1. Composition

Each syringe (1 ml) contains:

Active Ingredient
Glatiramer acetate (Copolymer-1)  20 mg or 40 mg

Other Ingredients
Mannitol, water for injection.

2. Mechanism of Action

Glatiramer acetate (Copolymer-1), the active ingredient of Copaxone®, consists of
the acetate salts of synthetic polypeptides, containing 4 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 (copolymer-1) is 5000-9000 daltons.

Glatiramer acetate (copolymer-1) is an immunomodulator which modifies myelin-
specific autoimmune responses.

The mechanism by which glatiramer acetate exerts its effects in patients with
multiple sclerosis (MS) is unknown.

Glatiramer acetate (copolymer-1) is thought to act however, by modifying immune
processes that are currently held to be responsible for the pathogenesis of MS. This
view of glatiramer acetate derives from knowledge that it reduces the incidence and
severity of experimental allergic encephalomyelitis (EAE)- a condition induced in
several animal species through immunization against CNS-derived material
containing myelin and often used as an experimental animal model of MS.

Because glatiramer acetate can modify immune function, concerns exist about its
potential to alter naturally occurring immune responses. Results of a limited battery of
tests designed to evaluate the risk produced no finding of concern; nevertheless,
there is no logical way to absolutely exclude this possibility (See Precautions).

3. Pharmacokinetics

Pharmacokinetic studies in humans have not been performed. It is assumed,
however, based in part on the results of animal studies, that a substantial fraction of
subcutaneous injection of glatiramer acetate is hydrolyzed locally. Some fraction of
injected material is presumed to enter the lymphatic circulation, enabling it to reach
regional lymph nodes and some may enter the systemic circulation intact.

4. Clinical Studies

4.1 Relapsing-Remitting Multiple Sclerosis (RRMS)

Evidence supporting the effectiveness of glatiramer acetate in decreasing the
frequency of relapses in patients with relapsing-remitting multiple sclerosis (RRMS)
derives from two placebo controlled trials, both of which used a glatiramer acetate
dose of 20 mg/day. (No other dose has been studied in placebo controlled trials of
relapsing- remitting multiple sclerosis):

Study 1

This trial was performed at a single center. It enrolled 50 patients (glatiramer
acetate: 25 patients, placebo: 25 patients) who were randomized to receive daily
doses of glatiramer acetate, 20 mg subcutaneously, or placebo. Patients were
diagnosed with RRMS by standard criteria, and had at least 2 exacerbations during
the 2 years immediately preceding enrollment.
Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Expanded Disability Scale Score (EDSS), 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 seen every 3 months for a period of 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g. the persistence of the lesion for at least 48 hours).

The protocol specified primary outcome measure was the 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 number of attacks compared to the rate of attacks in the previous 2 years.

The following table presents the results of analyses of the three outcomes described above, as well as several protocol-specified secondary measures. These analyses 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>
<thead>
<tr>
<th>Outcome</th>
<th>Glatiramer Acetate (N=25)</th>
<th>Placebo (N=25)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Relapse free</td>
<td>14/25 (56%)</td>
<td>7/25 (28%)</td>
<td>0.085</td>
</tr>
<tr>
<td>Mean Relapse Frequency</td>
<td>0.6/2 years</td>
<td>2.4/2 years</td>
<td>0.005</td>
</tr>
<tr>
<td>Change in Relapse Rate</td>
<td>3.2</td>
<td>1.6</td>
<td>0.025</td>
</tr>
<tr>
<td>Medium Time to First Relapse (days)</td>
<td>&gt;700</td>
<td>150</td>
<td>0.03</td>
</tr>
<tr>
<td>% Progression-Free*</td>
<td>20/25 (80%)</td>
<td>13/25 (52%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months

