PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGLATECT™

Glatiramer acetate injection

20 mg/1 mL
Pre-filled Syringes for Subcutaneous Injection

Immunomodulator

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PrGLATECT™

Glatiramer acetate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Subcutaneous	Solution for injection 20 mg/mL glatiramer acetate 1 mL prefilled syringes	40 mg mannitol in water for injection

INDICATIONS AND CLINICAL USE

GLATECT (glatiramer acetate injection) is indicated for:
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

The safety and efficacy of GLATECT in chronic progressive MS have not been established.

Geriatrics (> 65 years of age):
No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

Pediatrics (< 18 years of age):
No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

CONTRAINDICATIONS

Contraindicated in patients who are hypersensitive to this drug, to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION and PACKAGING** section.

WARNINGS AND PRECAUTIONS

The only recommended route of administration of GLATECT injection is the subcutaneous route. GLATECT should not be administered by the intravenous route or intramuscular routes.

General

Patients should be instructed in aseptic self-injection techniques to assure the safe administration of GLATECT, 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 with glatiramer acetate. 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 **ADVERSE REACTIONS**, **Part III – PATIENT MEDICATION INFORMATION**).

Carcinogenesis and Mutagenesis

Preclinical studies assessing the carcinogenic potential of glatiramer acetate in mice and rats did 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 few patients in the GATE trial receiving GLATECT experienced what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS**), others did not. The pathogenesis of this symptom is unknown. Patients enrolled in controlled clinical trials with another glatiramer acetate product were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

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

Hepatic
Very rare cases of severe liver injury, including liver failure, hepatitis with jaundice, and extremely rare cases of fulminant hepatitis leading to liver transplant, have been reported with glatiramer acetate during post-marketing experience in patients with and without relevant risk factors in their medical history, such as history of drug induced liver events with other disease modifying therapies (DMTs) indicated for the treatment of multiple sclerosis, concomitant treatment with drugs with known Drug Induced Liver Injury (DILI) risk or medical history of liver impairment. Hepatic adverse events have occurred from days to years after initiating treatment with glatiramer acetate and with a similar profile with both dose regimens (20 mg/mL daily and 40 mg/mL TIW), suggesting idiosyncratic drug induced liver injury in most cases. Some cases, reported in patients who previously experienced liver injury during treatment with other immunomodulatory therapies used to treat multiple sclerosis, were suggestive of autoimmune hepatitis. Most events resolved with discontinuation of treatment and a relationship to glatiramer acetate could not be excluded (see **ADVERSE REACTIONS, Post-Market Adverse Reactions).**

Caution is recommended when considering treatment with glatiramer acetate in patients who have preexisting liver disease or who have experienced liver injury previously during treatment with other drugs, including other disease modifying therapies (DMTs) for treatment of multiple sclerosis or with concomitant (DILI) risk drugs. Prior to initiating treatment with GLATECT, serum aminotransferase, alkaline phosphatase and total bilirubin levels should be obtained (within 6 months) for all patients. Patients should be monitored during treatment for signs of hepatic injury. Evaluation of transaminases is recommended during treatment, as clinically relevant (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**). Patients should be advised to immediately report any signs or symptoms of hepatotoxicity (e.g., jaundice, dark urine, abdominal pain, nausea, vomiting, loss of appetite, weight loss, unusual fatigue). Discontinue treatment if clinically significant liver injury induced by GLATECT is suspected.

Immune
Considerations Involving the Use of a Product Capable of Modifying Immune Responses: Glatiramer acetate is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether glatiramer acetate can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with glatiramer acetate 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. Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment. Maximum titer levels were detected in 91.9% of patients 3 months after initiation of treatment and, thereafter the titers declined but remained detectable up to 24 months of continued GLATECT treatment in 94.7% of patients. IgE type antibodies were not assayed for GLATECT.

Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

GLATECT 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 GLATECT in such patients.

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

Monitoring and Laboratory Tests

Renal
The pharmacokinetics of GLATECT 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 GLATECT. While there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

Liver function
Liver transaminases should be checked (within 6 months) before initiating treatment with GLATECT. Evaluation of transaminases is recommended during treatment, as clinically relevant (see **WARNINGS AND PRECAUTIONS, Hepatic; ADVERSE REACTIONS, Post-market Adverse Reactions**).

