PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr COPAXONE®

glatiramer acetate injection

20 mg / 1 mL and 40 mg / 1 mL
Pre-filled syringes for Subcutaneous Injection

Immunomodulator

Date of Revision: February 17, 2017

Distributed by:
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Toronto, Ontario M1B 2K9

Manufactured for:
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Montréal, Quebec H2Z 1S8

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Table of Contents

[Pr]COPAXONE®
glatiramer acetate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

COPAXONE (glatiramer acetate) is indicated for:

20 mg/mL once-daily:

- Treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain MRI:
  - To decrease the frequency of clinical exacerbations
  - To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.

40 mg/mL three times-a-week:

- 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.

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

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

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 or intramuscular routes.

General

Patients should be instructed in aseptic self-injection techniques to assure the safe administration of COPAXONE (glatiramer acetate), including a careful review of the **Part III – Patient Medication 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 post-marketing experience (see **ADVERSE REACTIONS**). 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 regular basis (see **Part III – Patient Medication Information**).

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**).

Cardiovascular

Symptoms of Potentially Cardiac Origin: A number of patients exposed to either COPAXONE 20 mg/mL once per day in 4 placebo-controlled trials, or COPAXONE 40 mg/mL three times per week in a single placebo-controlled trial, experienced at least one episode of what was described as transient chest pain (see **ADVERSE REACTIONS**). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS**), 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.

Immediate Post-Injection Reaction: COPAXONE has been associated with a constellation of symptoms appearing immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**).

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 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.

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.

Renal

The pharmacokinetics of COPAXONE in patients with impaired renal function have not been determined. In patients with renal impairment, renal function should be monitored while they are treated with COPAXONE. While there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

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 (20 mg/mL once per day), 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. In a 12-month placebo-controlled trial with COPAXONE (40 mg/mL three times per week) a total of nine pregnancies were reported. Of these, one patient experienced a spontaneous abortion at 13 weeks gestation and three patients had elective abortions. Five pregnancies were carried to term and all delivered healthy babies. Patients stopped treatment with COPAXONE prior to or upon learning that they were pregnant.

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
In patients with renal impairment, renal function should be monitored while they are treated with COPAXONE.

ADVERSE REACTIONS

Most Copaxone safety data were accumulated for COPAXONE 20 mg/mL administered as a subcutaneous injection once daily. This section presents accumulated safety data from 4 placebo-controlled trials with COPAXONE 20 mg/mL administered once daily, and from one placebo-controlled trial with COPAXONE 40 mg/mL administered three times a week.

<u>COPAXONE 20 mg/mL (administered once daily)</u>

Adverse Drug Reaction Overview
In 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 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 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.

COPAXONE 20 mg/mL (administered once daily)

The adverse reaction data in this section is derived from 4 pivotal, double-blind, placebo-controlled clinical trials which were conducted during pre-marketing and post-marketing 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. Lipoatrophy occurred in approximately 2% of patients exposed to COPAXONE 20 mg/mL once per day in the multicentre controlled trials (compared to none on placebo).

Table 1: Controlled Trials (COPAXONE 20 mg/mL per day): 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

MedDRA Version 10.0		GA 20 mg (N=512)	Placebo (N=509)
		% of Patients	% of Patients
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
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

MedDRA Version 10.0		GA 20 mg (N=512)	Placebo (N=509)
		% of Patients	% of Patients
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

** "Vasodilatation" includes the terms "feeling hot", "flushing", "hot flush", "hyperaemia" and "vasodilatation".

In the fourth trial noted above, an open-label treatment phase followed the placebo-controlled period. No new safety signals were observed during the open-label follow-up period of up to 5 years.

Data on adverse events occurring in the 4 controlled clinical trials were analyzed to evaluate sex-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 received at least one dose of COPAXONE (glatiramer acetate) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE in these clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), with a subset of patients continuing to 20 years (n=63) in an open-label extension 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:
Frequent: Liver function abnormality
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.

In the post-marketing clinical trials, more than 5500 individuals were exposed to glatiramer acetate (20 mg/day) as part of the clinical development program. Safety data collected in these trials have shown an adverse event profile similar to that presented above.