**Study 2**

The second trial was a multicenter trial of design similar to the first study, and was performed in 11 US centers. A total of 251 patients (glatiramer acetate: 125 patients; placebo: 126 patients) were enrolled. The primary outcome measure was the mean 2-year relapse rate. The table below presents the results of the analysis of this outcome for the intent-to-treat population, as well as other secondary measures:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Glatiramer Acetate (N=125)</th>
<th>Placebo (N=126)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Relapse Rate</td>
<td>1.19/2 years</td>
<td>1.68/2 years</td>
<td>0.055</td>
</tr>
<tr>
<td>% Relapse Free</td>
<td>42/125 (34%)</td>
<td>34/126 (27%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Medium Time to First Relapse (days)</td>
<td>287</td>
<td>198</td>
<td>0.23</td>
</tr>
<tr>
<td>% of Patients Progression-Free</td>
<td>98/125 (78%)</td>
<td>95/126 (75%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Mean Change in EDSS</td>
<td>-0.05</td>
<td>+0.21</td>
<td>0.023</td>
</tr>
</tbody>
</table>

In both studies glatiramer acetate exhibited a clear beneficial effect on relapse rate, and it is on this basis that glatiramer acetate is considered effective.
Study 3

A third study 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: n=119; 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. The table below summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

**Study 3 MRI Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Glatiramer Acetate (N=119)</th>
<th>Placebo (N=120)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medians of the Cumulative</td>
<td>11</td>
<td>17</td>
<td>0.0030</td>
</tr>
<tr>
<td>Number of T1 Gd-Enhancing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Median Cumulative Number of Gd-Enhancing Lesions**

![Median Cumulative Number of Gd-Enhancing Lesions](image)

p= 0.0030 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups
4.2 Single Clinical Event Suggestive of MS

One placebo-controlled study involving 481 patients (Copaxone n=243, placebo n=238) was performed in patients with a well-defined, single, unifocal neurological manifestation and MRI features highly suggestive of MS (at least two cerebral lesions on the T₂-weighted MRI above 6 mm diameter). Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded. The placebo-controlled period was followed by an open label treatment: Patients who either presented with MS symptoms or were asymptomatic for three years, whichever came first, were assigned to active drug treatment in an open-label phase for an additional period of two years, not exceeding a maximal total treatment duration of 5 years. Of the 243 patients initially randomized to Copaxone, 198 continued Copaxone treatment in the open-label phase. Of the 238 patients initially randomized to placebo, 211 switched to Copaxone treatment in the open-label phase.

During the placebo-controlled period of up to 3 years, Copaxone delayed the progression from the first clinical event to clinically definite multiple sclerosis (CDMS) according to Poser criteria in a statistically significant and clinically meaningful manner, corresponding to a risk reduction of 45% (Hazard Ratio = 0.55; 95% CI [0.40; 0.77], p-value=0.0005). The proportion of patients who converted to CDMS was 43% for the placebo group and 25% in the Copaxone group.

The favorable effect of treatment with Copaxone over placebo was also demonstrated in two secondary MRI endpoints, i.e., number of new T₂ lesions and T₂ lesion volume.

Post-hoc subgroup analyses were performed in patients with various baseline characteristics to identify a population at high risk to develop the second attack. For subjects with baseline MRI with at least one T₁ Gd-enhancing lesion and 9 or more T₂ lesions, conversion to CDMS was evident for 50% of the placebo subjects vs. 28% of the Copaxone subjects in 2.4 years. For subjects with 9 or more T₂ lesions at baseline, conversion to CDMS was evident for 45% of the placebo subjects vs. 26% on Copaxone in 2.4 years. However, the impact of early treatment with Copaxone on the long term evolution of the disease is unknown even in these high-risk subgroups as the study was mainly designed to assess the time to the second event. In any case, treatment should only be considered for patients classified at high risk.

The effect shown in the placebo-controlled phase was sustained in the long-term follow-up period of up to 5 years. The time progression from the first clinical event to CDMS was prolonged with earlier Copaxone treatment as compared to delayed treatment, reflecting a 41% risk reduction with earlier versus later treatment (Hazard Ratio = 0.59; 95% CI [0.44; 0.80], p-value=0.0005). The proportion of subjects in the Delayed Start group who progressed was higher (49.6%) compared to those in the Early Start group (32.9%).