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**). The potential risk for humans is not fully understood (See **ADVERSE REACTIONS, Post-Market Adverse Reactions, Pregnancy**). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. During the pivotal clinical trial with GLATECT, 13 women conceived while being treated (8 received GLATECT treatment; 5 received Copaxone® treatment). Of the 13 reported pregnancies, 3 patients discontinued pregnancy, 9 resulted in healthy infants and one in an infant with malformations that was not considered related to GLATECT treatment.

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 GLATECT should only be considered after careful risk/benefit assessment and be used with caution.

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (> 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

Monitoring and Laboratory Tests
In patients with renal impairment, renal function should be monitored while they are treated with GLATECT.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of GLATECT was evaluated in 794 RRMS patients who were randomized and treated with GLATECT (n = 353), Copaxone® (n = 357), or placebo (n = 84) for 9 months during the double-blind phase of a clinical equivalence (GATE) trial. An open-label treatment phase followed the placebo-controlled period where 728 patients from all groups continued onto GLATECT treatment for an additional 15 months. The most commonly observed adverse events associated with the use of GLATECT during the controlled double-blind part of the trial were injection site reactions and immediate post-injection reaction (IPIR) occurring at an incidence of 16.4% and 6.8% of patients, respectively, compared to 17.4% and 5.0% for Copaxone® treated patients, and 7.1% and 0.0% for placebo-treated patients.

Serious adverse events were observed in 6.3% of all patients during the 24-month trial and of those 1.5% were considered related to treatment. Adverse events that led to discontinuation of treatment and or trial over the total duration of the GATE trial were observed in 3.7% of all patients and these AEs were distributed over multiple System Organ Classes.

Immediate Post-Injection Reaction: An IPIR or IPIR-related symptom was reported by 9.3% of all patients during the 24-month GATE trial. An IPIR was defined as a constellation of symptoms occurring immediately after injection that includes one or more of the following: vasodilatation, chest pain, dyspnea, palpitation or tachycardia. The majority of the events reported were immediate post-injection reactions reported by 5.9% of patients and Tachycardia reported by 1.1% of patients. These symptoms were invariably transient, self-limited, and did not require specific treatment; symptoms may arise 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 GLATECT. 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 with glatiramer acetate products, there have been reports of patients with similar symptoms who received emergency medical care (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Chest Pain: Less than 1% of patients receiving GLATECT treatment experienced chest pain during the 2 year GATE trial. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, others 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. The pathogenesis of this symptom is unknown. Patients enrolled in clinical trials with another glatiramer acetate product 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**).

Localized Adverse Reactions Associated with Subcutaneous Use: Local injection site reaction (LISR) were recorded over 14-day reporting periods, starting at the Day 1 and Month 3 visits in the double-blind part and at the Month 9 and Month 12 visits in the open-label part. LISRs (Pain, Itchiness, Redness, Swelling and Lumps) were reported with similar incidence in the GLATECT and Copaxone® groups. Pain was the reaction most frequently rated as severe both after GLATECT and Copaxone® treatments. Switching from Copaxone® to GLATECT did not affect the LISR reporting profile.

The safety assessments performed in GATE demonstrate that GLATECT was well-tolerated and had a similar safety and tolerability profile compared to Copaxone®.

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 safety data in this section are derived from a single pivotal, double-blind, placebo-controlled 9-month equivalence trial with a 15-month open-label part in RRMS patients. In the double-blind part, GLATECT and Copaxone® were administered to 353 and 357 patients respectively, and placebo was administered to 84 patients; 728 patients continued to the open-label part where all patients were switched to GLATECT treatment. All adverse events were recorded by the clinical investigators and were summarized into standardized categories using MedDRA dictionary terminology.

The following table lists treatment-emergent signs and symptoms that occurred in at least 1% of patients treated with GLATECT or Copaxone®, and more frequent than placebo, over the double-blind study period of 9 months in the clinical trial.

