

Public Assessment Report
Mutual Recognition Procedure

**COPAXONE 20MG/ML SOLUTION FOR INJECTION,
REFILLED SYRINGE**

UK/H/0453/002/E01
UK licence no: PL 10921/0023

Teva Pharmaceuticals Limited

COPAXONE 20MG/ML SOLUTION FOR INJECTION, PREFILLED SYRINGE

LAY SUMMARY

On 25th September 2006, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia granted marketing authorisations to Teva Pharmaceuticals Limited for the medicinal product Copaxone 20mg/ml Solution for Injection, Prefilled Syringe (UK/H/0453/002/E01). Copaxone 20mg/ml Solution for Injection is used to reduce the number of times you suffer attacks of multiple sclerosis (MS).

The symptoms of MS are thought to be caused by a defect in the body's immune defence system. This produces patches of inflammation in the brain and spinal cord. Copaxone 20mg/ml Solution for Injection is a prescription-only medicine, containing the active substance glatiramer acetate, an immunomodulating agent that modifies the way in which the body's immune defence system works.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Copaxone 20mg/ml Solution for Injection outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Copaxone 20mg/ml Solution for Injection, Prefilled Syringe
Type of Application	Full dossier, Article 8.3
Active Substance	Glatiramer Acetate
Form	Solution for Injection
Strength	20mg/ml
MA Holder	Teva Pharmaceuticals Ltd, Denton Hall, 5 Chancery Lane, Cliffords Inn, London, EC4A 1BU, UK
RMS	UK
CMS	Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic, Slovenia
Procedure Number	UK/H/0453/002/E01
Timetable	Day 90 – 25 th September 2006

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Copaxone 20 mg/ml Solution for Injection, Pre-filled Syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 20 mg glatiramer acetate *, equivalent to 18 mg of glatiramer base per pre-filled syringe

* Glatiramer acetate is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine, in molar fraction ranges of 0.129-0.153, 0.392-0.462, 0.086-0.100 and 0.300-0.374, respectively. The average molecular weight of glatiramer acetate is in the range of 5,000-9,000 daltons.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection, Pre-filled Syringe

Clear solution free of visible particles

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Copaxone is indicated for the reduction in frequency of relapses in ambulatory patients (i.e. who can walk unaided) with relapsing, remitting multiple sclerosis (MS). In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding 2-year period (see Section 5.1).

Copaxone is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration

The recommended dosage in adults is 20 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection once daily.

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.

Paediatric Use: Children and adolescents: No prospective, randomized, controlled clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 18 years of age receiving Copaxone 20 mg subcutaneously every day is similar to that seen in adults. There is not enough information available on the use of Copaxone in children below 12 years of age to make any recommendation for its use. Therefore, Copaxone should not be used in this population.

Use in the Elderly: Copaxone has not been specifically studied in the elderly.

Use in Patients with Impaired Renal Function: Copaxone has not been specifically studied in patients with renal impairment (see Section 4.4).

Patients should be instructed in self-injection techniques and should be supervised by a health-care professional the first time they self-inject and for 30 minutes after.

A different site for injection should be chosen every day, so this will reduce the chances of any irritation or pain at the site of the injection. Sites for self-injection include the abdomen, arms, hips and thighs.

4.3 Contraindications

Copaxone is contraindicated under the following conditions:

- Hypersensitivity to glatiramer acetate or mannitol.
- Pregnant women

4.4 Special warnings and precautions for use

Copaxone should only be administered subcutaneously. Copaxone should not be administered by intravenous or intramuscular routes.

The initiation of Copaxone treatment should be supervised by a neurologist or a physician experienced in the treatment of MS.

The treating physician should explain to the patient that a reaction associated with at least one of the following: vasodilatation (flushing), chest pain, dyspnoea, palpitations or tachycardia, may occur within minutes of a Copaxone injection. The majority of these symptoms are short-lived and resolve spontaneously without any sequelae. Should a severe adverse event occur, the patient must immediately stop Copaxone treatment and contact his/her physician or any emergency doctor. Symptomatic treatment may be instituted at the discretion of the physician.

There is no evidence to suggest that any particular patient groups are at special risk from these reactions. Nevertheless, caution should be exercised when administering Copaxone to patients with pre-existing cardiac disorders. These patients should be followed up regularly during treatment.

Convulsions and/or anaphylactoid or allergic reactions have been reported rarely. Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis or urticaria) may rarely occur. If reactions are severe, appropriate treatment should be instituted and Copaxone should be discontinued.

Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with Copaxone. Maximal levels were attained after an average treatment duration of 3-4 months and, thereafter, declined and stabilised at a level slightly higher than baseline.

There is no evidence to suggest that these glatiramer acetate-reactive antibodies are neutralising or that their formation is likely to affect the clinical efficacy of Copaxone.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction between Copaxone and other medicinal products have not been formally evaluated.

There are no data on interaction with interferon beta.

An increased incidence of injection site reactions has been seen in Copaxone patients receiving concurrent administration of corticosteroids.

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.

4.6 Pregnancy and lactation

Pregnancy: There are no adequate data from the use of glatiramer acetate in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see Section 5.3). The potential risk for humans is unknown. Copaxone is contraindicated during pregnancy.

A contraceptive cover should be considered whilst using this medicinal product.

Lactation: Data regarding excretion of glatiramer acetate, its metabolites or antibodies in human milk are unavailable. Caution should be exercised when Copaxone is administered to a nursing mother. The relative risk and benefit to the mother and child should be taken into consideration.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In all clinical trials, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving Copaxone. In controlled studies, the proportion of patients reporting these reactions, at least once, was higher following treatment with Copaxone (82.5%) than placebo injections (48%). The most commonly reported injection-site reactions were erythema, pain, mass, pruritus, oedema, inflammation and hypersensitivity.

A reaction associated with at least one or more of the following symptoms: vasodilatation, chest pain, dyspnoea, palpitation or tachycardia has been described as the Immediate Post-Injection Reaction. This reaction may occur within minutes of a Copaxone injection. At least one component of this Immediate Post-Injection Reaction was reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo.

All adverse reactions, which were more frequently reported in Copaxone vs. placebo-treated patients, are presented in the table below. This data was derived from three pivotal, double-blind placebo-controlled clinical trials with 269 MS patients treated with Copaxone and 271 MS patients treated with placebo for up to 35 months.

System Organ Class (SOC)	Very Common (>1/10)	Common (>1/100, <=1/10)	Uncommon (>1/1000, <=1/100)
Infections And Infestations	Influenza	Bronchitis, Cystitis, Gastroenteritis, Herpes Simplex*, Otitis Media, Rhinitis, Vaginal Candidiasis*	Abscess, Cellulitis, Furuncle, Otitis Externa, Pyelonephritis
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)		Benign Neoplasm Of Skin*, Neoplasm	Skin Cancer
Blood And Lymphatic System Disorders		Lymphadenopathy*	Eosinophilia, Splenomegaly
Immune System Disorders		Hypersensitivity	
Endocrine Disorders			Goitre, Hyperthyroidism
Metabolism And Nutrition Disorders		Anorexia, Weight Increased*	Alcohol Intolerance, Gout
Psychiatric Disorders	Anxiety*, Depression	Abnormal Dreams, Agitation, Confusional State, Nervousness*	Euphoric Mood, Hallucination, Hostility, Mania, Personality Disorder, Suicide Attempt
Nervous System Disorders	Dizziness, Headache, Hypertonia	Amnesia, Dysgeusia, Migraine, Nystagmus, Peroneal Nerve Palsy, Somnolence, Speech Disorder, Stupor, Syncope*, Tremor*, Visual Field Defect	Myoclonus, Neuritis
Eye Disorders		Diplopia, Eye Disorder*	Cataract, Corneal Lesion, Eye Haemorrhage, Eyelid Ptosis, Mydriasis