<u>COPAXONE 40 mg/mL (administered three times per week)</u>

The safety of COPAXONE 40 mg/mL was assessed based on a double-blind, placebo-controlled clinical trial in RRMS patients with a total of 943 patients treated for 12 months with COPAXONE 40 mg/mL three times per week, and 461 patients treated with placebo. Among the 943 patients treated with COPAXONE 40 mg/mL, approximately 3% of the subjects discontinued treatment because of an adverse event. The most common adverse events were injection site reactions, which were also the most common cause of discontinuation.

No new adverse events were seen in patients treated with COPAXONE 40 mg/mL administered three times per week as compared to subjects treated with COPAXONE 20 mg/mL administered daily.

Injection site reactions were reported by 36% of the patients on COPAXONE 40 mg/mL compared to 5% on placebo. Immediate post-injection reaction was reported by approximately 2% of the patients on COPAXONE 40 mg/mL compared to none on placebo. Approximately 2% of patients exposed to COPAXONE 40 mg/mL three times per week in single placebo-controlled trial (compared to 1% of placebo patients) experienced at least one episode of what was described as transient chest pain.

Table 2 lists treatment-emergent AEs that occurred in at least 2% of patients treated with COPAXONE 40 mg/mL three times per week in the blinded, placebo-controlled trial. These AEs were numerically more common in patients treated with COPAXONE 40 mg/mL than in patients treated with placebo. Adverse events were usually mild in intensity.

Table 2: Controlled Trial (COPAXONE 40 mg/mL three times per week): Incidence of Glatiramer Acetate Adverse Events ≥2% and More Frequent than Placebo

MedDRA Version 15.0		GA 40 mg (N=943)	Placebo (N=461)
		% of Patients	% of Patients
Gastrointestinal Disorders	Nausea	2.3	1.3
General Disorders and Administration Site Conditions	Injection Site Erythema	20.9	1.5
	Injection Site Pain	10.4	2.0
	Injection Site Pruritus	5.9	0.0
	Injection Site Swelling	4.0	0.4
	Influenza Like Illness	3.2	1.5
	Injection Site Induration	3.1	0.0
	Pyrexia	2.4	1.3
	Chills	2.0	0.0
Infections and Infestations	Nasopharyngitis	10.6	8.5
	Influenza	3.8	3.7
	Respiratory Tract Infection Viral	2.5	1.5
	Pharyngitis	2.0	1.1
Musculoskeletal and Connective Tissue Disorders	Pain in Extremity	2.1	1.7
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	3.2	0.4

Data on adverse events occurring in the controlled clinical trial were analyzed to evaluate

differences based on sex. Injection site reactions, mainly erythema, pain and pruritus occurred with a higher incidence (≥5%) in females (13.7%) than males (8.1%) in patients treated with COPAXONE 40 mg/mL three times per week; the majority of patients in this trial were female (68%).

Other Clinical Trial Adverse Events

The following is a list of adverse events reported by COPAXONE-treated patients at an incidence rate of less than 2% and ≥ 0.3% higher than placebo, and including potentially important events that occurred at least once in the double-blind phase and open-label extension of the clinical trial. Events that were already included in Table 2 have been excluded. Although the events reported occurred during treatment with COPAXONE, they were not necessarily caused by COPAXONE.

Events are listed by body system in decreasing order of incidence in COPAXONE-treated patients.

Blood and Lymphatic System Disorders: lymphadenopathy (0.6%)

Cardiac Disorders: tachycardia (1.2%), palpitations (1%)

Ear and Labyrinth Disorders: tinnitus (0.3%)

Eye Disorders: vision blurred (0.3%)

Gastrointestinal Disorders: abdominal pain (1.2%), vomiting (0.7%), gastrooesophageal reflux disease (0.4%), pancreatitis (0.3%)