Table 1 – Treatment-Emergent Adverse Events for ≥1% of Patients in the GLATECT or Copaxone® Group and More Frequent than Placebo; Double-Blind Part

MedDRA System Organ Class Preferred Term	GLATECT N = 353 (%)	Copaxone® N = 357 (%)	Placebo N = 84 (%)
General disorders and administration site conditions			
Injection site reaction	16.4%	17.4%	7.1%
Immediate post-injection reaction	6.8%	5.0%	0.0%
Injection site swelling	4.0%	3.4%	3.6%
Injection site pain	3.1%	3.6%	1.2%
Injection site erythema	2.3%	2.0%	0.0%
Injection site pruritus	2.3%	1.4%	0.0%
Influenza like illness	0.3%	2.2%	1.2%
Infections and Infestations			
Bronchitis	1.4%	1.4%	0.0%
Urinary tract infection	0.6%	1.1%	0.0%
Nervous System Disorders			
Multiple sclerosis relapse	1.1%	1.7%	0.0%
Dizziness	0.6%	2.0%	0.0%
Gastrointestinal Disorders			
Nausea	1.4%	0.8%	0.0%
Skin and Subcutaneous Tissue Disorders			
Rash	1.1%	0.6%	0.0%
Urticaria	1.1%	0.6%	0.0%
Psychiatric Disorders			
Depression	1.7%	2.0%	0.0%
Anxiety	0.3%	1.1%	0.0%
Respiratory, Thoracic, and Mediastinal			
Dyspnoea	0.8%	1.1%	0.0%
Cough	0.6%	1.1%	0.0%
Blood and Lymphatic System Disorders			
Lymphadenopathy	0.6%	1.1%	0.0%
Cardiac Disorders			
Tachycardia	1.1%	0.8%	0.0%

In the 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 15 months.

Reported adverse event incidences were similar between genders. In the GATE clinical trial, 99.9% 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 GLATECT were between the ages of 18 and 45. 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 GLATECT. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both GLATECT and Copaxone® in the double-blind part of the clinical trial. No patient receiving GLATECT withdrew from the GATE trial over its total 24-month duration due to abnormal laboratory findings.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following is a list of adverse events reported by GLATECT or Copaxone® treated patients at an incidence rate of less than 1% and greater than 0.3% of patients and more frequent than placebo in the double-blind part, or ≥ 0.3% of total patients in the open label part; if the incidence was above 1% in the open-label part the incidence is specified. In addition, potentially important events that occurred at least once in the double-blind phase and open-label extension of the clinical trial are included.

Blood and lymphatic system disorders: Anaemia, leukocytosis, leukopenia, neutrophilia

Ear and labyrinth disorders: Vertigo, ear pain

Eye disorders: Vision blurred

Gastrointestinal disorders: Chronic gastritis, diarrhea, vomiting, constipation, abdominal adhesions, dental caries, pancreatitis acute

General disorders and administration site conditions: Hyperthermia, injection site hypoaesthesia, injection site oedema, chest pain, chills, injection site atrophy, injection site induration, gait disturbance, fatigue, asthenia, pyrexia

Hepatobiliary disorders: Hepatitis toxic, cholecystitis

Immune system disorders: Hypersensitivity, anaphylactoid reaction, anaphylactic reaction, drug hypersensitivity

Infections and infestations: Pneumonia, sinusitis, oral herpes, tonsillitis, varicella, viral infection, respiratory tract infection viral, respiratory tract infection, pharyngitis, acute sinusitis, influenza, rhinitis, vaginal infection, cystitis, laryngitis, upper respiratory tract infection, ear infection, salpingo-oophoritis, genital candidiasis, urea plasma infection, appendicitis

Injury, poisoning and procedural complications: Contusion, face injury, joint injury, brain

contusion, joint dislocation, hand fracture, ankle fracture, ligament sprain

Investigations: Alanine aminotransferase increased, blood pressure increased, lymphocyte count decreased, weight increased, weight decreased

Metabolism and nutrition disorders: Vitamin D deficiency, hypercholesterolemia

Musculoskeletal and connective tissue disorders: Back pain (1.4%), arthralgia, sympathetic posterior cervical syndrome, limb discomfort, musculoskeletal pain, osteoporosis, pain in extremity, osteochondrosis, osteoarthritis, patellofemoral pain syndrome

