Glatiramer Inj 2 x 0 GLT Title Case 0 20 Layout 3/20/ 3: PM Page

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SANDOZ

Glatopa™
(glatiramer acetate injection)

℞ only

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GLATOPA™ (glatiramer acetate injection), for subcutaneous use
Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Dosage and Administration: Recommended Dose (2.1)	01/2014
Dosage and Administration: Instructions for Use (2.2)	01/2014
Warnings and Precautions: Immediate Post-Injection Reaction (5.1)	01/2014
Warnings and Precautions: Chest Pain (5.2)	01/2014
Warnings and Precautions: Lipoatrophy and Skin Necrosis (5.3)	01/2014

INDICATIONS AND USAGE

Glatopa™ is indicated for the treatment of patients with relapsing-remitting multiple sclerosis (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous injection only. Glatopa 20 mg per mL dose is not interchangeable with glatiramer acetate 40 mg per mL dose (2.1)
- Glatopa™ 20 mg/mL per day (2.1)
- Bring the prefilled syringe to room temperature (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg/mL in a single-dose prefilled syringe with a white plunger (3)

CONTRAINDICATIONS

Known hypersensitivity to glatiramer acetate or mannitol (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- In controlled studies of glatiramer acetate injection 20 mg/mL, most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known if glatiramer acetate injection is excreted in human milk (8.3)
- Pediatric Use: The safety and effectiveness of Glatopa have not been established in patients under 18 years of age (8.4)

PATIENT COUNSELING INFORMATION

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Glatopa™ is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Glatopa is for subcutaneous use only. Do not administer intravenously. The recommended dose is:
- Glatopa 20 mg per mL: administer once per day

Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable.

2.2 Instructions for Use

Remove one blister-packaged prefilled syringe from the refrigerated carton. Let the prefilled syringe stand at room temperature for 20 minutes to allow the solution to warm to room temperature. Visually inspect the syringe for particulate matter and discoloration prior to administration. The solution in the syringe should appear clear, colorless to slightly yellow. If particulate matter or discoloration is observed, discard the syringe.

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

3 DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg per mL in a single-dose, prefilled syringe with a white plunger. For subcutaneous use only.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Immediate Post-Injection Reaction

Approximately 16% of patients exposed to glatiramer acetate injection 20 mg per mL in the 5 placebo-controlled trials compared to 4% of those on placebo experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. Typically, the symptoms were transient and self-limited and did not require treatment; however, there have been reports of patients with similar symptoms who received emergency medical care.

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

5.2 Chest Pain

Approximately 13% of glatiramer acetate injection 20 mg per mL patients in the 5 placebo-controlled studies, compared to 6% 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 only lasting a few minutes), often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

5.3 Lipoatrophy and Skin Necrosis

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

5.4 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 therefore, this risk cannot be excluded.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Incidence in Controlled Clinical Trials

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 treatment-emergent 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=563)	Placebo (n=564)
Blood And Lymphatic System Disorders	Lymphadenopathy	7%	3%
Cardiac Disorders	Palpitations	9%	4%
	Tachycardia	5%	2%
Eye Disorders	Eye Disorder	3%	1%
	Diplopia	3%	2%
Gastrointestinal Disorders	Nausea	15%	11%
	Vomiting	7%	4%
	Dysphagia	2%	1%
General Disorders And Administration Site Conditions	Injection Site Erythema	43%	10%
	Injection Site Pain	40%	20%
	Injection Site Pruritus	27%	4%
	Injection Site Mass	26%	6%
	Asthenia	22%	21%
	Pain	20%	17%
	Injection Site Edema	19%	4%
	Chest Pain	13%	6%
	Injection Site Inflammation	9%	1%
	Edema	8%	2%
	Injection Site Reaction	8%	1%
	Pyrexia	6%	5%
	Injection Site Hypersensitivity	4%	0%
	Local Reaction	3%	1%
	Chills	3%	1%
	Face Edema	3%	1%
	Edema Peripheral	3%	2%
	Injection Site Fibrosis	2%	1%
	Injection Site Atrophy*	2%	0%
Immune System Disorders	Hypersensitivity	3%	2%
Infections And Infestations	Infection	30%	28%
	Influenza	14%	13%
	Rhinitis	7%	5%
	Bronchitis	6%	5%
	Gastroenteritis	6%	4%
	Vaginal Candidiasis	4%	2%
Metabolism And Nutrition Disorders	Weight Increased	3%	1%
Musculoskeletal And Connective Tissue Disorders	Back Pain	12%	10%
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Neoplasm of Skin	2%	1%
Nervous System Disorders	Tremor	4%	2%
	Migraine	4%	2%
	Syncope	3%	2%
	Speech Disorder	2%	1%
Psychiatric Disorders	Anxiety	13%	10%
	Nervousness	2%	1%
Renal And Urinary Disorders	Micturition Urgency	5%	4%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	14%	4%
	Cough	6%	5%
	Laryngospasm	2%	1%
Skin And Subcutaneous Tissue Disorders	Rash	19%	11%
	Hyperhidrosis	7%	5%
	Pruritus	5%	4%
	Urticaria	3%	1%
	Skin Disorder	3%	1%
Vascular Disorders	Vasodilatation	20%	5%