General Disorders and Administration Site Conditions: injection site oedema (1.8%), injection site mass (1.7%), asthenia (1.6%), injection site inflammation (1.6%), injection site extravasation (1.5%), injection site reaction (1.5%), feeling hot (1.3%), injection site rash (1.1%), chest pain (0.8%), injection site haematoma (0.7%), injection site hypertrophy (0.7%), oedema peripheral (0.7%), chest discomfort (0.5%), injection site atrophy (0.4%), injection site irritation (0.4%), pain (0.4%), spinal pain (0.4%), discomfort (0.3%), hyperthermia (0.3%), injection site anaesthesia (0.3%), localised oedema (0.3%)

Hepatobiliary Disorders: hepatic steatosis (0.2%), drug-induced liver injury (0.1%), hepatitis toxic (0.1%)

Immune System Disorders: drug hypersensitivity (0.3%), anaphylactic reaction (0.2%), anaphylactic shock (0.1%)

Infections and Infestations: cystitis (1.7%), viral infection (0.8%), gastroenteritis viral (0.6%), oral herpes (0.5%), pyelonephritis chronic (0.5%), vulvovaginal mycotic infection (0.4%), herpes simplex (0.3%), papilloma viral infection (0.3%), pneumonia (0.3%), vaginitis bacterial (0.3%)

Injury, Poisoning and Procedural Complications: fall (0.8%), limb injury (0.3%), thermal burn (0.3%)

Investigations: weight decreased (0.7%), neutrophil count decreased (0.3%), red blood cell count decreased (0.3%)

Metabolism and Nutrition Disorders: hypercholesterolaemia (0.3%)

Musculoskeletal and Connective Tissue Disorders: myalgia (0.5%), musculoskeletal chest pain (0.4%), arthritis (0.3%), osteopenia (0.3%)

Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps): fibroadenoma of the breast (0.1%), intraductal papilloma of breast (0.1%)*, invasive ductal breast carcinoma (0.1%)*, breast neoplasm (0.1%)*

Nervous System Disorders: paraesthesia (1.4%), syncope (1%), trigeminal neuralgia (0.4%), tremor (0.3%)

Renal and Urinary Disorders: leukocyturia (1.1%), haematuria (0.6%)

Reproductive System and Breast Disorders: breast disorder (0.1%), breast discharge (0.1%), menstrual disorder (0.4%), breast calcifications (0.1%)*, breast dysplasia (0.1%)*

Respiratory, Thoracic and Mediastinal Disorders: cough (1.8%)

Skin and Subcutaneous Tissue Disorders: erythema (1.8%), hyperhidrosis (0.5%), skin reaction (0.5%), angioedema (0.4%), acne (0.3%), generalised erythema (0.3%), lipoatrophy (0.1%)

Surgical and Medical Procedures: mastectomy (0.1%)*

Vascular Disorders: flushing (1.0%), hypotension (0.7%), hyperaemia (0.6%), hot flush (0.3%)

*Events occurred during the open-label extension of the clinical trial

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 in 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 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.

Post-market safety analysis demonstrated that the safety profile of COPAXONE 40 mg/mL (administered three times per week) is compatible with the safety profile of COPAXONE 20 mg/mL (administered once daily).

Localized Adverse Reactions Associated with Subcutaneous Use
At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during post-marketing 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 regular basis (see **Part III – Patient Medication 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 and dosing schedule of COPAXONE (glatiramer acetate injection) for the treatment of Relapsing Remitting MS depends on the product strength selected:

- **COPAXONE 20 mg/mL:** Administer once per day

or

- **COPAXONE 40 mg/mL:** Administer three times per week and at least 48 hours apart

COPAXONE 20 mg/mL and COPAXONE 40 mg/mL are not interchangeable.

Administration

Please see **Part III - Patient Medication Information (Instructions for Use)** for instructions on the preparation and injection of COPAXONE.

Missed Dose

If a dose is missed it should be taken as soon as possible. If, however, it is closer to the time of the next dose, skip the missed dose and resume at the usual dosing schedule.

For COPAXONE 20 mg/mL, avoid giving 2 injections in the same 12-hour period.

For COPAXONE 40 mg/mL, ensure injections are at least 48 hours apart.

