods when the symptoms go away completely or partly (called *remissions*).

Although it is not a cure, patients treated with COPAXONE® experience fewer relapses.

What it does:
COPAXONE is a mixture of peptides (or small proteins) that resemble a protein in myelin. COPAXONE is thought to work by modifying the immune processes that are believed to cause MS.

When it should not be used:
Do NOT take COPAXONE if you had an allergic reaction to glatiramer or mannitol.

What the medicinal ingredient is:
Glatiramer acetate

What the nonmedicinal ingredients are:
40 mg mannitol in sterile water for injection

What dosage forms it comes in:
Each vial of COPAXONE® (glatiramer acetate for injection) contains 22 mg glatiramer acetate and 40 mg mannitol. COPAXONE® is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for Injection.

WARNINGS AND PRECAUTIONS

Before you begin using COPAXONE®, make sure you understand all the information provided about its possible benefits and risks. If you do not understand any of the information provided in this section, contact your doctor for further clarification. You may also contact Shared Solutions® by calling 1-800-283-0034 or at www.sharedsolutions.ca and info@sharedsolutions.ca.

COPAXONE® is not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are using this medication

Inform your physician if you are nursing.

Do not change the dose or dosing schedule without consulting your physician.

Do not stop using the drug without consulting your physician.

Post-Injection Reaction: Some patients have reported a transient, self-limited reaction immediately after injecting COPAXONE® (Post-Injection Reaction, see ***Side Effects and what to do about them***).

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor if you are taking any other prescription or non-prescription medicines. This includes any vitamin or mineral supplements, or herbal products.

PROPER USE OF THIS MEDICATION

The first time you use COPAXONE® you will be given full instructions and should be supervised by a doctor or nurse.

INSTRUCTIONS FOR RECONSTITUTING AND INJECTING COPAXONE®

The following instructions will help you through four basic steps: gathering the materials, adding Sterile Water For Injection (diluent) to the dry COPAXONE® (reconstitution), preparing the injection syringe and finally injecting yourself.

Gathering the Materials

First, assemble the items you will need on a clean flat surface in a well lighted area:

The item	Supplied in
* One brown vial of COPAXONE®	COPAXONE® drug product package
* One clear vial of Sterile Water For Injection, USP (diluent) * One 3 cc syringe * One injection needle (27 gauge, ½") * One Mixject Vial Adapter * Three alcohol preps (swabs)	Self Injection Administration Package
* Dry cotton ball	Not supplied

Please note:
One cubic centimeter (cc) represents the same amount as one milliliter (mL). Use the scale which appears on the syringe.

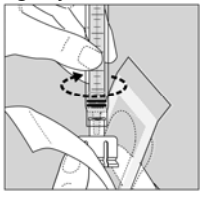
To prevent infection, wash and dry your hands. Do not touch your hair or skin, unnecessarily after washing your hands.

1) Remove the 3 cc syringe from its protective wrapper by peeling back the paper label.

2) Place the syringe on the clean surface.

3) Remove the injection needle from its protective wrapper by peeling back the paper label and place the injection needle on the clean surface. Do not remove the plastic needle shield yet.
4) Open the Mixject Vial Adapter package by peeling back the paper and the laminate. Peel back only half-way, do not open completely. Hold the wide side of the Mixject Vial Adapter through the package to avoid touch contamination.

5) Remove the plastic tip cap from the 3 cc syringe. Without removing the Mixject Vial Adapter from its package, connect the syringe to the Mixject Vial Adapter by rotation, making sure that the syringe is tightly secured to the Mixject Vial Adapter.

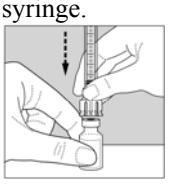


Place the package containing the Mixject Vial Adapter with the attached syringe on the clean surface.

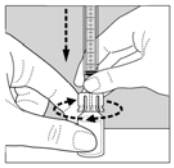
6) Remove the plastic cover from the clear diluent vial, and use an alcohol prep to clean the rubber top. Do the same for the brown COPAXONE® vial with a fresh alcohol prep. DO NOT TOUCH the rubber tops after they are cleaned. Let both rubber tops dry for a few seconds.

Important:
* Don't touch the needle, the piercing spike of the Mixject Vial Adapter or the top of either vial in order to keep them sterile.
* Use only the Sterile Water for Injection, USP (diluent) from the Self Injection Administration Package when reconstituting COPAXONE®.
* If you have questions, contact your physician or nurse before going further in reconstituting and injecting COPAXONE®. You may also contact **Shared Solutions**® by calling 1-800-283-0034.

