**COPAXONE®**
(glatiramer acetate for 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 4,700–11,000 daltons.

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

$$(\text{Glu, Ala, Lys, Tyr})_x \cdot x\text{CH}_3\text{COOH}$$
$$(\text{C}_5\text{H}_9\text{NO}_4 \cdot \text{C}_3\text{H}_7\text{NO}_2 \cdot \text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \cdot \text{C}_9\text{H}_{11}\text{NO}_3)_x \cdot x\text{C}_2\text{H}_4\text{O}_2$$
CAS - 147245-92-9

COPAXONE® is a white to off-white, sterile, lyophilized powder containing 20 mg of glatiramer acetate and 40 mg of mannitol. It is supplied in single-use vials for subcutaneous administration after reconstitution with the diluent supplied (Sterile Water for Injection).

## 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):

**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- | 3.2 | 1.6 | 0.025 |

| Study | | | |
|---|---|---|---|
| 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.

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.

**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 Patients Progression Free | 98/125 (78%) | 95/126 (75%) | 0.48 |
| Mean Change in DSS | -0.05 | +0.21 | 0.023 |

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 result for the primary outcome measures monitored during the trial for the intent-to-treat cohort.

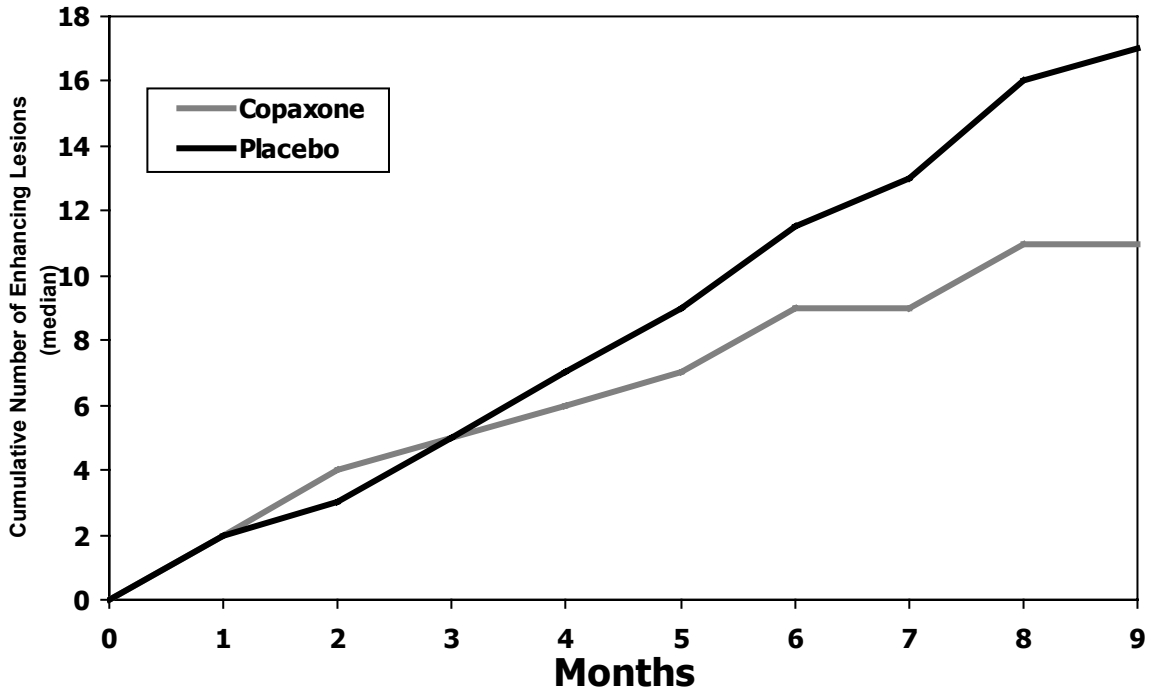
**Table 3: Study 3 MRI Results**

| Outcome | Glatiramer | Placebo | p-value |
|---|---|---|---|

| | Acetate (N=119) | (N=120) | |
|---|---|---|---|
| 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= 0.003 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups.