System Organ Class (SOC)	Very Common (>1/10)	Common (>1/100, <=1/10)	Uncommon (>1/1000, <=1/100)
Ear And Labyrinth Disorders		Ear Disorder, Ear Pain	
Cardiac Disorders	Palpitations*	Tachycardia*	Extrasystoles
Vascular Disorders	Vasodilatation*	Angiopathy, Hypertension	Pallor, Varicose Vein
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea*	Cough, Rhinitis Allergic, Rhinitis Seasonal	Apnoea, Dysphonia, Epistaxis, Laryngospasm, Lung Disorder
Gastrointestinal Disorders	Constipation, Diarrhoea, Nausea*	Anorectal Disorder, Dental Caries, Dysphagia, Faecal Incontinence, Stomatitis, Tooth Disorder, Vomiting*	Enterocolitis, Oesophageal Ulcer, Rectal Haemorrhage, Salivary Gland Enlargement
Hepatobiliary Disorders			Hepatomegaly
Skin And Subcutaneous Tissue Disorders	Hyperhidrosis*, Rash*	Ecchymosis, Skin Disorder, Urticaria	Angioedema, Dermatitis Contact, Erythema Nodosum, Skin Atrophy, Skin Nodule
Musculoskeletal And Connective Tissue Disorders	Arthralgia, Back Pain	Arthritis, Flank Pain, Neck Pain	Tendon Disorder, Tenosynovitis, Torticollis
Renal And Urinary Disorders		Micturition Urgency, Urinary Retention, Urinary Tract Disorder	Haematuria, Renal Pain, Urine Abnormality
Pregnancy, Puerperium And Perinatal Conditions			Abortion
Reproductive System And Breast Disorders		Dysmenorrhoea, Erectile Dysfunction, Menstrual Disorder, Smear Cervix Abnormal	Breast Engorgement, Ovarian Disorder, Priapism, Prostatic Disorder, Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder
General Disorders And Administration Site Conditions	Asthenia, Chest Pain*, Injection Site Reactions*, Pain*	Chills*, Cyst, Face Oedema*, Local Reaction*, Malaise, Oedema Peripheral, Oedema*, Pyrexia	Hangover, Hernia, Hypothermia, Inflammation, Mucous Membrane Disorder
Injury, Poisoning And Procedural Complications			Post Vaccination Syndrome

*More than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group.

Rare (>1/10000, <1/1000) and very rare (<1/10000) adverse reaction reports were collected from MS patients treated with Copaxone in uncontrolled clinical trials and from post-marketing experience with Copaxone. These include anaphylactoid reactions, convulsions, shifts in white blood cell counts and elevated levels of liver enzymes with no evidence of clinically significant sequelae.

At injection sites, localized lipoatrophy and, rarely, skin necrosis have been reported.

4.9 Overdose

A few cases of overdose with Copaxone (up to 80 mg glatiramer acetate) have been reported. These cases were not associated with any adverse reactions other than those mentioned in Section 4.8.

There is no clinical experience with doses higher than 80 mg glatiramer acetate.

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 4.8.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cytokines and immunomodulators

ATC code: L03AX13

The mechanism(s) by which glatiramer acetate exerts its effects in patients with 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 immunisation against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in MS patients suggest that upon its administration, glatiramer acetate-specific suppressor T cells are induced and activated in the periphery.

A total of 269 patients have been treated with Copaxone in three controlled trials. The first was a two-year study involving 50 patients (Copaxone n=25, placebo n=25) who were diagnosed with relapsing-remitting MS by the then-applicable standard criteria, and who had at least two attacks of neurological dysfunction (exacerbations) during the preceding two years. The second study applied the same inclusion criteria and included 251 patients treated for up to 35 months (Copaxone n=125, placebo n=126). The third study was a nine-month study involving 239 patients (Copaxone n=119, placebo n=120) where inclusion criteria were similar to those in the first and second studies with the additional criterion that patients had to have at least one gadolinium-enhancing lesion on the screening MRI.

In clinical trials in MS patients receiving Copaxone, a significant reduction in the number of relapses, compared with placebo, was seen.

In the largest controlled study, the relapse rate was reduced by 32% from 1.98 under placebo to 1.34 under glatiramer acetate.

Exposure data are available for up to twelve years in 103 patients treated with Copaxone.

Copaxone has also demonstrated beneficial effects over placebo on MRI parameters relevant to relapsing-remitting MS.

Copaxone had, however, no beneficial effect on progression of disability in relapsing-remitting MS patients.

There is no evidence that Copaxone treatment has an effect on relapse duration or severity.

There is currently no evidence for the use of Copaxone in patients with primary or secondary progressive disease.

5.2 Pharmacokinetic properties

Pharmacokinetic studies in patients have not been performed. *In vitro* data and limited data from healthy volunteers indicate that with subcutaneous administration of glatiramer acetate, the active substance is readily absorbed and that a large part of the dose is rapidly degraded to smaller fragments already in subcutaneous tissue.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity or carcinogenicity, beyond the information included in other sections of the SPC. Due to the lack of pharmacokinetic data in humans, margins of exposure between humans and animals can not be established.

Immune complex deposition in the glomeruli of the kidney was reported in a small number of rats and monkeys treated for at least 6 months. In a 2 years rat study, no indication of immune complex deposition in the glomeruli of the kidney was seen.

