PDR®

62 EDITION

2008

PHYSICIANS' DESK REFERENCE®

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nce ≥ 2% in AZILECT 1 mg group and ically more frequent than in placebo group

of the more common adverse events seemed dose- including weight loss, postural hypotension, and ith.

vents of potential clinical importance reported in by 1% or more of patients treated with rasagiline ay as adjunct to levodopa therapy, and at least as t as in the placebo group, in descending order of fre- include: skin carcinoma, anemia, albuminuria, ar- thritis, bursitis, cerebrovascular accident, confu- sphagia, epistaxis, leg cramps, pruritus, skin ulcer. vere no significant differences in the safety profile n age or gender.

dverse Events Observed During All Phase 2/3 Clin- ls

ine was administered to approximately 1361 pa- uring all PD phase 2/3 clinical trials. About 283 pa- eceived rasagiline for at least one year, approxi- 410 patients received rasagiline for at least two 16 patients received rasagiline for at least 3 years, 5 patients received rasagiline for more than 3 years, me patients treated for more than 5 years. The long- fety profile was similar to that observed with shorter n exposure.

quencies listed below represent the proportion of the ndividuals exposed to rasagiline who experienced of the type cited.

ts that occurred at least twice (or once for serious or ally serious events), except those already listed trivial events, terms too vague to be meaningful, ad- vents with no plausible relation to treatment, and that would be expected in patients of the age studied ported without regard to determination of a causal ship to rasagiline.

are further classified within body system categories amerated in order of decreasing frequency using the those occurring in fewer than 1/1000 patients.

Body as a whole: *Frequent:* asthenia *Infrequent:* chills, face edema, flank pain, photosensitivity reaction

Cardiovascular system: *Frequent:* bundle branch block *Infrequent:* deep thrombophlebitis, heart failure, migraine, myocardial infarct, phlebitis, ventricular tachycardia *Rare:* arterial thrombosis, atrial arrhythmia, AV block complete, AV block second degree, bigeminy, cerebral hemorrhage, cerebral ischemia, ventricular fibrillation

Digestive system: *Frequent:* gastrointestinal hemorrhage *Infrequent:* colitis, esophageal ulcer, esophagitis, fecal incontinence, intestinal obstruction, mouth ulceration, stomach ulcer, stomatitis, tongue edema *Rare:* hematemesis, hemorrhagic gastritis, intestinal perforation, intestinal stenosis, jaundice, large intestine perforation, megacolon, melena

Hemic and Lymphatic system: *Infrequent:* macrocytic anemia *Rare:* purpura, thrombocythemia

Metabolic and Nutritional disorders: *Infrequent:* hypocalcemia

Musculoskeletal system: *Infrequent:* bone necrosis, muscle atrophy *Rare:* arthrosis

Nervous system: *Frequent:* abnormal gait, anxiety, hyperkinesia, hypertonia, neuropathy, tremor *Infrequent:* agitation, aphasia, circumoral paresthesia, convulsion, delusions, dementia, dysarthria, dysautonomia, dysesthesia, emotional lability, facial paralysis, foot drop, hemiplegia, hypesthesia, incoordination, manic reaction, myoclonus, neuritis, neurosis, paranoid reaction, personality disorder, psychosis, wrist drop *Rare:* apathy, delirium, hostility, manic depressive reaction, myelitis, neuralgia, psychotic depression, stupor

Respiratory system: *Frequent:* cough increased *Infrequent:* apnea, emphysema, laryngismus, pleural effusion, pneumothorax *Rare:* interstitial pneumonia, larynx edema, lung fibrosis

Skin and Appendages: *Infrequent:* eczema, urticaria *Rare:* exfoliative dermatitis, leukoderma

Special senses: *Infrequent:* blepharitis, deafness, diplopia, eye hemorrhage, eye pain, glaucoma, keratitis, ptosis, retinal degeneration, taste perversion, visual field defect *Rare:* blindness, parosmia, photophobia, retinal detachment, retinal hemorrhage, strabismus, taste loss, vestibular disorder

Urogenital system: *Frequent:* hematuria, urinary incontinence *Infrequent:* acute kidney failure, dysmenorrhea, dysuria, kidney calculus, nocturia, polyuria, scrotal edema, sexual function abnormal, urinary retention, urination impaired, vaginal hemorrhage, vaginal moniliasis, vaginitis *Rare:* abnormal ejaculation, amenorrhea, anuria, epididymitis, gynecomastia, hydroureter, leukorrhea, priapism

DRUG ABUSE AND DEPENDENCE

AZILECT is not a controlled substance.

