

seek immediate emergency medical care in case of experiencing such symptoms. If an anaphylactic reaction occurs, treatment with glatiramer acetate injection must be immediately discontinued. Unless a clear alternative etiology is identified, glatiramer acetate injection must be permanently discontinued [see **Contraindications (4)**].

5.2 Immediate Post-Injection Reaction

Approximately 16% of patients exposed to glatiramer acetate injection 20 mg per mL in the 5 placebo-controlled trials compared to 4% of those on placebo, and approximately 2% of patients exposed to glatiramer acetate injection 40 mg per mL in a placebo-controlled trial compared to none on placebo, experienced a constellation of symptoms that may occur immediately (within seconds to minutes, with the majority of symptoms observed within 1 hour) after injection and included at least two of the following: flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria. These events are termed immediate post-injection reactions.

The symptoms of an immediate post-injection reaction may overlap with those of anaphylaxis; prompt identification of anaphylaxis is important to avoid a delay in treatment. In general, symptoms of an immediate post-injection reaction have onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. Typically, the symptoms were transient and self-limited and did not require treatment; however, there have been reports of patients with similar symptoms who developed fatal anaphylaxis and/or received emergency medical care. Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

5.3 Chest Pain

Approximately 13% of glatiramer acetate injection 20 mg per mL patients in the 5 placebo-controlled studies compared to 6% of placebo patients, and approximately 2% of patients exposed to glatiramer acetate injection 40 mg per mL in a placebo-controlled trial compared to 1% of placebo patients, experienced at least one episode of transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection was not always known. The pain was usually transient, often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

5.4 Lipotrophy and Skin Necrosis

At injection sites, localized lipotrophy and, rarely, injection site skin necrosis may occur. Lipotrophy occurred in approximately 2% of patients exposed to glatiramer acetate injection 20 mg per mL in the 5 placebo-controlled trials compared to none on placebo, and 0.5% of patients exposed to glatiramer acetate injection 40 mg per mL in a single placebo-controlled trial and none on placebo. Skin necrosis has only been observed in the postmarketing setting. Lipotrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipotrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites with each injection.

5.5 Potential Effects on Immune Response

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

Although glatiramer acetate injection is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with glatiramer acetate injection may result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in most patients receiving glatiramer acetate. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RRMS patients given glatiramer acetate injection 20 mg per mL, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance and has been reported with glatiramer acetate injection [see **Warnings and Precautions (5.1)**].

5.6 Hepatic Injury

Cases of hepatic injury, some severe, including liver failure and hepatitis with jaundice, have been reported with glatiramer acetate injection. Hepatic injury has occurred from days to years after initiating treatment with glatiramer acetate injection. If signs or symptoms of liver dysfunction occur, consider discontinuation of glatiramer acetate injection.

5.7 Glatiramer Acetate Products and Administration Errors
Medication errors have occurred when glatiramer acetate products are administered with incompatible autoinjectors. Some glatiramer acetate products can be administered by an optional compatible autoinjector, should one be available; however, not all glatiramer acetate products have a marketed optional compatible autoinjector for administration [see **Dosage and Administration (2.2)** and **How Supplied/Storage and Handling (16)**].

Using an optional autoinjector that is not compatible for use with glatiramer acetate injection may increase the risk for medication errors, such as dose omission or administration of a partial dose. If using an optional autoinjector for administration, ensure the device is compatible for use with the specific glatiramer acetate product by referring to the autoinjector labeling. The availability of compatible autoinjectors for each glatiramer acetate product may change with time.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Anaphylactic Reactions [see **Warnings and Precautions (5.1)**]
- Immediate Post-Injection Reaction [see **Warnings and Precautions (5.2)**]
- Chest Pain [see **Warnings and Precautions (5.3)**]
- Lipotrophy and Skin Necrosis [see **Warnings and Precautions (5.4)**]
- Potential Effects on Immune Response [see **Warnings and Precautions (5.5)**]
- Hepatic Injury [see **Warnings and Precautions (5.6)**]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Incidence in Controlled Clinical Trials

Glatiramer acetate injection 20 mg per mL per day
Among 563 patients treated with glatiramer acetate injection in blinded placebo-controlled trials, approximately 5% of the subjects discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity. The most common adverse reactions were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Table 1 lists signs and symptoms that occurred in at least 2% of patients treated with glatiramer acetate injection 20 mg per mL in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate injection than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 1: Adverse Reactions in Controlled Clinical Trials with an Incidence ≥2% of Patients and More Frequent with Glatiramer Acetate Injection (20 mg per mL Daily) than with Placebo