A consistent effect in favour of early treatment over delayed treatment across time was shown for the annualized number of lesions over the entire study period in new T₁ Gd-enhancing lesions (reduced by 54%; p<0.0001), new T₂ lesions (reduced by 42%; p<0.0001) and new T₁ hypointense lesions (reduced by 52%; p<0.0001). An effect in reductions in favour of early versus delayed treatment was also observed for the total number of new T₁ Gd-enhancing lesions (reduced by 46%; p=0.001), T₁ Gd-enhancing lesion volume (a mean difference of -0.06 ml; p<0.001), as well as the total number of new T₁ hypointense lesions (reduced by 46%; p<0.001) measured over the entire study period.
No appreciable differences between the Early Start and Delayed Start cohorts were observed for either hypointense T1 lesion volume or brain atrophy over 5 years. However, analysis of brain atrophy at last observed value (adjusted to treatment exposure) showed a reduction in favour of early treatment with GA (the mean difference of percent change in brain volume was 0.28%; p=0.0209).

5. Indications

**COPAXONE 20 mg/ml Prefilled Syringe**
Copaxone is indicated for the treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (CDMS). These patients should have MRI findings which are compatible with the diagnosis of multiple sclerosis (see section 4.2).

Copaxone® is indicated for reducing the frequency of relapses in patients with relapsing-remitting multiple sclerosis.

**COPAXONE 40 mg/ml Prefilled Syringe**
Copaxone 40 mg/ml is indicated for the reduction in frequency of relapses in patients with relapsing-remitting multiple sclerosis (MS).

6. Contraindications
Copaxone® is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

Pregnancy.

7. Warnings
The only recommended route of administration of Copaxone® injection is by the subcutaneous route. Copaxone® should not be administered by the intravenous route.

**Mutagenicity**
Glatiramer acetate was not mutagenic in 4 strains of *Salmonella typhimurium* and 2 strains of *Escherichia coli* (Ames test), or in the *in vitro* mouse lymphoma assay in L5178Y cells. Glatiramer acetate was clastogenic in 2 separate *in vitro* chromosomal aberration assays in cultured human lymphocytes; it was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

**Carcinogenicity**
Results of tests to assess the carcinogenic potential of glatiramer acetate in mice and rats are unavailable; these studies are in progress.

**Teratogenicity**
No adverse effects on embryofetal development occurred in reproduction studies in rats and rabbits receiving subcutaneous doses up to 37.5 mg/kg of glatiramer acetate during the period of organogenesis (18 and 36 times the human dose of 20 mg on a mg/m² basis, respectively). In a prenatal and postnatal study, in which rats received subcutaneous glatiramer acetate at doses 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.

**Effect on Fertility and Reproduction**
In a multi-generation reproduction and fertility study in rats, glatiramer acetate at subcutaneous doses up to 36 mg/kg (18 times the recommended human daily dose of 20 mg on a mg/m² basis) had no adverse effects on reproductive parameters.
Perinatal and Postnatal studies
In a prenatal and postnatal study, in which rats receiving subcutaneous Copaxone® at doses 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. The relevance of these findings to humans is unknown.

Use in Pregnancy
(see Contraindications)
There are no adequate and well-controlled studies in pregnant women. The potential risk for humans is unknown. Therefore, Copaxone® should not be used during pregnancy.

Use in Breastfeeding
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 mother.

Use in Pediatrics
The safety and effectiveness of Copaxone® have not been established in individuals below 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 Copaxone® in patients with impaired renal function has not been determined.
In patients with renal impairment, renal function should be monitored while they are treated with Copaxone. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

8. Adverse Reactions
During premarketing clinical trials, approximately 850 patients with MS and 50 patients in clinical pharmacology trials 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, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia.
Approximately 8% of the 893 subjects receiving glatiramer acetate discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reactions (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness, and tremor.

Immediate Post-Injection Reaction
Approximately 10% of patients with MS exposed to glatiramer acetate in premarketing studies experienced a constellation of symptoms immediately after injection that could include 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 in the course of treatment, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represents a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.
Whether these episodes are mediated by an immunologic or non-immunologic mechanism, or whether several similar episodes seen in a given patient have identical mechanisms is unknown.