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**
COPAXONE® 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® should not be administered by the intravenous route.

**PRECAUTIONS**
**General**
Patients should be instructed in self-injection techniques to assure the safe administration of COPAXONE® (see **PRECAUTIONS: Information for Patients** and the **COPAXONE® PATIENT INFORMATION** Booklet). 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®, 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®. Appropriate instructions for the reconstitution and self-injection of COPAXONE® should be given, including a careful review of the **COPAXONE® PATIENT INFORMATION** Booklet. 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® (see **ADVERSE REACTIONS** section). In addition, patients should be advised to read the **COPAXONE® PATIENT INFORMATION** Booklet and resolve any questions regarding it prior to beginning COPAXONE® therapy.

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

**Drug Interactions**
Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE ® with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE® 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® have not been established in individuals under 18 years of age.

**Use in the Elderly**
COPAXONE® 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 acetate in premarketing studies experienced a constellation of symptoms immediately after injection that included flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In clinical trials, the symptoms were generally transient and self-limited and did not require specific treatment. 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. 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 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 of glatiramer acetate was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. There has been only one episode of chest pain during which a full EKG was performed; that EKG showed no evidence of ischemia. 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.

***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.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis on which to estimate the relative contribution of drug and nondrug factors to the adverse reaction incidences in the population studied.

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

| | Glatiramer Acetate (N = 201) | | Placebo (N = 206) | |
|---|---|---|---|---|
| **Preferred Term** | **N** | **%** | **N** | **%** |
| **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 |

| | Glatiramer Acetate (N = 201) | | Placebo (N = 206) | |
|---|---|---|---|---|
| **Preferred Term** | **N** | **%** | **N** | **%** |
| 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 |

| | Glatiramer Acetate (N = 201) | | Placebo (N = 206) | |
|---|---|---|---|---|
| **Preferred Term** | **N** | **%** | **N** | **%** |
| 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 |

| | Glatiramer Acetate (N = 201) | | Placebo (N = 206) | |
|---|---|---|---|---|
| **Preferred Term** | **N** | **%** | **N** | **%** |
| **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 |

Other events which occurred in at least 2% of glatiramer acetate patients but were present at equal or greater rates in the placebo group included:

*Body as a Whole*: Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis, neck rigidity, and malaise.

*Digestive System*: Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth.

*Musculoskeletal:* Myasthenia and myalgia.

*Nervous System:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign,

abnormal thinking, twitching, euphoria, and sleep disorder.

*Respiratory System*: Pharyngitis, sinusitis, increased cough and laryngitis.

*Skin and Appendages:* Acne, alopecia, and nail disorder.

*Special Senses*: Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness.

*Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse reactions occurring in the controlled clinical trials 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 percentage reflects the racial composition of the MS population. In addition, the vast majority of patients treated with COPAXONE® 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.

Laboratory analyses were performed on all patients participating in the clinical program for glatiramer acetate. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both glatiramer acetate and placebo groups in blinded clinical trials. No patient receiving glatiramer acetate withdrew from any trial because of abnormal laboratory findings.

**Other Adverse Events Observed During Clinical Trials**
Glatiramer acetate was administered to 979 individuals during premarketing clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators, using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into standardized categories using COSTART dictionary terminology. All reported events occurring at least twice and potentially important events occurring once are listed below, except those already listed in the previous table, those too general to be informative, trivial events, and other reactions which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Additional adverse reactions reported during the post-marketing period are included.

Events are further classified within body system categories and listed in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring in less than 1/1000 patients.

*Body as a Whole:*

- *Frequent:* Injection site edema, injection site atrophy, abscess, injection site hypersensitivity.
- *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

*Cardiovascular:*

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

*Digestive:*

- *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

*Endocrine:*

- *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism.