Studies conducted in mice and rats did not reveal any potential for drug abuse and dependence. Clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence; however, systematic studies in humans designed to evaluate these effects have not been performed.

OVERDOSE

No cases of AZILECT overdose were reported in clinical trials.

Rasagiline was well tolerated in a single-dose study in healthy volunteers receiving 20 mg/day and in a ten-day study in healthy volunteers receiving 10 mg/day. Adverse events were mild or moderate. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg of rasagiline there were three reports of cardiovascular side effects (including hypertension and postural hypotension) which resolved following treatment discontinuation.

Symptoms of overdosage, although not observed with rasagiline during clinical development, may resemble those observed with non-selective MAO inhibitors.

Although no cases of overdose have been observed with rasagiline, the following description of presenting symptoms and clinical course is based upon overdose descriptions of non-selective MAO inhibitors.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

selective MAO inhibitors is symptomatic and supportive. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

A poison control center should be called for the most current treatment guidelines.

DOSAGE AND ADMINISTRATION

Tyramine-rich foods, beverages, or dietary supplements and amines (from over-the-counter cough/cold medications) should be avoided to prevent a possible hypertensive crisis/"cheese reaction" during rasagiline treatment. (See WARNINGS, *Need for Restriction of Dietary Tyramine and Amines Contained in Medications*).

Monotherapy

The recommended AZILECT dose for the treatment of Parkinson's disease patients is 1 mg administered once daily.

Adjunctive Therapy

The recommended initial dose is 0.5 mg administered once daily. If a sufficient clinical response is not achieved, the dose may be increased to 1 mg administered once daily.

Change of Levodopa Dose in Adjunct Therapy: When AZILECT is used in combination with levodopa, a reduction of the levodopa dosage may be considered based upon individual response. During the controlled trials of AZILECT as adjunct therapy to levodopa, levodopa dosage was reduced in some patients. In clinical studies, dosage reduction of levodopa was allowed within the first 6 weeks if dopaminergic side effects, including dyskinesia and hallucinations, emerged. In Study 1, levodopa dosage reduction occurred in 8% of patients in the placebo group and in 16% and 17% of patients in the 0.5 mg/day and 1 mg/day rasagiline groups, respectively. In those patients who had levodopa dosage reduced, the dose was reduced on average by about 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In Study 2, levodopa dosage reduction occurred in 6% of patients in the placebo group and in 9% in the rasagiline 1 mg/day group. In patients who had their levodopa dosage reduced, the dose was reduced on average by about 13% and 11% in the placebo and the rasagiline groups, respectively.

Patients with Hepatic Impairment: AZILECT plasma concentrations will increase in patients with hepatic impairment. Patients with mild hepatic impairment should use 0.5 mg daily of AZILECT. AZILECT should not be used in patients with moderate or severe hepatic impairment. (See **CLINICAL PHARMACOLOGY, Special Populations,** *Hepatic Insufficiency* and **WARNINGS,** *Hepatic Insufficiency*).

Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations are expected to double in patients taking concomitant ciprofloxacin and other CYP1A2 inhibitors. Therefore, patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should use 0.5 mg daily of AZILECT. (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions,** *Ciprofloxacin and Effect of Other Drugs on the Metabolism of AZILECT*; and **WARNINGS,** *Ciprofloxacin and Other CYP1A2 Inhibitors*).

HOW SUPPLIED

AZILECT 0.5 mg Tablets:
White to off-white, round, flat, beveled tablets, debossed with "GIL 0.5" on one side and plain on the other side. Supplied as bottles of 30 tablets (NDC 68546-142-56).