Chest Pain
Approximately 26% of glatiramer acetate patients in the multicenter controlled trial (compared to 10% 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 the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes) often unassociated with other symptoms and appeared to have no important clinical sequelae. ECG monitoring was not performed during any of these episodes. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of the symptom is unknown.

Incidence of Adverse Reactions in Controlled Clinical Trials
The following table lists treatment emergent signs and symptoms that occurred in at least 2% of patients with MS treated with glatiramer acetate in placebo controlled trials and that were numerically more common in patients treated with glatiramer acetate than in placebo-treated patients. These trials include the two controlled trials in relapsing-remitting multiple sclerosis patients and a controlled trial in patients with chronic progressive multiple sclerosis. Adverse events 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 to estimate the relative contribution of drug and non-drug factors to the adverse events incidences in the population studied.

### Controlled Trials in Patients with Multiple Sclerosis
#### Incidence of Glatiramer Acetate Adverse Experiences >1% and More Frequent than Placebo

<table>
<thead>
<tr>
<th>Body System</th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>83</td>
<td>41</td>
</tr>
<tr>
<td>Back pain</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Bacteria Infection</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Chest pain</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>Chills</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Cyst</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Face Edema</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Fever</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Infection</td>
<td>101</td>
<td>50</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>132</td>
<td>66</td>
</tr>
<tr>
<td>Body System</td>
<td>Glatiramer Acetate (N=201)</td>
<td>Placebo (N=206)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Injection Site Hemorrhage</td>
<td>11  5</td>
<td>6   3</td>
</tr>
<tr>
<td>Injection Site Induration</td>
<td>26  13</td>
<td>1   0</td>
</tr>
<tr>
<td>Injection Site Inflammation</td>
<td>98  49</td>
<td>22  11</td>
</tr>
<tr>
<td>Injection Site Mass</td>
<td>54  27</td>
<td>21  10</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>147 73</td>
<td>78  38</td>
</tr>
<tr>
<td>Injection Site Pruritus</td>
<td>80  40</td>
<td>12  6</td>
</tr>
<tr>
<td>Injection Site Urticaria</td>
<td>10  5</td>
<td>0   0</td>
</tr>
<tr>
<td>Injection Site Welt</td>
<td>22  11</td>
<td>5   2</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>16  8</td>
<td>9   4</td>
</tr>
<tr>
<td>Pain</td>
<td>56  28</td>
<td>52  25</td>
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</tbody>
</table>

**Cardiovascular System**

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>10  5</td>
<td>5   2</td>
</tr>
<tr>
<td>Palpitation</td>
<td>35  17</td>
<td>16  8</td>
</tr>
<tr>
<td>Syncope</td>
<td>10  5</td>
<td>5   2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>11  5</td>
<td>8   4</td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>55  27</td>
<td>21  10</td>
</tr>
</tbody>
</table>

**Digestive System**

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>17  8</td>
<td>15  7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25  12</td>
<td>23  11</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>6  3</td>
<td>2   1</td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>10   5</td>
<td>8   4</td>
</tr>
<tr>
<td>Nausea</td>
<td>44  22</td>
<td>34  17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13  6</td>
<td>8   4</td>
</tr>
</tbody>
</table>

**Hemic and Lymphatic System**

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecchymosis</td>
<td>16  8</td>
<td>13  6</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>25  12</td>
<td>12  6</td>
</tr>
</tbody>
</table>

**Metabolic and Nutritional**

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>5   3</td>
<td>1   0</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>14  7</td>
<td>8   4</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7   3</td>
<td>0   0</td>
</tr>
</tbody>
</table>

**Musculoskeletal System**

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athralgia</td>
<td>49  24</td>
<td>39  19</td>
</tr>
</tbody>
</table>