Anaphylaxis after administration to sensitised animals (guinea pigs or mice) was reported. The relevance of these data for humans is unknown.

Toxicity at the injection site was a common finding after repeated administration in animals.

6. PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Mannitol
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the container in the outer carton, in order to protect from light.

Store in refrigerator (2°C to 8°C).

If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C), once for up to 1 month.

After this 1-month period, if the Copaxone 20 mg/ml pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2°C to 8°C).

6.5 Nature and contents of the container

Copaxone solution for injection is contained in a pre-filled syringe, consisting of a Type I colourless glass barrel, a plastic plunger and a rubber stopper.

Packs containing 7 and 28 pre-filled syringes will be supplied.

Not all pack sizes may be marketed.

The volume of solution in the syringe is 1.0ml.

6.6 Special precautions for disposal

For single use only. Any unused product or waste material must be discarded.

7. MARKETING AUTHORISATION HOLDER

Teva Pharmaceuticals Ltd
5 Chancery Lane
Clifford's Inn
London EC4A 1BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 10921/0023

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
07/04/2003
- 10** **DATE OF REVISION OF THE TEXT**
15/07/2008

Module 3

Product Information Leaflet



COPAXONE®

20 mg/ml, Solution for Injection PRE-FILLED SYRINGE

Read all of this leaflet carefully before you start using Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe is and what it is used for
2. Before you use Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe
3. How to use Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe
4. Possible side effects
5. Storing Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe

Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe
Glatiramer acetate 20 mg/ml for subcutaneous use.

The marketing authorisation holder of this medicine is
Teva Pharmaceuticals Ltd.,
5 Chancery Lane,
Clifford's Inn, London EC4A 1BU, UK
Tel. 44 1296 719768 ; Fax 44 1296 719769

The manufacturer of this medicine is
Baxter Pharmaceutical Solutions LLC,
Bloomington, IN 47402, USA
Tel: 1 812 333 0887 ; Fax: 1 812 332 3079

TEVA Pharmaceuticals Europe B.V.,
PO Box 206, 3640 AE Mijdrecht,
THE NETHERLANDS
Tel: 31 297 290200 ; Fax: 31 297 290299

The distributor of this medicine is
Sanofi-aventis
One Onslow Street, Guildford
Surrey, GU1 4YS
UK
Tel. 44 1483 505 515 ; Fax 44 1483 535 432

1. WHAT COPAXONE 20 mg/ml SOLUTION FOR INJECTION PRE-FILLED SYRINGE IS AND WHAT IT IS USED FOR

Each Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe contains 20 mg of the active ingredient glatiramer acetate (equivalent to 18 mg per ml of glatiramer base) and also contains the inactive ingredient mannitol dissolved in water for injections. It is a sterile solution for injection, for subcutaneous (under the skin) use. Glatiramer acetate is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids (L-glutamic acid, L-alanine, L-tyrosine and L-lysine). It is an immunomodulating agent.

Each pack contains 28 Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringes with 1 ml solution each.

Copaxone 20 mg is used to reduce the number of times you suffer attacks of multiple sclerosis (MS).

The symptoms of MS are thought to be caused by a defect in the body's immune defence system. This produces patches of inflammation in the brain and spinal cord.

Copaxone 20 mg is a medicinal product which modifies the way in which the body's immune defence system works.

Copaxone 20 mg may not have any effect on the length of time an MS attack lasts, or how badly you suffer during an attack.

2. BEFORE YOU USE COPAXONE 20 mg/ml SOLUTION FOR INJECTION PRE-FILLED SYRINGE

Do not use Copaxone 20 mg:

- If you are allergic (have had a reaction such as a rash or wheezing) to glatiramer acetate or mannitol.
- If you have not been taught how to do the injections.
- If you are under 18 years of age.
- If you are pregnant.

Take special care with Copaxone 20 mg:
If you have any kidney problems or heart problems as you may need to have regular tests or check-ups. Ask your doctor for advice.

Special patient groups
Copaxone 20 mg has not been specifically studied with the elderly.

Travel
No effects on a patient's ability to travel have been observed.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Copaxone 20 mg should not be used during pregnancy.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Caution should be exercised when Copaxone 20 mg is administered to a nursing mother.

Driving and using machines
Copaxone 20 mg is not known to influence the ability to drive or operate machinery.

Using other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine - even those not prescribed.