AZILECT 1 mg Tablets:
White to off-white, round, flat, beveled tablets, debossed with "GIL 1" on one side and plain on the other side. Supplied as bottles of 30 tablets (NDC 68546-229-56).

Storage: Store at 25°C (77°F) with excursions permitted to 15°–30°C (59°–86°F).

Rx only

Manufactured by:
Teva Pharmaceutical Industries Ltd.
Kfar Saba 44102, Israel

Marketed by:
Teva Neuroscience, Inc.
Kansas City, MO 64131

Revision 05/06

Shown in Product Identification Guide, page 334

COPAXONE®

(glatiramer acetate injection)

℞

DESCRIPTION

COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, the active ingredient of COPAXONE®, 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.

Continued on next page

Copaxone—Cont.

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

COPAXONE® Injection is a clear, colorless to slightly yellow, sterile, non-pyrogenic solution for subcutaneous injection. Each 1.0 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of COPAXONE® is determined by its ability to block the induction of EAE in mice.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species 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. Results of a limited battery of tests designed to evaluate this risk produced no finding of concern; nevertheless, there is no logical way to absolutely exclude this possibility (see **PRECAUTIONS**).

Pharmacokinetics

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

Clinical Trials

Evidence supporting the effectiveness of glatiramer acetate in decreasing the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RR MS) derives from two placebo-controlled trials, both of which used a glatiramer acetate dose of 20 mg/day. (No other dose or dosing regimen has been studied in placebo-controlled trials of RR MS.)

One trial was performed at a single center. It enrolled 50 patients who were randomized to receive daily doses of either glatiramer acetate, 20 mg subcutaneously, or placebo (glatiramer acetate, n=25; placebo, n=25). Patients were diagnosed with RR MS 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: 1) the frequency of attacks during the trial, and 2) the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 1 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):

[See table 1 above]

The second trial was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (glatiramer acetate, 125; placebo, 126) were enrolled. The primary outcome measure was the Mean 2-Year Re- [illegible] presents the values of this out-

Table 1: Study 1 Efficacy Results

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

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

Table 2: Study 2 Efficacy Results

Outcome	Glatiramer Acetate (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

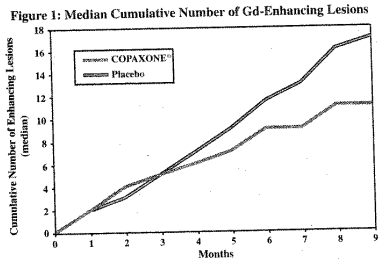
glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during 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 3 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 3: Study 3 MRI Results

Outcome	Glatiramer Acetate (N=119)	Placebo (N=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

The following figure displays the results of the primary outcome on a monthly basis.

Figure 1: Median Cumulative Number of Gd-Enhancing Lesions



p= 0.0030 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups

INDICATIONS AND USAGE

COPAXONE® Injection is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.

CONTRAINDICATIONS

COPAXONE® Injection is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS

The only recommended route of administration of COPAXONE® Injection is the subcutaneous route. COPAXONE® Injection should not be administered by the intravenous route.

Considerations Regarding the Use of a Product Capable of Modifying Immune Responses

Because glatiramer acetate can modify immune response, it could possibly interfere with useful immune functions. For example, treatment with glatiramer acetate might, in theory, 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 does this, but there has as yet been no systematic evaluation of this risk. Because glatiramer acetate 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 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 might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RR MS patients given glatiramer acetate, 20 mg, 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.

Information for Patients

To assure safe and effective use of COPAXONE® Injection, the following information and instructions should be given to patients:

1. Inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Do not stop taking the drug without consulting your physician.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE® Injection. Appropriate instructions for the self-injection of COPAXONE® Injection should be given, including a careful review of the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. They should use a puncture-resistant container for disposal of used needles and syringes. Patients should be [illegible] the safe disposal of full containers according

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

(Glu, Ala, Lys, Tyr)$_x$•$_x$CH$_3$COOH

(C$_5$H$_9$NO$_4$•C$_3$H$_7$NO$_2$•C$_6$H$_{14}$N$_2$O$_2$•C$_9$H$_{11}$NO$_3$)$_x$•$_x$C$_2$H$_4$O$_2$

CAS - 147245-92-9

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One trial was performed at a single center. It enrolled 50 patients who were randomized to receive daily doses of either glatiramer acetate, 20 mg subcutaneously, or placebo (glatiramer acetate, n=25; placebo, n=25). Patients were diagnosed with RR MS 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.