**Nervous System**

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer Acetate (N=201)</th>
<th>Placebo (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>8   4</td>
<td>4   2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>46  23</td>
<td>40  19</td>
</tr>
<tr>
<td>Body System</td>
<td>Glatiramer Acetate (N=201)</td>
<td>Placebo (N=206)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Confusion</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Foot Drop</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Speech Disorder</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Tremor</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Vertigo</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Laryngismus</td>
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<td>5</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td><strong>Skin and Appendages</strong></td>
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<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>8</td>
<td>4</td>
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<tr>
<td>Herpes Simplex</td>
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<td>Pruritus</td>
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<td>Rash</td>
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<tr>
<td>Skin Nodule</td>
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<td>2</td>
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<tr>
<td>Sweating</td>
<td>31</td>
<td>15</td>
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<tr>
<td>Urticaria</td>
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<td>4</td>
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<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ear Pain</td>
<td>15</td>
<td>7</td>
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<tr>
<td>Eye Disorder</td>
<td>8</td>
<td>4</td>
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<tr>
<td><strong>Urogenital System</strong></td>
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<tr>
<td>Dysmenorrhea</td>
<td>12</td>
<td>6</td>
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<tr>
<td>Urinary Urgency</td>
<td>20</td>
<td>10</td>
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<tr>
<td>Vaginal Moniliasis</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

Other events which occurred at least 2% of 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 liability, 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, menstrual disorder and vaginitis.

Data on adverse events occurring in the controlled clinical trials was 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 with multiple sclerosis. In addition, the vast majority of patients treated with Copaxone® were between the ages of 18 and 45. Consequently, inadequate data is available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for 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 due to abnormal laboratory findings.

Other Adverse Reactions Observed During Clinical Trials and the Postmarketing Period
Glatiramer acetate has been administered to approximately 900 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 a smaller number of standardized categories using COSTART II dictionary terminology.

The frequencies presented represent the proportion of the 979 individuals exposed to glatiramer acetate who had data available for this determination.

All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, and those not reasonably related to the drug. Additional adverse reactions reported during the postmarketing period are included.

Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients. Rare adverse reactions 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.
Rare: Allergic reaction, anaphylactoid reaction.
At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during postmarketing experience.

**Cardiovascular System**

*Frequent:* Hypertension.
*Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradyarrhythmia, 4th heart sound, postural hypotension, and varicose veins.

**Digestive System**

*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 System**

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

**Hemic and Lymphatic**

*Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematopenia, 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 System**

*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 System**

*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 System

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, prostatectomy, pyelonephritis, abnormal sexual function and urethritis.

Adverse Reactions in the Clinical Trial in Subjects with a Single Clinical Event Suggestive of MS

The safety profile of Copaxone in the study of subjects with a first clinical episode suggestive of MS is consistent with the known safety profile of Copaxone as demonstrated in RRMS patients during prior clinical trials and post-marketing surveillance. The safety issues with the greatest impact on drug tolerability continue to be injection site reactions, immediate post-injection reactions, hypersensitivity reactions including anaphylactic reactions, and skin and subcutaneous disorders.

Copaxone 40 mg/ml Administered Three Times per Week

The safety of Copaxone 40 mg/ml was assessed based on a double-blind, placebo-controlled clinical trial in RRMS patients with a total of 943 patients treated with Copaxone 40 mg/ml three times per week, and 461 patients treated with placebo for 12 months.

In general, the kind of adverse drug reactions seen in patients treated with Copaxone 40 mg/ml administered three times per week were those already known and labeled for Copaxone 20 mg/ml administered daily. In particular, adverse injection site reactions (ISR) and immediate post-injection reactions (IPIR) were reported at lower frequency for Copaxone 40 mg/ml administered three times per week than for Copaxone 20 mg/ml administered daily (35.5 % vs. 70 % for ISRs and 7.8 % vs. 31 % for IPIRs, respectively).

A few specific adverse reactions are noted:

- Anaphylactic response was seen rarely (>1/10000, <1/1000) in MS patients treated with Copaxone 20 mg/ml in uncontrolled clinical trials and from post-marketing experience. It was reported by 0.3% of the patients on Copaxone 40 mg/ml (Uncommon: 1/1,000 to < 1/100).
- No injection site necrosis was reported.
- Skin erythema and pain in extremity, not labelled for Copaxone 20 mg/ml, were reported each by 2.1% of the patients on Copaxone 40 mg/ml (Common: 1/100 to < 1/10).
- Drug-induced liver injury and toxic hepatitis, also seen rarely in MS patients treated with Copaxone 20 mg/ml in post marketing surveillance, were each reported by one patient (0.1%) on Copaxone 40 mg/ml (Uncommon: 1/1,000 to < 1/100).