	Glatiramer acetate injection 20 mg/mL (n=564) %	Placebo (n=564) %
Blood And Lymphatic System Disorders	Lymphadenopathy	7 3
Cardiac Disorders	Palpitations	9 4
	Tachycardia	5 2
Eye Disorders	Eye Disorder	3 1
	Diplopia	3 2
	Nausea	15 11
Gastrointestinal Disorders	Vomiting	7 4
	Dysphagia	2 1
General Disorders And Administration Site Conditions	Injection Site Erythema	43 10
	Injection Site Pain	40 20
	Injection Site Pruritus	27 4
	Injection Site Mass	26 6
	Asthenia	22 21
	Pain	20 17
	Injection Site Edema	19 4
	Chest Pain	13 6
	Injection Site Inflammation	9 1
	Edema	8 2
	Injection Site Reaction	8 1
	Pyrexia	6 5
	Injection Site Hypersensitivity	4 0
	Local Reaction	3 1
	Chills	3 1
	Face Edema	3 1
	Edema Peripheral	3 2
	Injection Site Fibrosis	2 1
	Injection Site Atrophy*	2 0
Immune System Disorders	Hypersensitivity	3 2
Infections And Infestations	Infection	30 28
	Influenza	14 13
	Rhinitis	7 5
	Bronchitis	6 5
	Gastroenteritis	6 4
	Vaginal Candidiasis	4 2
Metabolism And Nutrition Disorders	Weight Increased	3 1
Musculoskeletal And Connective Tissue Disorders	Back Pain	12 10
Neoplasms Benign, Malignant And Unspecified (Not Ovaries And Pylorus)	Benign Neoplasm of Skin	2 1
Nervous System Disorders	Tremor	4 2
	Migraine	4 2
	Syncope	3 2
	Speech Disorder	2 1
Psychiatric Disorders	Anxiety	13 10
	Nervousness	2 1
Renal And Urinary Disorders	Micturition Urgency	5 4
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	14 4
	Cough	6 5
	Laryngospasm	2 1
Skin And Subcutaneous Tissue Disorders	Rash	19 11
	Hyperhidrosis	7 5
	Pruritus	5 4
	Urticaria	3 1
	Skin Disorder	3 1
Vascular Disorders	Vasodilatation	20 5

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

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

Laboratory analyses were performed on all patients participating in the clinical program for glatiramer acetate injection. Clinically-significant laboratory values for hematology, chemistry, and urinalysis were similar for both glatiramer acetate injection and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia (16 x 10⁹/L), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials of glatiramer acetate injection 20 mg per mL were analyzed to evaluate differences based on sex. No clinically-significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with glatiramer acetate injection were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age subgroups.

Other Adverse Reactions

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

Body as a Whole:

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

Cardiovascular:

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

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cheilostyitis, 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, focal paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation and hay fever.
Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.
Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

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

Urogenital:

Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious papincolour smear, urinary frequency, and vaginal hemorrhage.
Infrequent: Vaginitis, flank pain (kidney), breast engorgement, breast enlargement, carcinoma in situ cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Glatiramer acetate injection 40 mg per mL, three times per week
Among 943 patients treated with glatiramer acetate injection 40 mg per mL three times per week in a blinded, placebo-controlled trial, approximately 3% of the subjects discontinued treatment because of an adverse reaction. The most common adverse reactions were injection site reactions, which were also the most common cause of discontinuation.

Table 2 lists signs and symptoms that occurred in at least 2% of patients treated with glatiramer acetate injection 40 mg per mL in the blinded, placebo-controlled trial. These signs and symptoms were numerically more common in patients treated with glatiramer acetate injection 40 mg per mL than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 2: Adverse Reactions in a Controlled Clinical Trial with an Incidence ≥2% of Patients and More Frequent with Glatiramer Acetate Injection (40 mg per mL, Three Times per Week) than with Placebo