*Gastrointestinal:*

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

*Hemic and Lymphatic:*

- *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

*Metabolic and Nutritional:*

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

*Musculoskeletal:*

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

*Nervous:*

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

*Respiratory:*

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

*Skin and Appendages:*

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

rash.

*Special Senses*:

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

*Urogenital:*

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

**Postmarketing Clinical Experience**

Postmarketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE ®(glatiramer acetate) not mentioned above that have been received since market introduction and that may have or not have causal relationship to the drug include the following:

Body as a Whole: sepsis; LE 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; hay fever

Special Senses: glaucoma; blindness; visual field defect

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

**DRUG ABUSE AND DEPENDENCE**

No evidence or experience suggests that abuse or dependence occurs with COPAXONE® therapy; however, the risk of dependence has not been systematically evaluated.

## DOSAGE AND ADMINISTRATION

The recommended dose of COPAXONE® for the treatment of RR MS is 20 mg/day injected subcutaneously.

### Instructions for Use

To reconstitute lyophilized COPAXONE® for injection, use a sterile syringe and Mixject Vial Adapter to transfer the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter.

Soon after reconstitution, withdraw the solution into the syringe. Replace the Mixject Vial Adapter with a 27 gauge, ½" needle and inject the solution subcutaneously. Sites for self-injection include arms, abdomen, hips, and thighs. A vial is suitable for single use only; unused portions should be discarded. (See the **COPAXONE® PATIENT INFORMATION** Booklet for **INSTRUCTIONS FOR INJECTING COPAXONE®**.)

## HOW SUPPLIED

COPAXONE® is supplied as a sterile, lyophilized material containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The drug is packaged in a USP Type 1 amber glass, single-use 2 mL vial. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) is included for each vial of drug.

The recommended storage condition for the unreconstituted product is refrigeration (2°C to 8°C / 36°F to 46°F). However, excursions from recommended storage conditions to room temperature conditions (15° to 30°C / 59° to 86° F) for up to one week have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided.

The diluent may be stored at room temperature.

COPAXONE® contains no preservative. It should be used immediately after reconstitution.

COPAXONE® is available in packs of 32 amber vials of sterile, lyophilized material for subcutaneous injection (NDC 0088–1150–03). The diluent for COPAXONE® is supplied in packs of 32 clear vials.

**Rx only.**

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**COPAXONE® (glatiramer acetate for injection)**

**PATIENT INFORMATION**

This booklet tells patients about COPAXONE® [coe PAX own] (glatiramer acetate for injection, formerly known as copolymer-1) and how to use COPAXONE® with the Mixject Vial Adapter. COPAXONE ® treats Relapsing-Remitting Multiple Sclerosis.

- Before you begin using COPAXONE®, make sure you understand all the information in this booklet about its possible benefits and risks. If you do not understand some of the information in this booklet, contact your doctor for help.

- COPAXONE® is not recommended for use in pregnancy. Therefore, tell your doctor if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medicine.

- Tell your doctor if you are nursing. We do not know if COPAXONE® is passed through the milk to the baby.

- Do not change the dose or dosing schedule without talking with your doctor.

- Do not stop taking the drug without talking with your doctor.

- The most common side effects of COPAXONE® are redness, pain, swelling, itching, or a lump at the site of injection. These reactions are usually mild and seldom require professional treatment. Be sure to tell your doctor about any side effects.

- Some patients report a short-term reaction right after injecting COPAXONE®. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes of an injection, last about 15 minutes, and go away by themselves without further problems.

- After you inject COPAXONE®, call your doctor right away if you develop hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, severe pain at the injection site or other uncomfortable changes in your general health. Make no more injections until your doctor tells you to begin again.

- If symptoms become severe, call the appropriate emergency phone number in your area. Make no more injections until your physician tells you to begin again.

- Your prescription includes two types of vials (small bottles): brown vials containing COPAXONE® and clear vials of sterile water (diluent).

- Store the brown vials of COPAXONE® in the refrigerator as soon as you bring them home.