8. Precautions

General

Patients should be instructed about self-injection techniques to assure the safe administration of Copaxone®.

Based on current data, no special caution is required in patients engaged in activities requiring mental alertness such as driving a car or operating machinery.
No evidence or experience suggests that abuse or dependence occurs with Copaxone® therapy; however, the risk of dependence has not been systematically evaluated.

**Considerations Involving the Use of a Product Capable of Modifying Immune Response:**

Because glatiramer acetate can modify immune response, consideration must be given to the possibility that it could interfere with useful immune function. 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 defenses against infections and tumor surveillance. There is no evidence that it does so, 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. Although there is no evidence that this occurs in humans, systematic surveillance for these effects have not been undertaken. Studies in both the rat and monkey, however, have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 patients with relapsing-remitting multiple sclerosis (RRMS) given glatiramer acetate, 20 mg subcutaneously every day for 2 years, serum IgG levels reached approximately 3 times baseline values in 80% of patients within 3 to 6 months of initiation of treatment. These values returned to about 50% greater than baseline during the remainder of treatment.

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.

Anaphylaxis can be associated with the administration of almost any foreign substance. Based on the protein nature of glatiramer acetate, the risk of anaphylaxis cannot be excluded. Of the approximately 900 patients treated in premarketing trials, none experienced anaphylactic shock.

Data collected during premarketing development do not suggest the necessity for routine laboratory monitoring.

**10. 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. An increased incidence of injection site reactions has been seen in Copaxone patients receiving concurrent administration of corticosteroids. Copaxone® has not been formally evaluated in combination with interferon-beta. However, 10 patients who switched from therapy with interferon-beta to Copaxone® have not reported any serious and unexpected adverse events thought to be related to treatment.

*In vitro* work suggests that glatiramer acetate in blood is highly bound to plasma proteins but that it is not displaced by, and does not itself displace, phenytoin or carbamazepine. Nevertheless, as Copaxone has, theoretically, the potential to affect the distribution of protein-bound substances, concomitant use of such medicinal products should be monitored carefully.

**11. Information for Patients**

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

1. Copaxone® is not recommended for use in pregnancy. Therefore, the physician should be informed in case a woman is planning to have a child, or if she becomes pregnant while taking this medication.
2. The physician should be informed in case of breastfeeding.
3. The dose or dosing schedule should not be changed without consulting the physician.
4. The administration of the drug should not be stopped without consulting the physician.
5. Awareness of Adverse Reactions: Physicians are advised to counsel patients about adverse reactions associated with the use of Copaxone® (see Adverse Reactions). In addition, patients should be advised to read the Copaxone® Patient Information Leaflet and resolve any questions regarding it prior to beginning Copaxone® therapy.

12. Dosage and Administration

**COPAXONE 20 mg/ml Prefilled Syringe**

The recommended dose of Copaxone® is 20 mg/day injected subcutaneously. Copaxone® should be administered at the same time every day.

**COPAXONE 40 mg/ml Prefilled Syringe**

The recommended dosage in adults is 40 mg of Copaxone (one pre-filled syringe), administered as a subcutaneous injection three times a week.

At the present time, it is not known for how long the patient should be treated.

A decision concerning long term treatment should be made on an individual basis by the treating physician.

**Overdose**

There are 13 reports to date of overdose with Copaxone which were confirmed by health care professionals. Most cases concern 2 or 3 injections given on the same day. The largest dose of Copaxone that has been administered is 280 mg on a single occasion. No adverse reactions occurred and the patient continued treatment.

In clinical trials, daily doses of up to 30 mg glatiramer acetate for up to 24 months were not associated with adverse reactions other than those mentioned in Section 8.

In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted.