Mixing COPAXONE® and Diluent (Reconstitution)
1) Holding the syringe in one hand, remove the paper wrap, taking care not to touch the Mixject Vial Adapter. Pull the plunger back to draw 1.1 cc of air into the syringe.

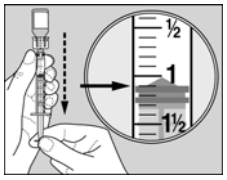


2) Hold the clear diluent vial on a stable surface with two fingers. While holding the connection between the Mixject Vial Adapter and the syringe with the other hand, insert the piercing spike of the Mixject Vial Adapter all the way in through the rubber top of the clean diluent vial, using a rotating and pushing movement.



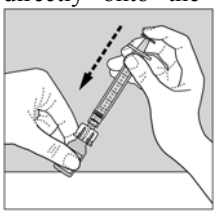
3) Push the plunger of the syringe all the way in. This will allow the water to be drawn from the vial easily.

4) Turn the connected syringe and vial upside down and pull the plunger back until the top of the black plunger ring (as shown by the arrow in the figure) is in line with the bottom of the 1.1 cc line on the syringe.



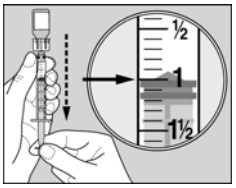
5) Holding the syringe, pull the adapter out of the clear vial and dispose of the vial by putting it in a safe hard-walled container, such as a liquid laundry detergent bottle.

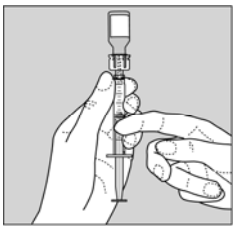
6) Holding the brown COPAXONE® vial on a stable surface with two fingers and the connection between the Mixject Vial Adapter and the syringe with the other hand, insert the piercing spike of the Mixject Vial Adapter all the way in through the rubber top of the COPAXONE® vial, using a rotating and pushing movement. Slowly inject all the diluent into the vial, keeping the vial at an angle. Avoid injecting the diluent directly onto the COPAXONE®, to avoid bubbles.



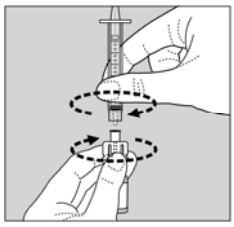
Preparing the Injection Syringe

1) Holding the syringe with one hand, raise the vial to position it upside down. To draw the required amount of dissolved COPAXONE®, slowly pull the plunger back until the top of the black plunger ring (as shown by the arrow in the figure) is in line with the bottom of the 1 cc line on the syringe. If there is air in the syringe, tap the side of the syringe to make the air bubbles float to the top. Inject the air back into the vial. Now you will probably need to draw a little more solution into the syringe to bring the level back to the 1 cc mark.





2) Keeping the brown vial of COPAXONE® and the Mixject Vial Adapter connected, disconnect them from the syringe by rotation. Dispose of the Mixject Vial Adapter and the connected vial by putting them in a safe hard-walled container.



3) Connect the injection needle (27 gauge, ½") to the syringe by rotation, making sure that the needle is tightly placed in its designated position. The syringe is now ready for use.

4) Place the ready to use syringe on the clean surface.

Giving Yourself the Injection

Before you begin the procedure to self-inject the COPAXONE® (glatiramer acetate for injection) dose, note these important points:

7) DO NOT SHAKE. Gently swirl the vial until all the medication dissolves and the solution looks clear. The COPAXONE® is now reconstituted. Let the vial and the adapter/syringe rest and warm up for about 5 minutes. Inspect it for particles. Do not use it if any are present. The reconstituted solution should be used within 8 hours.

Choosing the site for injection

- There are seven possible areas on your body for injection: back of the upper arms (2 areas), front and outside of thighs (2 areas), upper buttocks/rear hips (2 areas) and stomach (abdomen) (See figure-1).

- Each day of the week you should pick one of the seven areas, and from within that area, pick an injection site. Pick each injection area only once per week.

- Within each of the seven injection areas there are multiple injection sites. Rotate the injection sites within an area. **Choose a different injection site each time**. **Please note:** do not inject in any area that is

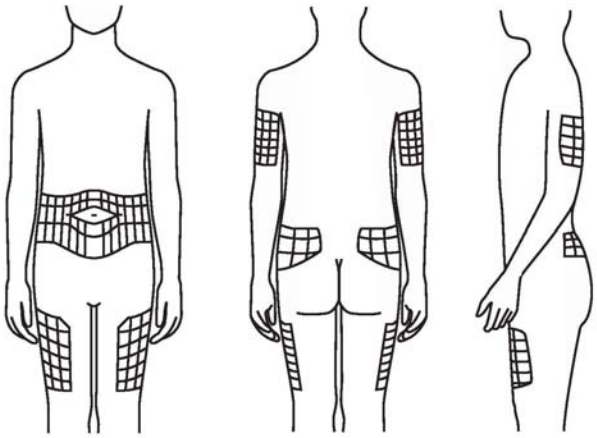
  painful or discoloured or where you feel firm knots or lumps.