OVERDOSAGE

Cases of overdose with COPAXONE (up to 300 mg glatiramer acetate) have been reported. These cases were not associated with any adverse reactions other than those mentioned in **ADVERSE REACTIONS**. In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

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

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

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

- COPAXONE (glatiramer acetate injection) single-use **20 mg/1 mL** pre-filled syringes have white plunger rods. Each pre-filled syringe contains glatiramer acetate, mannitol and sterile water for injection. Available in packs of 30 single-use 20 mg/1 mL pre-filled glass syringes.

- COPAXONE (glatiramer acetate injection) single use **40 mg/1 mL** prefilled syringes have blue plunger rods. Each pre-filled syringe contains glatiramer acetate, mannitol and sterile water for injection. Available in packs of 12 single-use 40 mg/1 mL prefilled glass syringes.

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$^{30\text{-}37}$]●nCH_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

COPAXONE 20 mg/mL (administered once daily)

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.

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 3) show that there was a statistically significant effect of glatiramer acetate on number of relapses.

Table 3 - 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 Poser 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 4 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 4 - 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 5 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 5 - 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
	Proportion of T1 Gd-Enhancing Lesion-Free Patients	46.4%	32.2%	0.0653

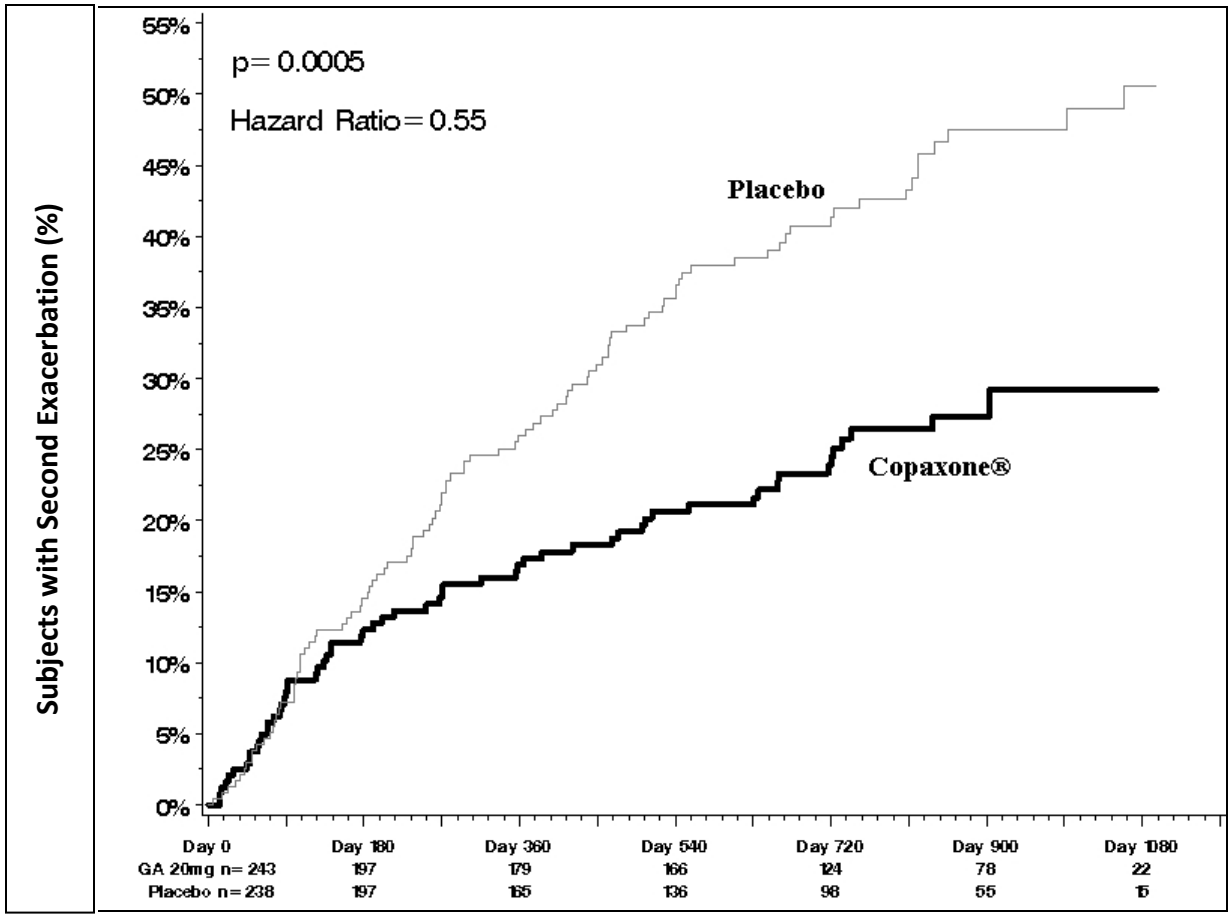
The mean number of relapses in this 9 month study was 0.50 for the COPAXONE® group and 0.77 for the placebo group (p = 0.0077).