**Instructions for Self-Administration**

*Copaxone® is intended for self-administration by the individual patient.*

**Copaxone® Solution for Injection in Pre-Filled Syringes.**

**Storage of Copaxone® Pre-Filled Syringes**

Copaxone® Pre-Filled Syringes should be stored in the refrigerator (at 2°C - 8°C).

If Copaxone® Pre-Filled Syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C - 25°C) for up to one month. Do not store Copaxone® Pre-Filled Syringes at room temperature for longer than one month.

**N.B:** Copaxone® Pre-Filled Syringes can be kept for up to one month outside the refrigerator at room temperature; this can be done only once. After one month, any Copaxone® Pre-Filled Syringes that have not been used and are still in their original packing must be returned to the refrigerator. The syringes must be stored in a shaded place and not exposed to light. A single Pre-Filled Syringe may be removed from the pack only prior to use – the rest of the Pre-Filled Syringes must be stored in their original package.
This medicine must not be frozen. If a Copaxone® Pre-Filled Syringe freezes, it must be discarded into a proper container.

**Instructions for Use Prior to Injection**

*For subcutaneous injection only.*

**Important Notes**

- The first injection must be performed in the presence of a professional person. Following that, injection should be made in the presence of an additional person who will be at the patient’s disposal during the injection and for 30 minutes afterwards.
- The syringe should be discarded after use. It must not be used again.
- In order to reduce the chance of local irritation or pain, a different area of the injection sites should be chosen every day. Areas for self-injection include: arms, thighs, abdomen and buttock.
- In order to prevent inflammation, the hands should be washed and dried. The hair or skin should not be touched afterwards.

**Instructions for Use**

1 - Gathering the materials and injection.

First the following items should be gathered on a clean and flat surface in a well-lit area:

- Single syringe pack – a single syringe pack should be removed from the syringe package. All other unused syringes should be kept in the carton package and the carton package returned to the refrigerator.
  - Cotton wool.
  - The blister pack with the syringe inside should be let to warm at room temperature for 20 minutes.
  - There may be small air bubbles in the syringe. To avoid loss of medicine upon use, the air bubbles should not be expelled from the syringe.

2 - Choice of the Injection Site

- There are 7 possible injection areas on your body: arms, thighs, hips and lower stomach area (abdomen)—Figure 1.
- A different injection site should be chosen every day. It is recommended to keep a record of the injection sites in order to avoid injection in the same area more than once a week.
- There are some sites in the body that may be hard to reach for self-injection and the patient may need assistance.
- Injection into sites where skin depression has occurred should be avoided, because further injections in these sites may make the depression deeper.

*Figure 1*
3 – Injecting the Medicine

In case the Autoject is used for injection, the leaflet for Autoject enclosed within the Autoject package should be referred to.

In case the injection is made manually this leaflet should be read continuously.
- The syringe should be removed from its pack by peeling back the back the paper label present at the end of the syringe pack.
- Prior to injection, the liquid inside the syringe should be inspected for particles. The syringe must not be used if any particles are present or if the solution is not clear.
- The injection site should be chosen.

- The syringe should be held in the strong hand of the patient, and the needle shield in the other hand. Care should be taken not to bend or twist the needle shield.
- The needle shield is then removed straight out –not by twisting it. The needle shield should be discarded into a container approved to collect sharp accessories.
- Using the other hand (the weaker), about a 5-cm fold of skin is pinched between the thumb and the index finger (figure 2).

![Figure 2](image)

- The medicine should be injected at a 90-degree angle – Figure 3.

- To inject the medicine the syringe should be held steady and the plunger pushed down until the syringe is emptied. Once all contents have been injected, the skin pinch is released.

![Figure 3](image)

- When all the medicine has been injected, the syringe should be discarded into a container approved to collect sharp accessories.
- Press the cotton wool on the injection site for a few seconds. The injection site must not be rubbed.
13. Drug Registration Numbers
Copaxone 20 mg/syringe (of 1 ml):
128 06 30681 00. 128 06 30681 01

Copaxone 40 mg/syringe (of 1 ml):
151 75 34057 00.

14. Manufacturer
Teva Pharmaceutical Industries Ltd.
P.O.Box 3190, Petah-Tikva.