	Glatiramer acetate injection 40 mg/mL (n=943) %	Placebo (n=461) %
General Disorders And Administration Site Conditions	Injection Site Erythema	22 2
	Injection Site Pain	10 2
	Injection Site Mass	6 0
	Injection Site Pruritus	6 0
	Injection Site Edema	6 0
	Pyrexia	3 2
	Influenza-like Illness	3 2
	Injection Site Inflammation	2 0
	Chills	2 0
	Chest Pain	2 1
Infections And Infestations	Nasopharyngitis	11 9
	Respiratory Tract Infection Viral	3 2
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	3 0
Vascular Disorders	Vasodilatation	3 0
Gastrointestinal Disorders	Nausea	2 1
Skin And Subcutaneous Tissue Disorders	Erythema	2 0
	Rash	2 1

No new adverse reactions appeared in subjects treated with glatiramer acetate injection 40 mg per mL, three times per week as compared to subjects treated with glatiramer acetate injection 20 mg per mL per day in clinical trials and during postmarketing experience. Data on adverse reactions occurring in the controlled clinical trial of glatiramer acetate injection 40 mg per mL were analyzed to evaluate differences based on sex. No clinically-significant differences were identified. Ninety-eight percent of patients in this clinical trial were Caucasian and the majority were between the ages of 18 and 50. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age groups.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of glatiramer acetate injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; allergic reaction

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

Digestive System: tongue edema; stomach ulcer; hemorrhage; eruption

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

Hepatobiliary Disorders: cholelithiasis; liver function abnormality; cirrhosis of the liver; hepatitis; hepatic injury [see **Warnings and Precautions (5.6)**]

Immune System Disorders: hypersensitivity reactions (including anaphylactic reactions) [see **Boxed Warning and Warnings and Precautions (5.1)**]

Metabolic and Nutritional Disorders: hypercholesterolemia
Musculoskeletal System: rheumatoid arthritis; generalized spasm
Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

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

Special Senses: glaucoma; blindness

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from pharmacovigilance and published observational studies over decades of use with glatiramer acetate during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes (see **Data**). Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on embryofetal or offspring development (see **Data**).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Data from pharmacovigilance and published observational studies have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes when glatiramer acetate was used during pregnancy. However, the published comparative observational studies have methodological limitations, such as short exposure duration during pregnancy, confounding, selection bias, and exposure misclassification.

Animal Data

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

8.2 Lactation

Risk Summary

There are no data on the presence of glatiramer acetate in human milk. Based on the low systemic exposure because of substantial local hydrolysis of glatiramer acetate following subcutaneous administration, breastfeeding is not expected to result in clinically relevant exposure of the infant to the drug [see **Clinical Pharmacology (12.3)**]. There are no data on the effects of glatiramer acetate on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for glatiramer acetate injection and any potential adverse effects on the breastfed infant from glatiramer acetate injection or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of glatiramer acetate injection have not been established in patients under 18 years of age.

8.5 Geriatric Use

Glatiramer acetate injection has not been studied in elderly patients.

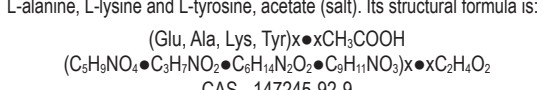
8.6 Use in Patients with Impaired Renal Function

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

11 DESCRIPTION

Glatiramer acetate, the active ingredient of glatiramer acetate injection, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-lysine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.

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



Glatiramer acetate injection is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of glatiramer acetate injection solution contains 20 mg of glatiramer acetate and the following inactive ingredient: 40 mg of mannitol. The pH of the solutions is approximately 5.5 to 7.0. The biological activity of glatiramer acetate is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS are not fully understood. However, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. There is no evidence that glatiramer acetate does this, but this has not been systematically evaluated [see **Warnings and Precautions (5.5)**].

12.3 Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m² basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² basis). No increase in neoplasms was observed.

Mutagenesis

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

Impairment of Fertility

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m² basis) no adverse effects were observed on reproductive or developmental parameters.

14 CLINICAL STUDIES

Evidence supporting the effectiveness of glatiramer acetate injection derives from five placebo-controlled trials, four of which used a glatiramer acetate injection dose of 20 mg per mL per day and one of which used a glatiramer acetate injection dose of 40 mg per mL three times per week.