Patients with early RRMS

A fourth study (GA/9010) 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). It was performed in patients with a well-defined, single, unifocal neurological presentation and with at least two cerebral lesions on T2-weighted MRI (previously referred to as "clinically isolated syndrome"). The primary outcome measure in the study was the time to development of a second exacerbation according to Poser criteria. 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 the glatiramer acetate group corresponding to a risk reduction of 45% (Hazard Ratio = 0.55; 95% CI [0.40; 0.77], p=0.0005) (Figure 1).

Figure 1: Time to Second Exacerbation (ITT Analysis)



Glatiramer acetate prolonged the time to second exacerbation 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 experienced a second exacerbation 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).

However, the impact of early treatment with COPAXONE 20 mg/mL once-daily on the long term evolution of the disease is unknown as the study was mainly designed to assess the time to the second exacerbation event.

COPAXONE 40 mg/mL (administered three times per week)

Study MS-GA-301 was a double-blind, placebo-controlled, multinational trial with a total of 1404 patients with RRMS randomized in a 2:1 ratio to receive either COPAXONE 40 mg/mL (n=943) or placebo (n=461) three times a week for 12 months. Patients had a median of 2 relapses in the 2 years prior to screening and had not received any interferon-beta for at least 2 months prior to screening. Baseline EDSS scores ranged from 0 to 5.5 with a median of 2.5. Neurological evaluations were performed at baseline, every three months, and at unscheduled visits for suspected relapse or early termination. MRI was performed at baseline, months 6 and 12, or early termination. A total of 91% of those assigned to COPAXONE and 93% of those assigned to placebo completed treatment at 12 months.

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

Table 6 – Study MS-GA-301: Efficacy and MRI Results in the ITT population

	COPAXONE 40 mg/mL (n=943)	**Placebo (n=461)**	**P-Value**
Clinical Endpoints			
Number of confirmed relapses during the 12-month placebo-controlled phase			
Adjusted Mean Estimates Relative risk reduction	0.331 34%	0.505	<0.0001
MRI Endpoints			
Cumulative number of new or enlarging T2 lesions at Months 6 and12			
Adjusted Mean Estimates Relative risk reduction	3.650 35%	5.592	<0.0001
Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12			
Adjusted Mean Estimates Relative risk reduction	0.905 45%	1.639	<0.0001

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- and 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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

COPAXONE®
glatiramer acetate injection

Read this carefully before you start taking COPAXONE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about COPAXONE.

What is COPAXONE used for?

COPAXONE **20 mg/mL** (**once-daily)** is used to treat patients with Relapsing Remitting Multiple Sclerosis (RRMS), including those who have experienced one episode of nervous system symptoms and who have abnormalities on their brain scan that may be the first signs of Multiple Sclerosis.

COPAXONE **40 mg/mL (three times-a-week)** is used to treat patients with Relapsing Remitting Multiple Sclerosis (RRMS).

COPAXONE is not a cure. Patients treated with COPAXONE experience fewer relapses (flare-ups of the disease).

How does COPAXONE work?

Multiple Sclerosis (MS) is thought to be a disease where your immune system causes your body to attack its own cells. This leads to loss of myelin, a substance that covers your nerve fibers. The loss of myelin eventually leads to the symptoms of MS.

COPAXONE is a mixture of small proteins. These small proteins are similar to a protein found in myelin. COPAXONE is thought to work by modifying the immune processes that are believed to cause MS.