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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: 1) the frequency of attacks during the trial, and 2) the change in the number of attacks compared with the number which occurred during the previous 2 years.

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[See table 1 above]

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

[See table 2 above]

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

A third study was a multi-national study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RR MS (119 on glatiramer acetate and 120 on placebo) 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 3 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

% Relapse-Free Patients	[illegible]	[illegible]	[illegible]
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Pre-Study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

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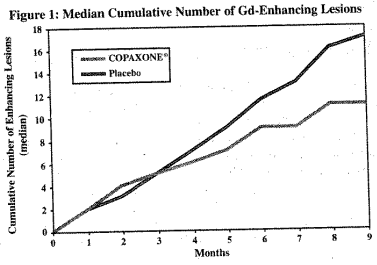

p= 0.0030 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups

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WARNINGS

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PRECAUTIONS

General

Patients should be instructed in self-injection techniques to assure the safe administration of COPAXONE® Injection (see **PRECAUTIONS: Information for Patients** and the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet). Current data indicate that no special caution is required for patients operating an automobile or using complex machinery.

Considerations Regarding the Use of a Product Capable of Modifying Immune Responses

Because glatiramer acetate can modify immune response, it could possibly interfere with useful immune functions. For example, treatment with glatiramer acetate might, in theory, 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 does this, but there has as yet been no systematic evaluation of this risk. Because glatiramer acetate 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 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 might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RR MS patients given glatiramer acetate, 20 mg, 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.

Information for Patients

To assure safe and effective use of COPAXONE® Injection, the following information and instructions should be given to patients:

1. Inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Do not stop taking the drug without consulting your physician.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE® Injection. Appropriate instructions for the self-injection of COPAXONE® Injection should be given, including a careful review of the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. They should use a puncture-resistant container for disposal of used needles and syringes. Patients should be instructed on the safe disposal of full containers according to local laws.

Awareness of Adverse Reactions: Physicians are advised to counsel patients about adverse reactions associated with the use of COPAXONE® Injection (see **ADVERSE REACTIONS** section). In addition, patients should be advised to read the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet and resolve any questions regarding it prior to beginning COPAXONE® Injection therapy.

Laboratory Tests
Data collected during premarketing development do not suggest the need for routine laboratory monitoring.

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

Drug/Laboratory Test Interactions
None are known.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
In a two-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 on a mg/m^2 basis). No increase in systemic neoplasms was observed. In males of the high dose group (60 mg/kg/day), but not in females, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.
In a two-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/m^2 basis). No increase in systemic neoplasms was observed.
Mutagenesis
Glatiramer acetate was not mutagenic in four strains of *Salmonella typhimurium* and two strains of *Escherichia coli* (Ames test) or in the *in vitro* mouse lymphoma assay in L5178Y cells. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes; it was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.
Impairment of Fertility
In a multigeneration reproduction and fertility study in rats, glatiramer acetate at subcutaneous doses of up to 36 mg/kg (18 times the human therapeutic dose on a mg/m^2 basis) had no adverse effects on reproductive parameters.
Pregnancy
Pregnancy Category B. No adverse effects on embryofetal development occurred in reproduction studies in rats and rabbits receiving subcutaneous doses of up to 37.5 mg/kg of glatiramer acetate during the period of organogenesis (18 and 36 times the therapeutic human dose on a mg/m^2 basis, respectively). In a prenatal and postnatal study in which rats received 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.
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, glatiramer acetate should be used during pregnancy only if clearly needed.

Labor and Delivery
In a prenatal and postnatal study, in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery were observed. The relevance of these findings to humans is unknown.

Nursing Mothers
It is not known whether glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE® is administered to a nursing woman.

Pediatric Use
The safety and efficacy of COPAXONE® Injection have not been established in individuals under 18 years of age.

Use in the Elderly
COPAXONE® Injection has not been studied specifically in elderly patients.