- Store the clear vials labeled “Sterile Water for Injection” (diluent) at room temperature.

▲ Keep COPAXONE® out of the reach of children.

**INSTRUCTIONS FOR MIXING (RECONSTITUTING) AND INJECTING COPAXONE®**

**Read all of the following instructions before you reconstitute and inject COPAXONE®.**

**Are you left-handed?**
Drawings in this leaflet show patients who are right-handed. If you are left-handed, do what comes naturally. You will probably find it most comfortable to hold the syringe in your left hand, and hold the vial between thumb and forefinger of your right hand.

**Safety Tips:**
- Use only the supplies provided with your COPAXONE® kit.
- Wash your hands well before beginning. Do not touch your hair or skin after washing.
- Keep the items sterile. Do not touch the needle, the piercing spike of the vial adapter, or the tops of the cleaned vials.
- Make sure none of the items in your kit have been opened.
- Never mix COPAXONE® with tap water.
- Do not reuse opened materials. Throw away unused portions of the COPAXONE® and sterile water (diluent).
- Throw away used syringes in a proper container. Ask your doctor if you do not know how to do this.
- Contact your doctor if you have questions.

There are 4 basic steps for injecting COPAXONE®:
1. Gathering the materials.
2. Mixing COPAXONE® and sterile water (reconstitution). This involves adding sterile water to the dry COPAXONE®.
3. Preparing the injection syringe.
4. Giving yourself the injection.

***STEP 1. Gathering the Materials***

1) Put the items you will need on a clean flat surface in a well-lighted area. The items and where you will find them are listed in the table below.

| The item | Supplied in |
|---|---|
| • 1 brown vial of COPAXONE® | COPAXONE® drug product package |

| | |
|---|---|
| • 1 clear vial of Sterile Water For Injection, USP (diluent)<br>• 1 syringe (3cc)*<br>• 1 injection needle (27 gauge, ½")<br>• 1 Mixject Vial Adapter<br>• 3 alcohol wipes (preps or swabs) | Self Injection Administration Package |
| • 1 Dry cotton ball | Not supplied |

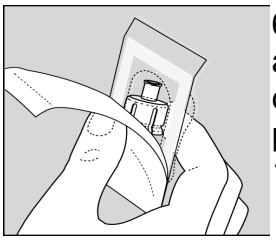
**One cubic centimeter (cc) represents the same amount as one-milliliter (mL). Use the scale that is on the syringe.*

2) To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.

3) Remove the 3-cc syringe from its protective wrapper by peeling back the paper label.

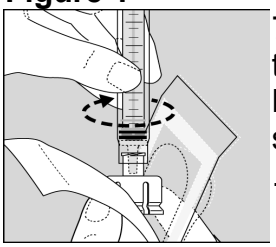
4) Place the syringe on the clean surface.

5) Remove the injection needle from its protective wrapper by peeling back the paper label. Place the injection needle on the clean surface. Do not remove the plastic needle shield yet.



6) Open the Mixject Vial Adapter package by peeling back the paper and the plastic. Peel back only half-way. Do not open the package completely. Hold the wide side of the Mixject Vial Adapter through the package so you will not get germs on the Mixject Vial Adapter (Figure 1).

**Figure 1**



7) Remove the plastic tip cap from the 3-cc syringe. Without removing the Mixject Vial Adapter from its package, connect the syringe to the Mixject Vial Adapter by twisting the syringe (rotation). Make sure that the syringe is tightly attached to the Mixject Vial Adapter (Figure 2).
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**Figure 2**

8) Place the package containing the Mixject Vial Adapter with the attached syringe on the clean surface.

9) Remove the plastic cover from the clear sterile water (diluent) vial. Use an alcohol wipe to clean the rubber top. Do the same for the brown COPAXONE® vial with a fresh alcohol wipe. **Do not touch the rubber tops after they are cleaned**. Let both rubber tops dry for a few seconds.