Neoplasms benign, malignant and unspecified (including cysts and polyps): Uterine leiomyoma, metastases to central nervous system, glioblastoma multiforme, fibroadenoma of breast, small intestine carcinoma

Nervous system disorders: Balance disorder, loss of consciousness, hypoesthesia, epilepsy, sciatica, status epilepticus, headache (2.2%), paraesthesia, autonomic nervous system imbalance, somnolence, syncope, tremor, radiculitis cervical, radicular pain secondary progressive multiple sclerosis

Psychiatric disorders: Insomnia, anxiety disorder

Renal and urinary disorders: Urinary incontinence, proteinurea, micturition urgency, urinary retention, renal colic, nephrolithiasis

Reproductive system and breast disorders: Erectile dysfunction, menstrual disorder, dysmenorrhoea, ovarian cyst, endometriosis

Respiratory, thoracic and mediastinal disorders: Paranasal sinus mucosal hypertrophy, oropharyngeal pain, rhinitis allergic, paranasal cyst

Skin and subcutaneous tissue disorders: Angioedema, pruritis, psoriasis, erythema

Vascular disorders: Hypotension, flushing, hypertension (1.1%), peripheral artery thrombosis

Adverse Events Reported in >2% of patients in Placebo-Controlled Clinical Trials with Other Glatiramer Acetate Products and More Frequently than with Placebo

Reports of adverse events not previously noted in the above sections occurring in 4 placebo-controlled clinical trials during treatment with another marketed glatiramer acetate product are listed below. These trials were conducted in a total of 512 patients receiving active treatment and 509 patients treated with placebo for up to 36 months:

Cardiac disorders: Palpitations

Eye disorders: Eye disorder, diplopia

Gastrointestinal disorders: Vomiting, constipation, dyspepsia, dysphagia, faecal incontinence

General disorders and administration site conditions: Asthenia, pain, chest pain, injection site inflammation, injection site hypersensitivity, local reaction, edema peripheral, injection site fibrosis

Infections and infestations: Infection, influenza, rhinitis, bronchitis, gastroenteritis, vaginal candidiasis, otitis media, herpes simplex

Metabolic and nutritional disorders: Weight increased, anorexia.

Musculoskeletal and connective tissue disorders: Back pain, arthralgia, neck pain.

Nervous system disorders: Hypertonia, tremor, migraine.

Psychiatric disorders: Nervousness

Renal and urinary disorders: Micturition urgency, pollakiuria

Respiratory, thoracic and mediastinal disorders: Cough

Skin and subcutaneous tissue disorders: Hyperhidrosis, ecchymosis, skin disorder

Vascular disorders: Vasodilatation**

** “Vasodilatation” includes the terms “feeling hot”, “flushing”, “hot flush”, “hyperaemia”, and “vasodilation”

Other Adverse Events Observed During Clinical Trials with Other Glatiramer Acetate Products

In pre-marketing clinical trials with another glatiramer acetate 20 mg product, approximately 900 individuals received at least one dose of glatiramer acetate in controlled and uncontrolled clinical trials.

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 tables, 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: Moon face, injection site hematoma, 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

Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory analyses were performed on all patients participating in the clinical program for GLATECT (Glatiramer acetate). Clinically significant changes in laboratory values for

hematology, chemistry, and urinalysis were similar for both glatiramer acetate and placebo groups in blinded clinical trials. No patient receiving glatiramer acetate withdrew from any placebo-controlled trial due to abnormal laboratory findings which were assessed as possibly related to glatiramer acetate.

Post-Market Adverse Drug Reactions

Reports of the adverse reactions occurring under treatment with other marketed glatiramer acetate products from spontaneous reports and that may or may not have a 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 disorders: Hypercholesteremia

Musculoskeletal and connective tissue disorders: Rheumatoid arthritis, generalized spasm

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus

Skin and subcutaneous tissue disorders: Herpes simplex, pruritus, 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 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**).

Pregnancy: To date, post-market information was received on more than 2,000 prospectively reported pregnancies with known outcome in patients exposed to conventional dose regimens of glatiramer acetate. In this cohort, the reported rates of fetal loss and congenital anomalies or disorders were found the be within the range in a normal pregnant population, indicating no malformative or feto/neonatal toxicity of glatiramer acetate. However, since there are no adequate and well controlled studies in pregnant women with MS, glatiramer acetate should be used during pregnancy only if clearly needed.