Use in Patients with Impaired Renal Function
The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

During premarketing clinical trials approximately 900 individuals received at least one dose of glatiramer acetate.
In controlled clinical trials the most commonly observed adverse experiences associated with the use of glatiramer acetate and not seen at an equivalent frequency among placebo-treated patients were: injection site reactions, vasodilatation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia.
Approximately 8% of the 893 subjects receiving glatiramer acetate discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilatation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness, and tremor.

Immediate Post-Injection Reaction
Approximately 10% of MS patients exposed to glatiramer

Controlled Trials in Patients with Multiple Sclerosis: Incidence of Glatiramer Acetate Adverse Reactions ≥2% and More Frequent than Placebo

Preferred Term	Glatiramer Acetate (N = 201) N	Glatiramer Acetate (N = 201) %	Placebo (N = 206) N	Placebo (N = 206) %
Body as a Whole				
Asthenia	83	41	78	38
Back Pain	33	16	30	15
Bacterial Infection	11	5	9	4
Chest Pain	43	21	22	11
Chills	8	4	2	1
Cyst	5	2	1	0
Face Edema	12	6	2	1
Fever	17	8	15	7
Flu Syndrome	38	19	35	17
Infection	101	50	99	48
Injection Site Erythema	132	66	40	19
Injection Site Hemorrhage	11	5	6	3
Injection Site Induration	26	13	1	0
Injection Site Inflammation	98	49	22	11
Injection Site Mass	54	27	21	10
Injection Site Pain	147	73	78	38
Injection Site Pruritus	80	40	12	6
Injection Site Urticaria	10	5	0	0
Injection Site Welt	22	11	5	2
Neck Pain	16	8	9	4
Pain	56	28	52	25
Cardiovascular System				
Migraine	10	5	5	2
Palpitations	35	17	16	8
Syncope	10	5	5	2
Tachycardia	11	5	8	4
Vasodilatation	55	27	21	10
Digestive System				
Anorexia	17	8	15	7
Diarrhea	25	12	23	11
Gastroenteritis	6	3	2	1
Gastrointestinal Disorder	10	5	8	4
Nausea	44	22	34	17
Vomiting	13	6	8	4
Hemic and Lymphatic System				
Ecchymosis	16	8	13	6
Lymphadenopathy	25	12	12	6
Metabolic and Nutritional				
Edema	5	3	1	0
Peripheral Edema	14	7	8	4
Weight Gain	7	3	0	0
Musculoskeletal System				
Arthralgia	49	24	39	19
Nervous System				
Agitation	8	4	4	2
Anxiety	46	23	40	19
Confusion	5	2	1	0
Foot Drop	6	3	4	2
Hypertonia	44	22	37	18
Nervousness	4	2	2	1
Nystagmus	5	2	2	1
Speech Disorder	5	2	3	1
Tremor	14	7	7	3
Vertigo	12	6	11	5
Respiratory System				
Bronchitis	18	9	12	6
Dyspnea	38	19	15	7
Laryngismus	10	5	7	3
Rhinitis	29	14	27	13
Skin and Appendages				
Erythema	8	4	4	2
Herpes Simplex	8	4	6	3
Pruritus	36	18	26	13
Rash	37	18	30	15
Skin Nodule	4	2	1	0
Sweating	31	15	21	10
Urticaria	9	4	5	2
Special Senses				
Ear Pain	15	7	12	6
Eye Disorder	8	4	1	0
Urogenital System				
Dysmenorrhea	12	6	10	5
Urinary Urgency	20	10	17	8
Vaginal Moniliasis	16	8	9	4

Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.
Whether an immunologic or non-immunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

Chest Pain
Approximately 21% of glatiramer acetate patients in the pre-marketing controlled studies (compared to 11% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes were [illegible] rienced 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.

Incidence in Controlled Clinical Studies: The following table lists treatment-emergent signs and symptoms that occurred in at least 2% of MS patients treated with glatiramer acetate in the pre-marketing placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo. These trials include the first two controlled trials in RR MS patients and a controlled trial in patients with Chronic-Progressive MS. Adverse reactions were usually mild in intensity.

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