3. HOW TO USE COPAXONE 20 mg/ml SOLUTION FOR INJECTION PRE-FILLED SYRINGE

The recommended dosage in adults is 20 mg of glatiramer acetate (one Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe), administered as a subcutaneous injection once daily.

It is very important to inject Copaxone 20 mg properly:

- into the subcutaneous tissue under the skin only (see "Instructions for Use" below).
- At the dose and times instructed by your doctor. Do not change these without consulting your doctor first.
- Each Solution for Injection Pre-Filled Syringe is intended for single use only.
- The content of Copaxone 20 mg should not be mixed or co-administered with any product.

The first time you use Copaxone 20 mg you will be given full instructions and will be supervised by a doctor or nurse. They will be with you while you give yourself the injection and for half an hour afterwards, just to make sure you do not have any problems.

Never use the same Solution for Injection Pre-Filled Syringe more than once. Do not put used syringes into the household waste but dispose of them carefully in a puncture-proof container as recommended by your doctor or nurse.

3.1 Instructions for use

Read these instructions very carefully before using Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe.

- 3.1.1 Before injecting make sure you have everything you need:
 - One blister with Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe.
 - Disposal unit for used needles and syringes.
- 3.1.2 Remove only one blister with Solution for Injection Pre-Filled Syringe at a time from the Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe's package. Keep all unused syringes in the refrigerator.
- 3.1.3 Wash your hands thoroughly with soap and water.
- 3.1.4 Expose the blister with the syringe inside to room temperature for at least 20 minutes to ensure that the solution has warmed up to room temperature.
- 3.1.5 If the solution contains particles, throw it away and start again from step 3.1.1, using a new pre-filled syringe.
- 3.1.6 Choose the injection site, using the diagrams in Figure 1. There are seven possible areas on your body for injection: arms, thighs, buttocks and abdomen (stomach). Choose a different site for the injection every day, as this will reduce the chances of any irritation or pain at the site of the injection. Within each injection area there are multiple injection sites. Rotate the injection sites within an area. Do not use the exact same site each time. Please note: do not inject in any area that is painful or discolored or where you feel firm knots or lumps. It is recommended to have a planned rotating injection site schedule and to note it in a diary. There are some sites in your body that may be difficult for self-injection (like the back of your arm), and you may require assistance.

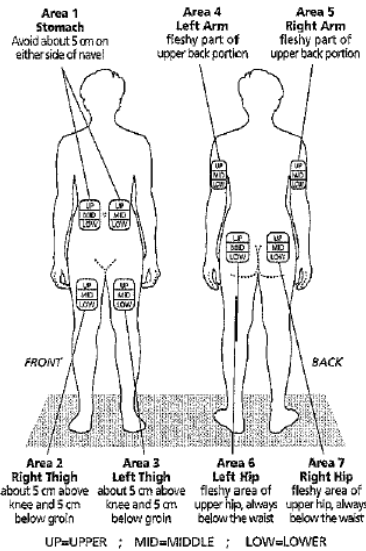


Figure 1

- 3.1.7 Remove the syringe from its protective blister by peeling back the paper label.
- 3.1.8 Using the hand you write with, hold the syringe as you would a pencil. Remove the needle shield from the needle.
- 3.1.9 Gently pinch up the skin with your thumb and forefinger (Figure 2).
- 3.1.10 Push the needle into the skin (Figure 3). Inject the medicine by steadily pushing the plunger all the way down until the syringe is empty.



Figure-2

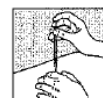


Figure-3

- 3.1.11 Pull the syringe and needle straight out.

- 3.1.12 Discard the syringe in a safe disposal container.

If you have the impression that the effect of Copaxone 20 mg is too strong or too weak, talk to your doctor.

If you have used more Copaxone 20 mg than you should, talk to a doctor immediately.
 If you forget to use Copaxone 20 mg Use it as soon as you remember, but do not use a double dose to make up for forgotten individual doses. Use the next dose 24 hours later.

Do not stop using Copaxone 20 mg without consulting your doctor.

4. POSSIBLE SIDE EFFECTS

Copaxone 20 mg can have side effects.

If any of the following happen, stop taking Copaxone 20 mg and tell your doctor immediately or go to the casualty department at your nearest hospital:

- rash (red spots or nettle rash)
- swelling of the eyelids, face or lips
- sudden wheeziness
- convulsions (fits)
- fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to Copaxone 20 mg. You may need urgent medical attention or hospitalisation.