**Important:**

- **To avoid spreading germs, do not touch any of the following:**

the needle
the piercing spike of the Mixject Vial Adapter
the top of either vial

- Use only the Sterile Water for Injection, USP (diluent) from the Self Injection Administration Package when mixing (reconstituting) COPAXONE®.

- If you have questions, contact your doctor or nurse before going further in reconstituting and injecting COPAXONE®. You may also contact **Shared Solutions**™ by calling 1-800-887-8100.

***STEP 2. Mixing COPAXONE® and Diluent (Reconstitution)***

1) Hold the syringe with one hand. Remove the Mixject Vial Adapter from its paper wrapper. Do not touch the Mixject Vial Adapter. Pull the plunger back to the 1.1 cc line to draw air into the syringe (see insert, Figure 5).

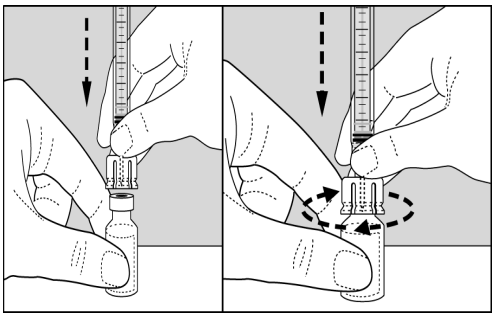


**Figure 3**

2) With 2 fingers of one hand, hold the clear diluent vial on a stable surface like a table or kitchen counter. Hold the connection between the Mixject Vial Adapter and the syringe with the other hand. Insert the piercing spike of the Mixject Vial Adapter all the way in through the rubber top of the clear sterile water vial, using a rotating and pushing movement. (Figure 3)

3) Push the plunger of the syringe all the way in.

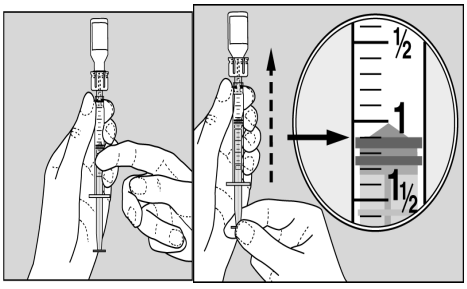
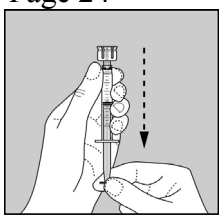



Figure 4 Figure 5

4) Turn the connected syringe and vial upside down and pull the plunger out until all the diluent is drawn into the syringe. If there are air bubbles inside the syringe, tap the side of the syringe to make them float to the top (Figure 4). Push the plunger in until the top of the black plunger ring is in line with the bottom of the 1.1 cc line on the syringe (as shown by the arrow in Figure 5).

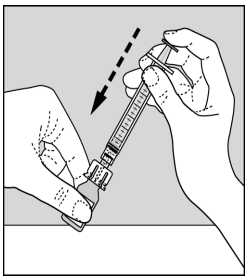
5) Holding the syringe containing the sterile water (diluent) and the Mixject Vial Adapter, remove the clear vial. Throw it away by putting it in a safe hard-walled container, such as an empty liquid laundry detergent container.



6) Take the 3 cc syringe containing the sterile water (diluent) and pull the plunger back to the 2.0 cc line to draw air into the syringe (Figure 6).

**Figure 6**

7) Hold the brown COPAXONE® vial on a stable surface with 2 fingers of one hand. Hold the connected Mixject Vial Adapter and the syringe with the other hand. Insert the piercing spike of the Mixject Vial Adapter all the way in through the rubber top of the COPAXONE® vial, using a rotating and pushing movement.



8) Slowly inject all the sterile water and air into the vial by pressing the plunger all the way in. To avoid bubbles, do not inject the sterile water directly onto the COPAXONE®. Instead, inject the sterile water so it runs down the inside of the vial glass. You can do this if you keep the vial tilted while injecting (Figure 7).