Severe Liver Injury: Very rare cases of severe liver injury (including liver failure, hepatitis with jaundice, fulminant hepatitis leading to liver transplant) have been reported with glatiramer acetate. Most instances of severe liver injury resolved with discontinuation of treatment and a relationship to glatiramer acetate could not be excluded (see **WARNINGS AND PRECAUTIONS, Hepatic; WARNINGS AND PRECAUTIONS, *Monitoring and Laboratory Tests***).

DRUG INTERACTIONS

Interactions between glatiramer acetate and other drugs have not been fully evaluated.

Observations from existing clinical trials do not suggest any significant interactions of glatiramer acetate with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. Glatiramer acetate 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 glatiramer acetate 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

GLATECT *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 GLATECT (glatiramer acetate) injection is the subcutaneous route. GLATECT should not be administered by the intravenous route or the intramuscular route.

Recommended Dose and Dosage Adjustment

The recommended dose of GLATECT (glatiramer acetate injection) for the treatment of Relapsing Remitting MS is a daily injection of 20 mg given subcutaneously.

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.

Avoid giving 2 injections in the same 12-hour period.

Administration
Please see the **Part III – PATIENT MEDICATION INFORMATION** for instructions on the preparation and injection of GLATECT.

OVERDOSAGE

One patient received two GLATECT injections daily (i.e. a dose of 40 mg/day instead of the recommended 20 mg/day) during approximately one month. The patient did not report any adverse events, nor was there any sign in changed clinical laboratory values. Overdose with other glatiramer acetate products (up to 300 mg glatiramer acetate) have been reported. These cases were not associated with any adverse events 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
GLATECT is a sterile solution of glatiramer acetate which consists of the acetate salts of a mixture of synthetic polypeptides containing the four naturally occurring amino acids L-tyrosine, L-alanine, L-glutamic acid and L-lysine with an average molar fraction of 0.086 to 0.100; 0.392 to 0.462; 0.129 to 0.153 and 0.300 to 0.374, respectively.

The precise mechanism by which glatiramer acetate exerts its therapeutic effect on Multiple Sclerosis (MS) is not fully elucidated, but may involve immunomodulation by inducing a regulatory phenotype of antigen presenting cells (e.g. dendritic cells, monocytes, and B cells), which may exert direct effects and/or support regulatory and anti-inflammatory T cell populations.

Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses, but this has not been systematically evaluated (see **WARNINGS AND PRECAUTIONS, Immune**).

Pharmacokinetics
Results obtained in pharmacokinetic studies performed with glatiramer acetate 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 GLATECT must be refrigerated immediately upon receipt (2° - 8°C). DO NOT FREEZE.

Store in the original package in order to protect from light. If you cannot have refrigerator storage, pre-filled syringes of GLATECT can be stored at room temperature (15° - 25°C) once for up to 1 month. After this one-month period, if the pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2° - 8°C). Each pre-filled syringe is for single use only.