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

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

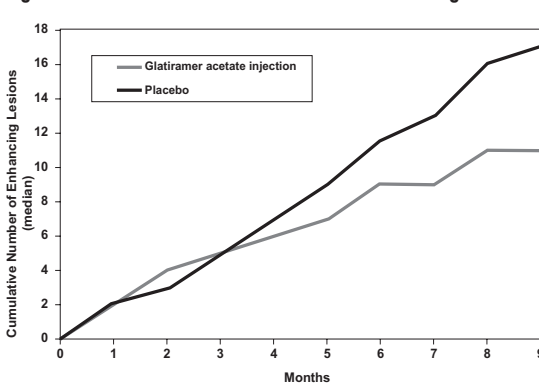
The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: the

Table 5: Study 4 MRI Results

	Glatiramer acetate injection 20 mg/mL (n=119)	Placebo (n=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

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

Figure 2: Median Cumulative Number of Gd-Enhancing Lesions



Glatiramer acetate injection 40 mg per mL three times per week
 Study 5 was a double-blind, placebo-controlled, multinational study with a total of 1404 patients with RRMS randomized in a 2:1 ratio to receive either glatiramer acetate injection 40 mg per mL (n=943) or placebo (n=461) three times a week for 12 months. Patients had a median of 2 relapses in the 2 years prior to screening and had not received any interferon-beta for at least 2 months prior to screening. Baseline EDSS scores ranged from 0 to 5.5 with a median of 2.5. Neurological evaluations were performed at baseline, every three months, and at unscheduled visits for suspected relapse or early termination. MRI was performed at baseline, months 6 and 12, or early termination. A total of 91% of those assigned to glatiramer acetate injection 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 glatiramer acetate injection on several magnetic resonance imaging (MRI) variables, including number of new or enlarging T2 lesions and number of enhancing lesions on T1-weighted images, was also measured at months 6 and 12.

Table 6 presents the results for the intent-to-treat population.

Table 6: Study 5 Efficacy and MRI Results

	Glatiramer acetate injection 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	0.331	0.505	<0.0001
Relative risk reduction	34%		
MRI Endpoints			
Cumulative number of new or enlarging T2 lesions at Months 6 and 12			
Adjusted Mean Estimates	3.650	5.592	<0.0001
Relative risk reduction	35%		
Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12			
Adjusted Mean Estimates	0.905	1.639	<0.0001
Relative risk reduction	45%		

16 HOW SUPPLIED/STORAGE AND HANDLING

Glatiramer acetate injection is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution supplied as:

- 20 mg per mL in a single-dose, pre-filled syringe with a natural (clear) plunger, in individual blister packages supplied in 30-count cartons (NDC 47335-990-02).

Some glatiramer acetate products can be administered by an optional compatible autoinjector. Compatible autoinjectors are supplied separately if available, but the availability of compatible autoinjectors may change with time [see *Warnings and Precautions* (5.7) and *Patient Counseling Information* (7)].

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Important Administration Instructions

Advise patients with new or existing glatiramer acetate prescriptions to consult their pharmacist or healthcare provider if they would like information about using an optional compatible autoinjector device, if available.

Additionally, advise patients who would like to use an autoinjector for administration, should one be available, that not all available autoinjectors are compatible with all glatiramer acetate products and the availability of compatible autoinjectors may change with time. If you have questions about the availability or compatibility of an autoinjector, contact the manufacturer of the prescribed glatiramer acetate product for more information.

Advise patients that using an optional autoinjector that is not compatible with the glatiramer acetate product may increase the risk for medication errors, such as missing a dose or administration of a partial dose [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.7)].

Anaphylactic Reactions

Advise patients and their caregivers that glatiramer acetate injection may cause life-threatening and fatal anaphylactic reactions shortly after injection, and that reactions may occur months to years after initiation of treatment [see *Warnings and Precautions* (5.1)]. Inform patients and their caregivers about the signs and symptoms specific for anaphylactic reactions, and that signs and symptoms of anaphylactic reactions may overlap with those of immediate post-injection reactions. Instruct them to seek immediate emergency medical care if they experience any signs or symptoms of an anaphylactic reaction [see *Warnings and Precautions* (5.1, 5.2)]. Patients should be advised to also contact their healthcare provider, and that treatment should be discontinued immediately and permanently if anaphylactic reactions occur.

Immediate Post-Injection Reaction

Advise patients that glatiramer acetate injection may cause immediate post-injection reactions, characterized by various symptoms after injection, including flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria [see *Warnings and Precautions* (5.2)]. These symptoms occur within seconds to minutes after injection and are generally transient, self-limited, and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

Advise patients that the symptoms of an immediate post-injection reaction may overlap with those of an anaphylactic reaction. Advise patients to contact their healthcare provider if they experience any signs or symptoms of an immediate post-injection reaction [see *Warnings and Precautions* (5.1, 5.2)].