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

Adverse reactions which occurred only in 4 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 x10⁹/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-two percent of patients in these clinical trials were Caucasian. This is representative of the population 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, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:
Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

The following adverse events occurring under treatment with glatiramer acetate injection 20 mg per mL since market introduction and not mentioned above have been identified during postapproval use of glatiramer acetate injection. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction

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

Digestive System: tongue edema; stomach ulcer hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

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

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

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

Special Senses: glaucoma; blindness

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

7 DRUG INTERACTIONS

Interactions between glatiramer acetate injection and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of glatiramer acetate injection with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. Glatiramer acetate injection has not been formally evaluated in combination with interferon beta.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Glatopa should be used during pregnancy only if clearly needed.

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/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 Labor and Delivery

The effects of Glatopa on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

It is not known if glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Glatopa is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

$$(Glu, Ala, Lys, Tyr)_x \cdot xCH_3COOH$$

$$(C_5H_9NO_4 \cdot C_3H_7NO_2 \cdot C_6H_{14}N_2O_2 \cdot C_9H_{11}NO_3)_x \cdot xC_2H_4O_2$$

CAS - 147245-92-9

Glatopa is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of glatiramer acetate solution contains 20 mg of glatiramer acetate and the following inactive ingredient: 40 mg of mannitol. The pH of the solution 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 (5.4)]*.

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

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.

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

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/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 three placebo-controlled trials, two of which used a glatiramer acetate injection dose of 20 mg per mL per day.

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 had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

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

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: the frequency of attacks during the trial, and the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 2 presents the values of the three outcomes described above, as well as several protocol-specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment).

Table 2: Study 1 Efficacy Results

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

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

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

Table 3: Study 2 Efficacy Results

	Glatiramer Acetate Injection 20 mg/mL (n=125)	Placebo (n=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68/2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

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

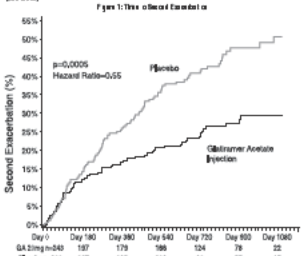
In Study 3, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either glatiramer acetate injection 20 mg per mL (n=243) or placebo (n=238). The primary outcome measure was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

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

(See Reverse)

(Continued)

Figure 1: Time to Second Exacerbation



Patients treated with glatiramer acetate injection demonstrated a 45% reduction in the risk of developing clinically definite MS compared to placebo (hazard ratio = 0.55; 95% confidence interval 0.40 to 0.77). Additionally, the median time to clinically definite MS was 722 days for placebo compared to 336 days for glatiramer acetate injection (a ratio of 0.55).

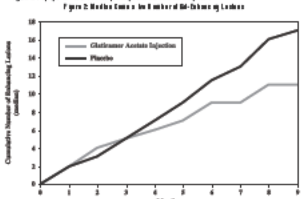
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (glatiramer acetate injection n=119 and placebo n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion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

Table 4: Study 4 MRI Results

	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



16 HOW SUPPLIED/STORAGE AND HANDLING

Glatopa (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection supplied as single-dose, glass syringes with attached 1/2 inch needles and 29 gauge needles supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger. Individual blister packages are supplied in a 30-count carton with 34 alcohol preps (NDC 0781-3234-34).

Store Glatopa refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store Glatopa 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 Glatopa. If a Glatopa syringe freezes, it should be discarded.

17 PATIENT COUNSELING INFORMATION

(See Patient Information Leaflet (Patient Information and Instructions for Use))

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

Pregnancy

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

Immediate Post-Injection Reaction

Advise patients that Glatopa may cause various symptoms after injection, including flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms are generally transient and self-limited and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

Chest Pain

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation. Inform patients that the pain should be transient. 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. Instruct patients to follow proper injection technique and to rotate injection areas and sites with each injection to minimize these risks.

Instructions for Use

Instruct patients to read the Glatopa Patient Information leaflet carefully. Glatopa 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 on a daily basis. 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 Glatopa is refrigeration at 36°F to 46°F (2°C to 8°C). If needed, the patient may store Glatopa at room temperature 59°F to 86°F (15°C to 30°C) for up to one month, but refrigeration is preferred. Glatopa should not be exposed to higher temperatures or intense light. Do not freeze Glatopa.