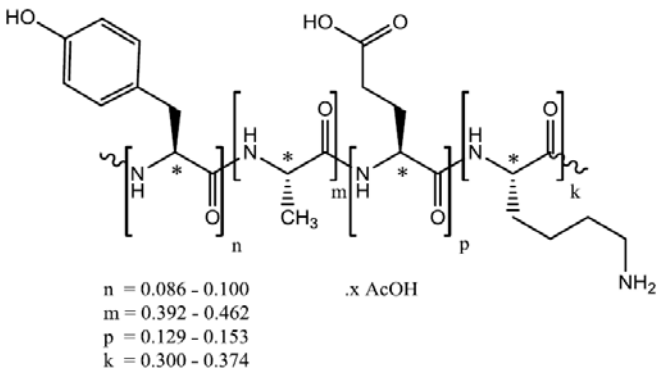
DOSAGE FORMS, COMPOSITION AND PACKAGING

Pre-filled Syringe
GLATECT is a single-use 1 mL pre-filled glass syringe containing a clear sterile solution of 20 mg glatiramer acetate and 40 mg mannitol in water for injection. GLATECT is available in packs of 30 single-use 1 mL pre-filled glass syringes.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Glatiramer acetate
Chemical name:	Poly(L-Alanine-*ran*-L-glutamic acid-*ran*-L-lysine-*ran*-L-Tyrosine) acetate
Description:	Glatiramer acetate consists of the acetate salts of a mixture of synthetic polypeptides containing four naturally occurring amino acids in random order but in a defined molar fraction. The amino acids present are L-tyrosine (L-Tyr), L-alanine (L-Ala), L-glutamic acid (L-Glu), and L-lysine (L-Lys) with an average molar fraction of 0.086 to 0.100, 0.392 to 0.462, 0.129 to 0.153 and 0.300 to 0.374, respectively.
Molecular formula:	Poly[L-Tyr^{n}, L-Ala^{m}, L-Glu^{p}, L-Lys^{k}] x $C_2H_4O_2$
Molecular mass:	The average molecular weight of glatiramer acetate is 5,000 to 9,000 daltons.
Structural formula:	
Physicochemical properties:	Glatiramer acetate is a white to off white powder and is soluble in water and insoluble in heptane. A solution of 1 % (m/V) in water has a pH value of 5.5 – 7.0.

CLINICAL TRIALS

Physico-chemical characterization studies and non-clinical pharmacology and toxicology studies have demonstrated similarity between GLATECT and Copaxone® to support the use of surrogate MRI endpoints for evaluation of therapeutic equivalence.

GLATECT was evaluated in a multi-center, pivotal, randomized, double-blind, placebo-controlled, parallel-group, 9-month, equivalence trial (GATE) comparing the efficacy and safety and tolerability of GLATECT to Copaxone® in patients with RRMS. This was followed by 15 months of open-label treatment with GLATECT to evaluate the long-term safety and efficacy. In this study, a dose of 20 mg/day was used. The primary objective in the double-blind phase was to demonstrate that the efficacy of GLATECT is equivalent to Copaxone® as measured by the number of gadolinium-enhancing (GdE) lesions on T1-weighted MRIs during Months 7 to 9.

Study Demographics and Trial Design

Table 3 - Summary of Clinical Trial Patient Demographics

Study	Trial Design	Dosage, Route of Administration	Number of Patients	Mean Age (Range)	Gender
GATE	Double-blind, randomized, placebo and active controlled, equivalence trial - 9 months	1 ml sc injection once daily: GLATECT 20 mg Copaxone® 20 mg Placebo	GLATECT: 353 Copaxone®: 357 Placebo: 84	33.1 (18-56)	Females: 66.5 % Males: 33.5%
	Uncontrolled open-label safety trial - 15 months	1 ml sc injection once daily: GLATECT 20 mg	GLATECT/GLATECT: 324 Copaxone®/ GLATECT: 323 Placebo/GLATECT: 81	33.1 (18-56)	Females: 66.2 % Males: 33.8%

GLATECT: Glatiramer acetate 20 mg/mL prefilled syringe; s.c.: subcutaneous

The equivalence trial was conducted in a representative RRMS population with clinically and radiographically active disease. The treatment groups were comparable for demographic and other baseline and disease characteristics. Patients were diagnosed with RRMS according to the revised McDonald criteria (2010) and experienced at least one relapse in the year before first

screening assessment. Patients also had at least one T1-GdE lesion on routine brain MRI taken within 3 months of screening and had scores of no more than 5.5 on the Kurtzke Expanded Disability Status Scale (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS).

Study Results

The primary efficacy analysis consisted of 2 parts: the assay sensitivity to determine whether the combined active treatments GLATECT and Copaxone® were superior to placebo and the equivalence analysis to determine whether GLATECT was equivalent to Copaxone® in the number of T1-GdE lesions at Months 7, 8 and 9. The outcome in the Full Analysis Set (FAS) was considered the primary outcome for the trial; the outcome was also supported from results in the Per Protocol Set.

In the FAS, the upper limit of the 95% CI for the ratio of the number of T1-GdE lesions during Months 7 to 9 of GLATECT and Copaxone® combined over placebo was less than 1 (upper limit 95% CI: 0.651), indicating that the combined active treatments were superior to placebo, hence confirming that the trial was appropriate to assess equivalence.