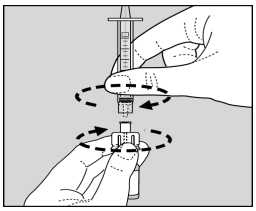
**Figure 7**

9) **Do not shake the vial.** Gently swirl the COPAXONE® vial until all the medicine dissolves and the solution looks clear. The COPAXONE® is now mixed (reconstituted). Keeping the vial, adapter, and syringe connected, leave the vial at room temperature for about 5 minutes.

10) Look for particles in the solution. Do not use the solution if there are any particles in it.

***STEP 3: Preparing the Injection Syringe***

1) Hold the syringe with one hand and make sure that the plunger is pressed all the way in. Turn the vial upside down. To give the full dose of COPAXONE®, withdraw all of the solution into the syringe and Mixject Vial Adapter by slowly pulling the plunger out. This amount will be about 1.1 cc. Again, if there are air bubbles inside the syringe, tap the side of the syringe to make them float to the top. Inject any air back into the vial by pushing the plunger in gently.



2) Keep the brown vial of COPAXONE® and the Mixject Vial Adapter connected to each other. Disconnect them from the syringe by turning them together (rotation) (Figure 8). Throw away the COPAXONE® vial and the Mixject Vial Adapter by putting them in a safe hard-walled container.

**Figure 8**

3) When you connect the injection needle (27 gauge, ½") to the syringe, keep the plastic cover on the needle. Make sure that the needle is tightly placed in its proper position. The syringe is now ready to use.

4) Place the ready-to-use syringe on the clean surface.

***STEP 4: Giving Yourself the Injection***

Before you begin the procedure to self-inject the COPAXONE®:

- **Decide where you will inject yourself.** There are seven injection sites on your body, and **you should not use any site more than once each week**. Marking a calendar each day will help you keep track of the sites you have used (Figure 9).

- **Be consistent.** Give yourself the injection at the same time each day. Choose a time when you feel strongest.

- **Have a friend or relative with you if you need help.** You may have had a friend attend the injection training session as your assistant. Especially when you first start giving yourself injections, your assistant should be with you.