- It is recommended to have a planned rotating injection site schedule and to note it in a daily planner.

- There are some areas on your body that may be difficult for self-injection (like the back of the arm), and you may require assistance.

- Do not inject sites where skin depression has occurred because further injections in these sites may make the depression deeper.

Arms	**Stomach**
Administer the injection in the upper back portion of the arm.	Administer the injection leaving 5 cm (2") around the navel



Buttocks	**Thighs**
Administer the injection in the upper outer rear quadrant.	Administer the injection in the front and outer part of the thigh, 5 cm (2") above the knee and 5 cm (2") below the groin.

Figure 1

1) Clean the injection site with a fresh alcohol wipe, and let it dry.

2) Pick up the 3 cc syringe you already filled with COPAXONE® as you would a pencil, using the hand you write with. Remove the plastic cover from the needle.

3) Then pinch about a 5 centimeter (2 inch) fold of skin between thumb and index finger of your other hand.

4) Insert the needle at a perpendicular angle (90°), resting the heel of your hand against your body.

5) When the needle is all the way in, release the fold of skin.

6) Inject the medication by holding the syringe steady while pushing down on the plunger. The injection should take just a few seconds.

7) Pull the needle straight out.

8) Press a dry cotton ball on the injection site for a few seconds.

9) Discard the syringe, needle cap, Mixject Vial Adapter, and the used vials in a safe, hard-walled container, such as a liquid laundry detergent bottle.

How do I reach the upper back portions of my arms?

For these two injection areas, it is not possible to pinch 5 centimeters (2 inches) of skin with one hand and inject yourself with the other hand. Ask your nurse for instruction on how to use these areas.

- **If you experience dizziness, skin eruptions with irritation, sweating, chest pain, difficulty in breathing, or other uncomfortable changes in your general health, call your physician immediately. Make no more injections until the physician tells you to begin again.**

- **If symptoms become severe, call the appropriate emergency phone number in your area. Make no more injections until the physician tells you to begin again. Be sure to inform your physician about any side effects.**

Proper use of needles and syringes:
Needles, syringes, adapters and vials should be used for only one injection. Discard all used syringes, needles, adapters and vials in a hard-walled plastic container, such as a liquid laundry detergent bottle. Keep the cover of this container closed tightly and out of reach of children. When the container is full, check with your physician, pharmacist or nurse about proper disposal, as local laws may vary.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most commonly observed adverse reactions associated with the use of COPAXONE® are redness, pain, inflammation, itching, or a lump at the site of injection. These reactions are usually mild and seldom require professional treatment. A permanent depression under the skin at the injection site may also occur, due to a destruction of fat tissue at that site.

Some patients have reported a transient, self-limited reaction immediately after injecting COPAXONE® (Post-Injection Reaction). Symptoms associated with this reaction could include flushing, chest pain/chest tightness, heart palpitations, anxiety, difficulty in breathing, constriction of the throat and urticaria. These symptoms occurred rarely, generally appeared within minutes of an injection, lasted approximately 15 minutes, and resolved without further problems. These symptoms may occur at the beginning of treatment or several months after you started treatment with COPAXONE®. You may also experience these symptoms in more than one occasion.

After you inject COPAXONE®, if you experience hives, skin eruption with irritation, dizziness, sweating, chest pain, difficulty in breathing, severe pain at the injection site or other uncomfortable changes in your general health, **call your physician immediately**. Discontinue your injections until your physician tells you to begin again.

If symptoms become severe, **call the appropriate emergency phone number in your area**. Discontinue your injections until your physician tells you to begin again. Be sure to inform your physician about any side effects.

This is not a complete list of side effects. For any unexpected effects while taking COPAXONE®, contact your doctor or pharmacist.

HOW TO STORE IT

Your prescription includes two packages: the smaller one contains 32 brown vials of COPAXONE® and the larger one, labeled "Self Injection Administration Package" contains 32 clear vials of sterile water along with syringes, needles, vial adapters and alcohol prep pads necessary for reconstitution and administration of the drug. Store the vials of COPAXONE® in the refrigerator immediately after bringing them home. The vials of COPAXONE® may be stored at room temperature (15° to 30°C) for up to 14 days when refrigeration is unavailable.

Store the vials labeled "Sterile Water for Injection" (diluent) at room temperature.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

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By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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