Chest Pain

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation [see *Warnings and Precautions* (5.3)]. Inform patients that the pain should be transient. Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patients should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

Lipoatrophy and Skin Necrosis at Injection Site

Advise patients that localized lipoatrophy, and rarely, skin necrosis may occur at injection sites [see *Warnings and Precautions* (5.4)]. Instruct patients to follow proper injection technique and to rotate injection areas and sites with each injection to minimize these risks.

Hepatic Injury

Advise patients that hepatic injury, including hepatic failure and hepatitis with jaundice, has been reported with the use of glatiramer acetate injection. Educate patients about the signs and symptoms of hepatic injury and instruct patients to report them immediately to their healthcare provider [see *Warnings and Precautions* (5.6)].

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking glatiramer acetate injection they should inform their healthcare provider [see *Use in Specific Populations* (8.1)].

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed during glatiramer acetate injection therapy [see *Use in Specific Populations* (8.2)].

Instructions for Use

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

Storage Conditions

Advise patients that the recommended storage condition for glatiramer acetate injection is refrigeration at 36°F to 46°F (2°C to 8°C). If needed, the patient may store glatiramer acetate injection at room temperature, 59°F to 86°F (15°C to 30°C), for up to one month, but refrigeration is preferred. Glatiramer acetate injection should not be exposed to higher temperatures or intense light. Do not freeze glatiramer acetate injection.

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Do not take glatiramer acetate injection:

- if you are allergic to glatiramer acetate or mannitol. Serious allergic reactions including life-threatening or anaphylactic reactions that can lead to death have happened. See the end of this leaflet for a complete list of the ingredients in glatiramer acetate injection.

Before you use glatiramer acetate injection, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. Talk to your healthcare provider who will advise if you should take glatiramer acetate injection during your pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if glatiramer acetate injection passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using glatiramer acetate injection.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Glatiramer acetate injection may affect the way other medicines work, and other medicines may affect how glatiramer acetate injection works.

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

How should I use glatiramer acetate injection?

- For detailed instructions, see the **Instructions for Use** at the end of this leaflet for complete information on how to use glatiramer acetate injection.
- Your healthcare provider will tell you how much glatiramer acetate injection to use and when to use it.
- Glatiramer acetate injection is given by injection under your skin (subcutaneously).
- Use glatiramer acetate injection exactly as your healthcare provider tells you to use it.
- Since every body type is different, talk with your healthcare provider about the injection areas that are best for you.
- You should receive your first dose of glatiramer acetate injection with a healthcare provider or nurse present. This might be at your healthcare provider's office or with a visiting home health nurse who will teach you how to give your glatiramer acetate injections.
- Some glatiramer acetate products can be used with an optional compatible autoinjector. Compatible autoinjectors are supplied separately if available, but the availability of compatible autoinjectors may change with time.
 - Check with your healthcare provider when you fill or refill your medicine to make sure the autoinjector you have is meant to be used with your glatiramer acetate product. Not all optional autoinjectors are meant to be used with all glatiramer acetate products. If you use the wrong autoinjector, you might not get the correct dose of your medicine. Contact the manufacturer of your glatiramer acetate product to find out if there is an autoinjector that is meant to be used with your glatiramer acetate product.
- Read your Instructions for Use and talk to your healthcare provider about the best way for you to use glatiramer acetate injection.

What are the possible side effects of glatiramer acetate injection? Glatiramer acetate injection may cause serious side effects, including:

- Immediate Post-Injection Reactions.** Serious side effects may happen right after or within minutes after you inject glatiramer acetate injection at any time during your course of treatment. Some signs and symptoms may be the same as those of a serious allergic reaction (anaphylaxis). **See What is the most important information I should know about glatiramer acetate injection?** Call a healthcare provider right away if you have any of these immediate post-injection reaction symptoms including:
 - redness to your cheeks or other parts of the body (flushing)
 - chest pain
 - fast heartbeat
 - anxiety
 - breathing problems or tightness in your throat
 - swelling, rash, hives, or itching
 If you have symptoms of an immediate post-injection reaction, do not give yourself more injections until a healthcare provider tells you to.
- Chest Pain.** You can have chest pain as part of an immediate post-injection reaction or by itself. This type of chest pain usually lasts a few minutes and can begin around 1 month after you start using glatiramer acetate injection. Call your healthcare provider right away if you have chest pain while using glatiramer acetate injection.
- Damage to your skin.** Damage to the fatty tissue just under your skin's surface (lipoatrophy) and, rarely, death of your skin tissue (necrosis) can happen when you use glatiramer acetate injection. Damage to the fatty tissue under your skin can cause a "dent" at the injection site that may not go away. You can reduce your chance of developing these problems by:
 - following your healthcare provider's instructions for how to use glatiramer acetate injection
 - choosing a different injection area each time you use glatiramer acetate injection. See Step 4 in the Instructions for Use, "Choose your injection area".
- Liver problems.** Liver problems, including liver failure, can occur with glatiramer acetate injection. Call your healthcare provider right away if you have symptoms, such as:
 - nausea
 - loss of appetite
 - tiredness
 - dark colored urine and pale stools
 - yellowing of your skin or the white part of your eye
 - bleeding more easily than normal
 - confusion
 - sleepiness

The most common side effects of glatiramer acetate injection are:

- skin problems at your injection site, including:
 - redness
 - pain
 - swelling
 - lumps
 - itching
- rash
- shortness of breath
- flushing (vasodilation)
- chest pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of glatiramer acetate injection. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store glatiramer acetate injection?

- Store glatiramer acetate injection in the refrigerator between 36°F to 46°F (2°C to 8°C).
- When you are not able to refrigerate glatiramer acetate injection, you may store it for up to 1 month at room temperature between 59°F to 86°F (15°C to 30°C).
- Protect glatiramer acetate injection from light or high temperature.
- Do not freeze glatiramer acetate injection syringes. If a syringe freezes, throw it away in a sharps disposal container. **See Step 13 in the Instructions for Use, "Dispose of your needles and syringes".**

Keep glatiramer acetate injection and all medicines out of the reach of children.

General information about the safe and effective use of glatiramer acetate injection.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use glatiramer acetate injection for a condition for which it was not prescribed. Do not give glatiramer acetate injection to other people, even if they have the same symptoms as you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about glatiramer acetate injection that is written for health professionals.

For more information, go to www.sunpharmaceuticals.com or call 1-800-818-4555.

What are the ingredients in glatiramer acetate injection?

Active ingredient: glatiramer acetate
Inactive ingredients: mannitol

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Step 3: Look closely at your glatiramer acetate injection pre-filled syringe.

- There may be small air bubbles in the syringe. Do not try to push the air bubble from the syringe before giving your injection so you do not lose any medicine.
- Check the liquid medicine in the syringe before you give your injection. The liquid in the syringe should look clear, and colorless, and may look slightly yellow. If the liquid is cloudy or contains any particles, do not use the syringe and throw it away in a sharps disposal container. **See Step 13 below, "Dispose of your needles and syringes."**

Step 4: Choose your injection area. **See Figure C.**

See the injection areas you should use on your body. Talk with your healthcare provider about the injection areas that are best for you.

- The possible injection areas on your body include (See Figure C):
 - your stomach area (abdomen) around the belly button
 - the back of your upper arms
 - upper hips (below your waist)
 - your thighs (above your knees)

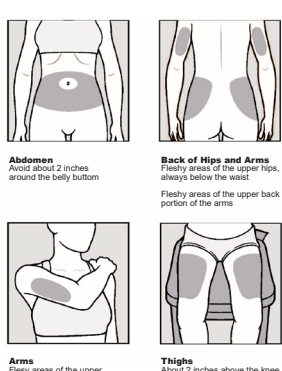


Figure C

- For each glatiramer acetate injection dose, choose a different injection area from 1 of the areas shown above. **See Figure C.**
- Do not stick the needle in the same place (site) more than 1 time each week.** Each injection area contains multiple injection sites for you to choose from. Avoid injecting in the same site over and over again.
- Keep a record of the sites where you give your injection each day so you will remember where you already injected.

Step 5: Prepare to give your injection.

- There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.
- Do not inject in sites where the skin has scarring or "dents". Using scarred or dented skin for your injections may make your skin worse.

Step 6: Clean your injection site.