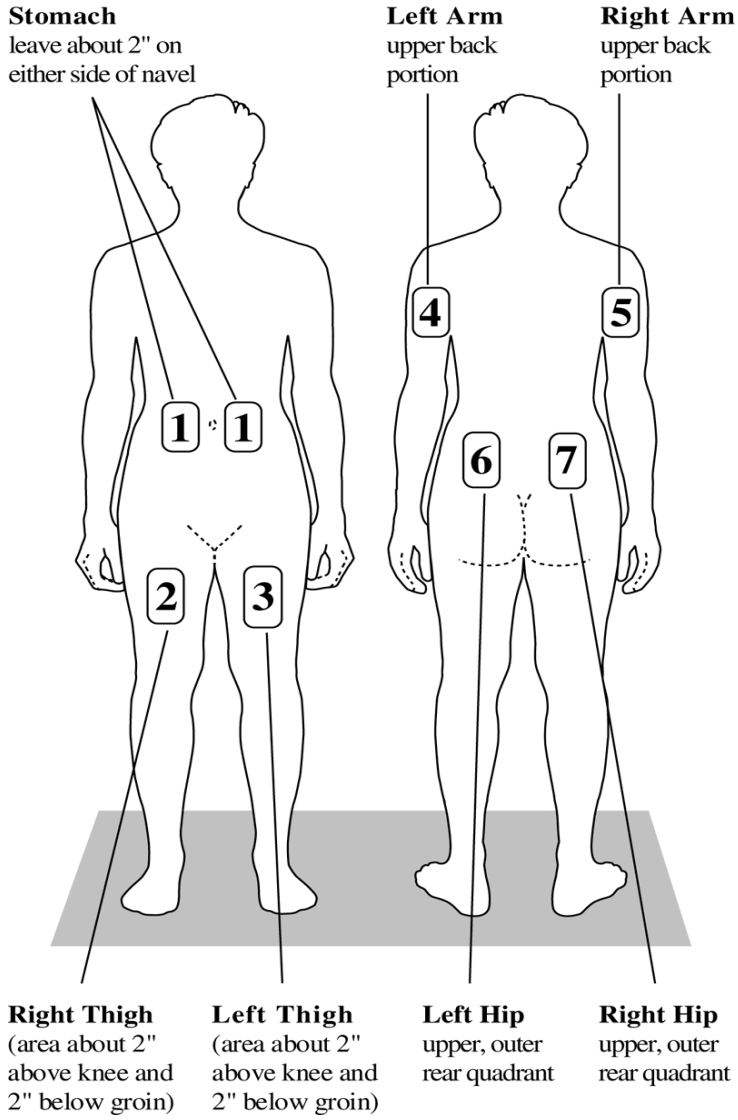



**Figure 9**

1) Clean the injection site with a fresh alcohol wipe. Let the site dry.

2) Pick up the 3-cc syringe you already filled with COPAXONE® as you would pick up a pencil, using the hand you write with. Remove the plastic cover from the needle.

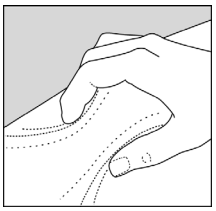


**Figure 10**

3) For sites that are **not** on the back of your arms, pinch about a 2-inch fold of skin between your thumb and index finger of your other hand. (Figure 10).

4) Holding the syringe straight up and down insert the needle into the 2-inch fold of skin. It may help to steady your hand by resting the heel of your hand against your body.

**How do I reach the upper back of my arms?**
For the 2 injection sites on the upper back of the arms, it is not possible to pinch 2 inches of skin with one hand and inject yourself with the other hand. Ask your nurse for instructions on how to use these sites.

5) When the needle is all the way in, release the fold of skin.

6) Inject the medicine by holding the syringe steady while pushing down on the plunger. The injection should take just a few seconds (Figure 11).

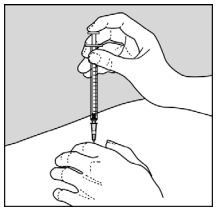


**Figure 11**

7) Pull the needle straight out.

8) Press a dry cotton ball on the injection site for a few seconds. Do not rub or massage the site.

9) Put the plastic cover back on the needle.

10) Throw away the needle, syringe, Mixject Vial Adapter, and the used vials in a safe, hard-walled container, according to your physician's instructions and the laws of your state.

**What is the proper use of needles and syringes?**
Needles, syringes, and vials should be used for only one injection each. Place all used syringes, needles, and vials in a hard-walled plastic container, such as an empty liquid laundry detergent container. Keep the cover of this container tight and out of the reach of children. When the container is full, check with your doctor or nurse about proper disposal, as laws vary from state to state.

**How should COPAXONE® and the sterile water (diluent) be stored?**
Store the brown vials of sterile, lyophilized material for subcutaneous injection COPAXONE® in a refrigerator (36-46° F / 2-8° C). If you cannot have refrigerator storage, COPAXONE® can be stored at room temperature (59-86°F / 15-30°C) for up to one week. Do not store COPAXONE® at room temperature for longer than one week. Avoid exposure to higher temperatures or very bright light.

The clear vials of sterile water (diluent) may be stored at room temperature.

**What is the shelf-life of COPAXONE®?**
Do not use COPAXONE® after the expiration date (EXP) printed on the vial label.

COPAXONE® does not contain preservatives. Therefore, it should be used right away after you reconstitute (mix) it. If you cannot use it right away after reconstitution, throw it away.

Manufactured For:
**TEVA Neuroscience LLC**
Kansas City, MO 64134

Manufactured By:
**Ben Venue Laboratories**
Bedford, OH 44146
or
**TEVA Pharmaceutical Industries, Ltd.**
Kfar-Saba, 44102, Israel

Rev.