All of these very serious side effects are rare.

Occasionally, shortly after injecting Copaxone 20 mg, some people may experience one or more of the following symptoms:

- flushing of the chest or face
- a feeling of tightness in the chest
- shortness of breath
- rapid heartbeat (palpitations).

These symptoms do not normally cause any problems and usually disappear within half an hour. If these symptoms do last longer than 30 minutes, they are serious side effects. You may need urgent medical attention.

Tell your doctor immediately or go to the casualty department at your nearest hospital. Serious side effects are rare.

Tell your doctor if you notice any of the following:

- weakness
- nausea (feeling sick)
- headache
- dizziness
- stiffness
- sweating
- tremor
- joint pain
- pain, redness, mass, swelling or inflammation at the injection site.

These are all mild side effects of Copaxone 20 mg. The injection site reactions are common, and usually decrease over time. At injection sites, localized loss of fat beneath the skin has been reported (usually shown as a depression in the skin surface). Rarely an area of skin overlying an injection site has been lost.

Some treatments for MS may affect the level of white cells and other substances in your blood. Your doctor may want to check this by doing a blood test.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING COPAXONE 20 mg/ml SOLUTION FOR INJECTION PRE-FILLED SYRINGE

In-use storage time and conditions prior to use are the responsibility of the user. Keep Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe out of the reach and sight of children.

Store in a refrigerator 2°C to 8°C.

DO NOT FREEZE.

If Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not store Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringes at room temperature for longer than one month.

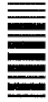
After this one-month period, if the Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringes have not been used and are still in their original package, they must be returned to storage in the refrigerator (2°C to 8°C).

Keep the container in the outer carton, in order to protect from light.

Do not use if it contains particles.

Do not use Copaxone 20 mg/ml Solution for Injection Pre-Filled Syringe after the expiry date which appears on the package.

This leaflet was approved: March 2007



Module 4 Labelling

15.8.2007



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

On 25th September 2006, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia granted marketing authorisations to Teva Pharmaceuticals Limited for the medicinal product Copaxone 20mg/ml Solution for Injection, Prefilled Syringe (UK/H/0453/002/E01). This application was made by a repeat-wave Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS). A national licence had previously been granted in the UK on 7th April 2003 (PL 10921/0023) and marketing authorisations had also been granted in Austria, Belgium, Germany, Denmark, Finland, Greece, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain and Sweden on 12th January 2004 by a first-wave MRP (UK/H/0453/002/MR).

These are applications made under Article 8.3 of 2001/83 EC for Copaxone 20mg/ml Solution for Injection, Prefilled Syringe, a line-extension to an already granted product, Copaxone Powder for Injection (PL 10921/0019), with the proposed product being a different pharmaceutical form.

Glatiramer acetate (previously known as Copolymer-1), the active ingredient of Copaxone, is the acetate salt of a mixture of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine.

Glatiramer acetate is intended for the treatment of relapsing-remitting multiple sclerosis.

The peptide mixture in Copaxone 20mg/ml Solution for Injection, Prefilled Syringe is thought to have an immunomodulatory effect, and clinical trials of Copaxone have shown a similar reduction in relapse rate in patients with RR MS to that demonstrated by beta interferon.

Copaxone 20mg/ml Solution for Injection, Prefilled Syringe is a prescription-only medicine, indicated for the reduction in frequency of relapses in ambulatory patients (i.e. who can walk unaided) with relapsing, remitting multiple sclerosis (MS) characterised by at least two attacks of neurological dysfunction over the preceding 2-year period.

No new preclinical or clinical studies were conducted, which is acceptable given that the application is a line-extension of a previously granted product.

The UK was assured that acceptable standards of GMP are in place for this product at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the UK has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Copaxone 20mg/ml Solution for Injection, Prefilled Syringe
Name(s) of the active substance(s) (USAN)	Glatiramer acetate
Pharmacotherapeutic classification (ATC code)	Immunomodulating agent (L03A X13)
Pharmaceutical form and strength(s)	Solution for injection 20mg/ml
Reference numbers for the Mutual Recognition Procedure	UK/H/0453/002/E01
Reference Member State	United Kingdom
Member States concerned	Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic, Slovenia
Marketing Authorisation Number(s)	PL 10921/0023
Name and address of the authorisation holder	Teva Pharmaceuticals Ltd, Denton Hall, 5 Chancery Lane, Cliffords Inn, London, EC4A 1BU, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

USAN: Glatiramer acetate

Chemical Name: L-Glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt)

Molecular formula: Poly [L-Glu¹³⁻¹⁵, L-Ala³⁹⁻⁴⁶, L-Tyr^{8,6-10} L-Lys³⁰⁻³⁷].n (CH₃ CO₂H)
n= range of acetic acid moieties per 100 amino acid residues = 15-24

Average mol wt: 5,000 – 9,000 daltons

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance glatiramer acetate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. To date, all efforts have been made by the company to provide appropriate proof of structure for the active pharmaceutical ingredient, as well as to identify and characterize the known impurities.