The least-squares mean of T1-GdE lesions at Months 7 to 9 was 0.447 in the GLATECT group and 0.408 in the Copaxone® group, thus the point estimate of the GLATECT/Copaxone® T1-GdE lesion ratio was 1.095 with a 95% CI of [0.883; 1.360] in the FAS. The 95% CI value was within the pre-defined equivalence interval [0.727; 1.375], indicating that GLATECT was therapeutically equivalent to Copaxone® in reducing the number of active brain lesions in patients with RRMS.

During the double-blind part of the study, formation of glatiramer acetate-reactive antibodies (ADA) was reported for a similar proportion of patients and comparable serum glatiramer ADA titer levels were reported in both groups. Switching from Copaxone® to GLATECT treatment in the open-label part had no impact on the incidence or titer levels of ADA.

Clinical Trials Conducted To Support Approval of COPAXONE®(Glatiramer Acetate)

The efficacy of another glatiramer acetate product 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 4) show that there was a statistically significant effect of

glatiramer acetate on number of relapses.

Table 4 - 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 5 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 5 - 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 6 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 6 - 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 Glatiramer Acetate 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).

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.

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).

Glatiramer acetate partially cross-reacts with myelin basic protein (MBP) at 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 major histocompatibility complex (MHC) class II molecules. Glatiramer acetate binds with high affinity to MHC Class II molecules on the surface of antigen presenting cells. *In vitro* studies demonstrate that the affinity of glatiramer acetate is sufficient to competitively displace MBP, MOG and PLP from MHC Class II. Specificity of glatiramer acetate binding is demonstrated by the observation that anti-MHC Class II DR antibodies but not anti-MHC I or anti-MHC Class II DQ antibodies inhibit interaction of glatiramer acetate with MHC Class II.

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. 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, IL-2 secretion or cytotoxic responses in human MBP-specific T-cells. In addition, glatiramer acetate has been shown to inhibit MBP-specific T-cell cytotoxicity.

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 demonstrated that ^{125}I-Glatiramer acetate is rapidly degraded at the site of injection. Tissue homogenate studies suggested 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.

Repeat-dose toxicity studies were performed to demonstrate comparability of the toxicological profiles of GLATECT and Copaxone®. In rats, treatment with 10 or 40 mg/kg/day GLATECT for up to 90 days resulted in effects that were comparable in nature, incidence and severity to those seen with Copaxone® at equivalent dosing levels. The tissue responses at the injection sites represented a normal tissue response to the presence of foreign material, and by the end of the recovery periods had partially or completely resolved. No additional safety issues were identified.

Carcinogenicity

Two life-span carcinogenicity studies with glatiramer acetate, one in mice and one in rats, were completed. Results from these 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 the 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 administered 140 mg/kg glatiramer acetate, equivalent to approximately 60% of the LD50/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

PrGLATECT™
(glatiramer acetate injection)

Read this carefully before you start taking GLATECT 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 GLATECT.

What is GLATECT used for?
GLATECT 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.

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

How does GLATECT 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.

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

What are the ingredients in GLATECT?
Medicinal ingredients: Glatiramer acetate
Non-medicinal ingredients: Mannitol in water for injection

GLATECT comes in the following dosage form:
Once-daily solution: 20 mg/1 mL pre-filled syringe.

Do not use GLATECT 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 GLATECT. Talk about any health conditions or problems you may have, including if you:
- have heart disease. Some patients taking GLATECT experienced chest pain.
- have a history of developing severe allergic reactions
- have chronic obstructive pulmonary disease (COPD)
- have asthma

- have kidney and / or liver problems
- are pregnant, planning to become pregnant, or if you become pregnant while you are using this medication. GLATECT is not recommended for use in pregnancy.
- are nursing
- are under 18 years of age

Other warnings you should know about:

Post-injection reaction
You may experience a post-injection reaction right after you inject GLATECT. Usually the symptoms of the reaction:
- do not last long and do not require specific treatment.
- may happen at the beginning of treatment or any time during the course of the treatment.