What are the ingredients in COPAXONE?

Medicinal ingredients: Glatiramer acetate
Non-medicinal ingredients: Mannitol in sterile water for injection

COPAXONE comes in the following dosage forms:

Once-daily solution: 20 mg/1 mL pre-filled syringe.
Three times-a-week solution: 40 mg/1 mL pre-filled syringe.

Do not use COPAXONE if:

- you are allergic to glatiramer or mannitol.
- the solution in the pre-filled syringe is cloudy, leaking or contains any particles.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take COPAXONE. Talk about any health conditions or problems you may have, including if you:

- have heart disease. Some patients taking COPAXONE experience chest pain.
- have a history of developing severe allergic reactions.
- have chronic obstructive pulmonary disease (COPD).
- have asthma.
- have kidney problems.
- are pregnant, planning to become pregnant, or if you become pregnant while you are using this medication. COPAXONE is not recommended for use in pregnancy.
- are nursing.
- are under 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take COPAXONE:
The **first** time you use COPAXONE you:

- will be given full instructions on how to use it.
- should be supervised by a doctor or nurse.

Each pre-filled syringe should be:

- used only once.
- used only for subcutaneous injection.

Usual Adult Dose:

- **COPAXONE 20 mg/1 mL** is injected once a day.
- **COPAXONE 40 mg/1 mL** is injected 3 times each week on the same 3 days each week, if possible (for example, Monday, Wednesday and Friday). The injections are given at least 48 hours (2 days) apart.

Your doctor will prescribe the correct dose for you. Do NOT change the dose or dosing schedule without consulting your doctor.

Do NOT stop using COPAXONE without consulting your doctor.

COPAXONE 20 mg/mL (once-daily) and COPAXONE 40 mg/mL (three times-a-week) are not interchangeable because they are different in their strength and dosing schedule.

INSTRUCTIONS FOR USE

Step 1: Gathering the materials

- Collect one of each of the items you will need on a clean, flat surface in a well-lit area.
    - 1 COPAXONE pre-filled syringe. (Each syringe is contained inside a protective blister. Holding the package of syringes, tear off only 1 blister at a time. Keep all unused syringes in the refrigerator.)
    - Alcohol swab (not supplied) or access to soap and water
    - Dry cotton ball (not supplied)

- Ensure that the solution is at room temperature. Let the unopened blister containing the syringe stand at room temperature for at least 20 minutes.

- **Before you inject** wash and dry your hands. Avoid touching your hair or skin, after you have washed your hands. This will help prevent infection.

- Do **NOT** try to force small air bubbles out of the syringe before injecting the medicine.

Step 2: Choosing the site for injection

You should have a planned schedule for your chosen injection sites and make note of it in a diary.

- There are **7** possible areas on your body for injection **(see Figure 1)**:
    - back of upper arms (right and left)
    - front and outside of thighs (right and left)
    - upper buttocks/rear of hips (right and left)
    - stomach (abdomen)

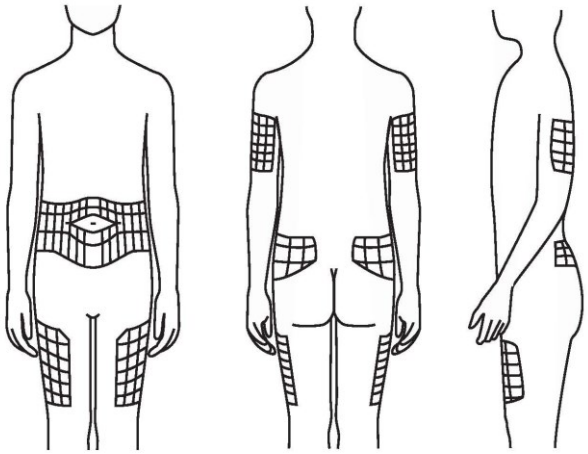
- If you are taking **COPAXONE 20 mg/1 mL (once-daily)**, pick a different area each day (one for each day of the week).

- If you are taking **COPAXONE 40 mg/1 mL (three times-a-week),** pick each injection area only once per week.