Batch analysis data are provided that comply with the proposed specification.

Certificates of analysis have been provided for all reference standards used.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

Appropriate stability data have been generated. The data support a retest period of 24 months, at the recommended storage temperature of $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients mannitol and water for injections. These are both controlled to their respective European Pharmacopeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for these applications.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is contained in a pre-filled syringe, consisting of a Type I colourless glass barrel, a plastic plunger and a rubber stopper. The finished product is packed in sizes of 7 and 28 syringes. Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting mock-ups of all packaging before they are marketed.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and comply with guidelines concerning materials in contact with parenteral products.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set, with the following storage conditions: “Keep the container in the outer carton, in order to protect from light.”, “Store in refrigerator (2°C to 8°C).”, “If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C), once for up to 1 month.”, “After this 1-month period, if the Copaxone 20 mg/ml pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2°C to 8°C).”

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling

The SPC, PIL and labelling are pharmaceutically satisfactory.

No results from user testing of the PIL have been provided. However, the marketing authorisation holder has committed to supplying the results from user testing of the PIL in a variation application.

MAA Form

The MAA form is pharmaceutically satisfactory.

Expert Report

The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

This product has already been approved in the UK as Copaxone 20mg Powder for Injection (PL 10921/0019) and its respective solvent and throughout Europe as Copaxone Powder and Solvent for Solution for Injection. No new preclinical data have been submitted and none are required for this line extension of a new pharmaceutical form.

A preclinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

III.3 CLINICAL ASPECTS

This product has already been approved in the UK and throughout Europe as Copaxone 20mg Powder for Injection (PL 10921/0019) and its respective solvent. No new clinical data have been submitted and none are required for this line extension of a new pharmaceutical form.

A clinical expert report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

The SPC, PIL and labelling are medically satisfactory and are consistent with those for the original product Copaxone Powder for Injection (PL 10921/0019), upon which this line-extension is based.

The MAA form is medically satisfactory.

The grant of a marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Copaxone 20mg/ml Solution for Injection, Prefilled Syringe are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical studies were conducted. The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Copaxone 20mg/ml Solution for Injection, Prefilled Syringe beyond those already described.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the original product Copaxone Powder for Injection (PL 10921/0019), where appropriate.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with glatiramer acetate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
08-08-2007	IB	To extend the maximum permitted single exposure of the finished product, at room temperature, prior to use from 7 days to 1 month.	Granted 09-03-2007
09-02-2007	IA	To change the name and address of the marketing authorisation holder in Austria from the currently registered 'Aventis Pharma GmbH, Altmannsdorferstrasse 104, A - 1121 Wien' to 'Sanofi-Aventis GmbH, Leonard-Bernstein-Strasse 10, Saturn Tower, A - 1220 Wien'.	Granted 28-03-2007
27-06-2007	IB	To align the storage conditions of glatiramer acetate with ICH Q1A (R2) requirements, $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$.	Granted 21-08-2007
03-11-2007	II	To revise the currently approved wording of sections 4.1 (Therapeutic indications) and 5.1 (Pharmacodynamic properties) of the SPC in order to align the indication with current medical practice while maintaining the use of the product in patients with a diagnosis of MS, and to also include available information on the use of the product in paediatric patients in section 4.2 (Posology and method of administration) of the SPC.	Granted 15-07-2008
03-11-2007	IA	To register a change in address of the marketing authorisation holder, Teva Pharmaceuticals CR, s.r.o, in the Czech Republic and Slovak Republic only, from 'Drazni 7, 627 00 Brno, Czech Republic', to 'Radlicka 3185/1c, 150 00 Prague 5, Czech Republic'.	Granted 14-11-2007
29-02-2008	IB	To add a new pack size (of 7-syringe pack) outside the range of the currently approved pack sizes in Germany only.	Granted 29-04-2008