You may experience serious side effects that you may need to get immediate medical help to resolve. These could include side effects such as:
- chest tightness
- chest pain
- irregular heartbeat
- difficulty breathing
- dizziness

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
There are no known interactions between GLATECT and other drugs, vitamins, minerals, natural supplements, or alternative medicines.

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

- You will use one 20 mg/1 mL syringe of GLATECT each day.
- You will give yourself a subcutaneous injection of GLATECT. This means that you will inject GLATECT just under your skin, by following the instructions below.
- 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 GLATECT without consulting your doctor.

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.
    - One GLATECT 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

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

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

- Pick a different area each day (one for each day of the 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**.

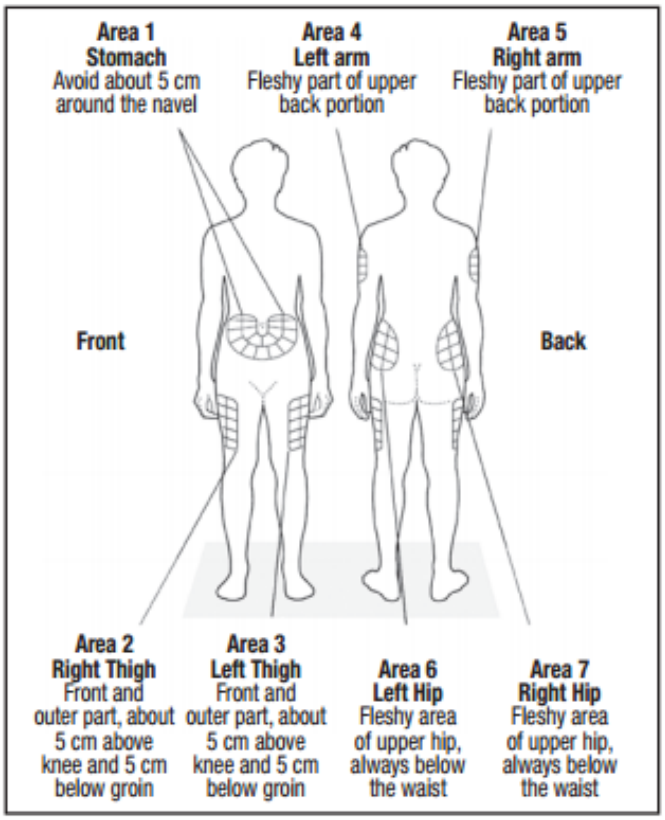

Figure 1

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 GLATECT 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 on a 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 degree angle. When the needle is all the way in the skin, let go the fold of skin **(**See **Figure 3)**.

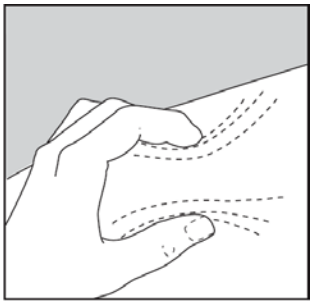

Figure 2

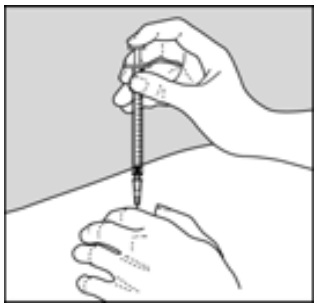

Figure 3

6. To inject the medication, hold the syringe steady and push down on the plunger. This should take just 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 GLATECT, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
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.

What are possible side effects from using GLATECT?

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

The most common side effects of GLATECT are:

- Skin reactions at the injection site. These include:
  - Redness
  - Pain
  - Inflammation
  - Itching
  - Swelling
  - Lumps
  - Shortness of breath
- A permanent "dent" under the skin at the injection site may also occur, due to a destruction of fat tissue at that site.

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		✓	
Irregular heartbeat: 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			✓

VERY RARE **Liver injury:** Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, weight loss, unusual tiredness			✓

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 report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax, or
- calling toll-free at 1-866-234-2345 (toll-free)

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
- Store in the original package in order to protect from light.
- If you cannot store GLATECT in the refrigerator, it can be stored once for 1 month at room temperature (15° - 25°C).
- **Keep out of the reach and sight of children.**

If you want more information about GLATECT:

- 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) or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc., Montréal, QC, H4P 2T4.

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