- Clean the injection site using the alcohol wipe and allow your skin to air dry. **See Figure D.**



Figure D

Step 7: Pick up the syringe with 1 hand and hold it like a pencil. Remove the needle cover with your other hand and set it aside. **See Figure E.**

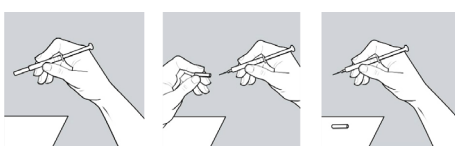


Figure E

Step 8: Pinch about a 2 inch fold of skin between your thumb and index finger. **See Figure F.**



Figure F

Step 9: Giving your injection.

- Rest the heel of your hand holding the syringe against your skin at the injection site. Insert the needle at a 90 degree angle straight into your skin. **See Figure G.**

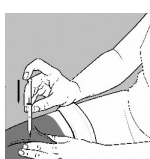


Figure G

- When the needle is all the way into your skin, release the fold of skin. **See Figure H.**



Figure H

Step 10: Give your glatiramer acetate injection.

To inject the medicine, hold the syringe steady and slowly push down the plunger. **See Figure I.**



Figure I

Step 11: Remove the needle.

After you have injected all of the medicine, pull the needle straight out. **See Figure J.**

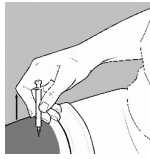


Figure J

Step 12: Use a clean, dry cotton ball to gently press on the injection site for a few seconds. Do not rub the injection site or re-use the needle or syringe. **See Figure K.**



Figure K

Step 13: Dispose of your needles and syringes.

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
 - If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

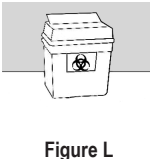


Figure L

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Instructions for Use GLATIRAMER ACETATE injection (gla tir' a mer as' e late) for subcutaneous use

For subcutaneous injection only.
 Do not inject glatiramer acetate injection in your veins (intravenously). Do not re-use your glatiramer acetate injection pre-filled syringes. Do not share your glatiramer acetate injection pre-filled syringes with another person. You may give another person an infection or get an infection from them.

You should receive your first dose of glatiramer acetate injection with a healthcare provider or nurse present. This might be at your healthcare provider's office or with a visiting home health nurse who will show you how to give your own injections.

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

If you plan to use your glatiramer acetate product with an autoinjector, ask your healthcare provider or pharmacist to make sure that your autoinjector is meant to be used with your glatiramer acetate product. If you use an autoinjector that is not meant to be used with your glatiramer acetate product, you might not get the correct dose of your medicine.

Instructions for Using Your Glatiramer Acetate 20 mg Prefilled Syringe:

- Glatiramer acetate injection 20 mg** is injected 1 time each day, in the fatty layer under your skin (subcutaneously).
- Each glatiramer acetate injection 20 mg prefilled syringe is for single use (1 time use) only.
- The glatiramer acetate injection 20 mg dose is packaged in boxes of 30 prefilled syringes with needles attached. Glatiramer acetate injection 20 mg prefilled syringes have **natural (clear)** plungers.

How do I inject glatiramer acetate injection?

Step 1: Gather the supplies you will need to inject glatiramer acetate injection. **See Figure A.**

- 1 blister pack with a glatiramer acetate injection pre-filled syringe with needle attached
- Alcohol wipe (not supplied)
- Dry cotton ball (not supplied)
- A place to record your injections, like a notebook (not supplied)
- Sharps disposal container (not supplied). **See Step 13 below, "Dispose of your needles and syringes".**

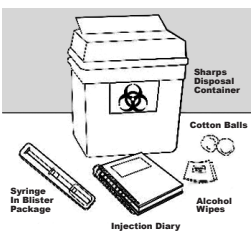


Figure A

Step 2: Remove only 1 blister pack from the glatiramer acetate injection pre-filled syringe carton. **See Figure B.**

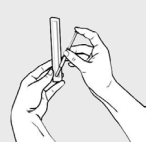


Figure B

- Place the supplies you will need on a clean, flat surface in a well-lit area.
- After you remove 1 blister pack from the carton, keep all unused syringes in the carton and store them in the refrigerator.
- Let the blister pack, with the syringe inside, warm to room temperature for about 20 minutes.
- Wash your hands. Be careful not to touch your face or hair after washing your hands.

Medication Guide GLATIRAMER ACETATE injection (gla tir' a mer as' e late) for subcutaneous use

Read this Medication Guide before you start using glatiramer acetate injection