PATIENT INFORMATION
Glatopa™ (Glatiramer Acetate Injection)
for Subcutaneous Use

Read this Patient Information before you start using Glatopa and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is Glatopa?

Glatopa is a prescription medicine used for the treatment of people with relapsing forms of multiple sclerosis (MS).

It is not known if Glatopa is safe and effective in children under 18 years of age.

Glatopa is the same as Copaxone (glatiramer acetate injection) 20 mg/mL administered once daily.

Who should not use Glatopa?

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

What should I tell my doctor before using Glatopa? Before you use Glatopa, tell your doctor if you:

- are pregnant or plan to become pregnant. It is not known if Glatopa will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if glatiramer acetate passes into your breast milk. Talk to your doctor about the best way to feed your baby while using Glatopa.

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

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

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

How should I use Glatopa?

- For detailed instructions, see the Instructions for Use at the end of this leaflet for complete information on how to use Glatopa.
- Your doctor will tell you how much Glatopa to use and when to use it.
- Glatopa is given by injection under your skin (subcutaneously).
- Use Glatopa exactly as your doctor tells you to use it.
- Since every body type is different, talk with your doctor about the injection areas that are best for you.
- You should receive your first dose of Glatopa with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will show you how to give your Glatopa injections.

What are the possible side effects of Glatopa?

Glatopa may cause serious side effects, including:

- **Post-Injection Reactions.** Serious side effects may happen right after or within minutes after you inject Glatopa at any time during your course of treatment. Call your doctor right away if you have any of these post-injection reaction symptoms including:
  - redness to your cheeks or other parts of the body (flushing)
  - chest pain
  - fast heart beat
  - anxiety
  - breathing problems or tightness in your throat
  - swelling, rash, hives, or itching

If you have symptoms of a post-injection reaction, do not give yourself more injections until a doctor tells you to.

- **Chest Pain.** You can have chest pain as part of a 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 Glatopa. Call your doctor right away if you have chest pain while using Glatopa.
- **Damage to your skin.** Damage to the fatty layer under your skin ("lipoatrophy") and, rarely, death of your skin tissue ("necrosis") can happen when you use Glatopa. Damage to the fatty layer 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 doctor's instructions for how to use Glatopa
  - choosing a different injection area each time you use Glatopa.

See Step 4 in the Instructions for Use, "Choose your injection area".

The most common side effects of Glatopa include:

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

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

These are not all the possible side effects of Glatopa. For more information, ask your doctor 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 Glatopa?

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

Keep Glatopa and all medicines out of the reach of children.

General information about the safe and effective use of Glatopa.

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

This Patient Information leaflet summarizes the most important information about Glatopa. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Glatopa that is written for health professionals.

For more information, go to www.glatopa.com or call Sandoz at Glatopa Connect 1-855-452-8672.

What are the ingredients in Glatopa?

Active ingredient: glatiramer acetate

Inactive ingredient: mannitol

INSTRUCTIONS FOR USE
Glatopa™ (Glatiramer Acetate Injection)
for Subcutaneous Use

For subcutaneous injection only.

Do not inject Glatopa in your veins (intravenously).

Do not re-use your Glatopa prefilled syringes.

Do not share your Glatopa prefilled syringes with another person. You may give another person an infection or get an infection from them.

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

Glatopa comes as a 20 mg Prefilled Syringe with needle attached.

Instructions for Using Your Glatopa 20 mg Prefilled Syringe dose:

- Glatopa 20 mg is injected 1 time each day in the fatty layer under your skin (subcutaneously).
- Each Glatopa 20 mg prefilled syringe is for single use (1 time use) only.
- The Glatopa 20 mg dose is packaged in boxes of 30 prefilled syringes with needles attached. Glatopa 20 mg prefilled syringes have white plungers.

How do I inject Glatopa?

Step 1: Gather the supplies you will need to inject Glatopa. See Figure A.

- 1 blister pack with a Glatopa prefilled syringe with needle attached
- Alcohol wipe
- 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 needles and syringes".

Figure A

Step 2: Remove only 1 blister pack from the Glatopa prefilled 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.

Step 3: Look closely at your Glatopa prefilled 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 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 doctor 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 Glatopa dose, choose a different injection area from 1 of the areas shown above. See Figure C.
- Do not inject the medicine 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 sites for your injection 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.

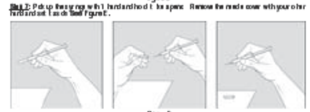


Figure E

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 in) into your skin. See Figure G.

Figure G

- When the needle is all the way in, slowly release the fold of skin. See Figure H.

Figure H

Step 10: Give your Glatopa 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

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

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