- Within each of the 7 areas there are many sites where you can inject the drug. Rotate the injection sites within the chosen area. **Choose a different injection site each time**.

Figure 1:

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



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

- **Please note:** do NOT inject in any area that is:
  - painful.
  - discoloured.
  - where you feel firm knots or lumps.
  - where skin depression has occurred (a "dent" at the injection site). Further injections in these sites may make the depression deeper.

Hard to inject areas: There may be some areas on your body that may be hard for you to inject the drug yourself (such as the back of your arms). You should ask your doctor or nurse for instructions on how to inject COPAXONE in these areas.

<u>Step 3</u>: Injection

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

2. Clean the site you have chosen to inject by using:

   - a fresh alcohol swab. (Let it air dry for 1 minute to reduce any stinging.)

or

- soap and water

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. While resting the heel of your hand against your body, **insert** the needle at a 90^{o} angle. When the needle is all the way in the skin, let go the fold of skin **(See Figure 3)**.

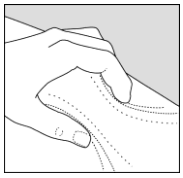


Figure 2

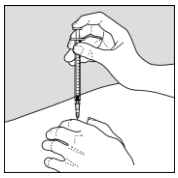


Figure 3

6. To inject the medication, hold the syringe steady and push down on the plunger. This should take only a few seconds. **(See Figure 3)**

7. Pull the needle straight out.

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

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

Proper disposal of needles:

- Throw out all used syringes in a hard-walled plastic container (such as a Sharps container from a pharmacy).
- Keep the cover of this container closed tight and **out of the reach and sight of children.**
- When the container is full, check with your doctor, pharmacist or nurse about proper disposal.

Overdose:

If you think you have taken too much COPAXONE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

COPAXONE 20 mg/mL (once daily): If you miss a dose, you should take it as soon as you remember. If it is less than 12 hours before your next dose, skip the missed dose and take your next dose at the usual time. Do NOT give yourself 2 injections in the same 12-hour period.

COPAXONE 40 mg/mL (three times-a-week): If you miss a dose, you should take it as soon as you remember. If it is less than 48 hours before your next dose, skip the missed dose and take your next dose at the usual time. Do NOT give yourself 2 injections in the same 48-hour period.

What are possible side effects from using COPAXONE?

These are not all the possible side effects you may feel when taking COPAXONE. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of COPAXONE are:

- Skin reactions at the injection site. These include:
  - Redness
  - Pain
  - Inflammation
  - Itching
  - Swelling
  - Lumps
- A permanent "dent" under the skin at the injection site, caused by damage to the fatty tissue at that site.
- Rash
- Hives
- Headache
- A feeling of worry, nervousness, unease (anxiety)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Post-injection Reaction:** Flushing, dizziness, skin eruptions with irritation, sweating, chest pain, chest tightness, irregular heartbeat, anxiety, difficulty in breathing, tightness in the throat, hives appearing immediately after injection			√
Low blood pressure: dizziness, fatigue, nausea		√	
High blood pressure: headache, dizziness, blurred vision or shortness of breath		√	
Breathing problems: shortness of breath, difficulty breathing		√	
Fast heart beat or skipping a beat		√	
Chest pain: pressure or tightness in the chest		√	
Back, neck or joint pain	√		
Angioedema: Swelling of the arms, legs or face	√		
Depression: change in weight, difficulty sleeping, lack of interest in regular activities	√		
Changes to your vision	√		
RARE **Serious Allergic Reactions**: rash, hives, swelling of the face, lips, throat, difficulty swallowing or breathing			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by**:**
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: *Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

Storage:

- Refrigerate (2° - 8°C) immediately. Do NOT FREEZE
- If you cannot store COPAXONE in the refrigerator, it can be stored for 1 month at room temperature (15° - 30°C). Do NOT store for longer than 1 month at room temperature.
- Protect from light. This drug is sensitive to light.

Keep out of reach and sight of children.

If you want more information about COPAXONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca), the manufacturer's website (http://www.tevacanadainnovation.ca), or by calling 1-800-283-0034.

This leaflet was prepared by Teva Canada Innovation.

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