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

4.1. Therapeutic indications

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) (see Section 5.1).

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) characterised by at least two attacks of neurological dysfunction over the preceding two-year period.

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 is short-lived and resolves 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 Fertility, 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.

Breast-feeding: 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 (70%) than placebo injections (37%). The most commonly reported injection-site reactions, which were more frequently reported in Copaxone vs. placebo-treated patients, 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 31% of patients receiving Copaxone compared to 13% 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 four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with Copaxone and 509 patients treated with placebo for up to 36 months. Three trials in relapsing-remitting MS (RRMS) included a total of 269 patients treated with Copaxone and 271 patients treated with placebo for up to 35 months. The

fourth trial in patients who have experienced a first clinical episode and were determined to be at high risk of developing clinically definite MS included 243 patients treated with Copaxone and 238 patients treated with placebo for up to 36 months.

System Organ Class (SOC)	Very Common (>1/10)	Common (>1/100,<=1/10)	Uncommon (>1/1000,<=1/100)
Infections And Infestations	Infection, Influenza	Bronchitis, Gastroenteritis, Herpes Simplex, Otitis Media, Rhinitis, Tooth Abscess, Vaginal Candidiasis*	Abscess, Cellulitis, Furuncle, Herpes Zoster, Pyelonephritis
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)		Benign Neoplasm Of Skin, Neoplasm	Skin Cancer
Blood And Lymphatic System Disorders		Lymphadenopathy*	Leukocytosis, Leukopenia, Splenomegaly Thrombocytopenia, Lymphocyte Morphology Abnormal
Immune System Disorders		Hypersensitivity	
Endocrine Disorders			Goitre, Hyperthyroidism
Metabolism And Nutrition Disorders		Anorexia, Weight Increased*	Alcohol Intolerance, Gout, Hyperlipidaemia, Blood Sodium Increased, Serum Ferritin Decreased
Psychiatric Disorders	Anxiety*, Depression	Nervousness	Abnormal Dreams, Confusional State, Euphoric Mood, Hallucination, Hostility, Mania, Personality Disorder, Suicide Attempt
Nervous System Disorders	Headache,	Dysgeusia, Hypertonia, Migraine, Speech Disorder, Syncope, Tremor*	Carpal Tunnel Syndrome, Cognitive Disorder, Convulsion, Dysgraphia, Dyslexia, Dystonia, Motor Dysfunction, Myoclonus, Neuritis, Neuromuscular Blockade, Nystagmus, Paralysis, Peroneal Nerve Palsy, Stupor, Visual Field Defect
Eye Disorders		Diplopia, Eye Disorder*	Cataract, Corneal Lesion, Dry Eye, Eye Haemorrhage, Eyelid Ptosis, Mydriasis, Optic Atrophy
Ear And Labyrinth Disorders		Ear Disorder	
Cardiac Disorders		Palpitations*, Tachycardia*	Extrasystoles, Sinus Bradycardia, Tachycardia Paroxysmal
Vascular Disorders	Vasodilatation*		Varicose Vein

System Organ Class (SOC)	Very Common (>1/10)	Common (>1/100,<=1/10)	Uncommon (>1/1000,<=1/100)
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea*	Cough, Rhinitis Seasonal	Apnoea, Epistaxis, Hyperventilation, Laryngospasm, Lung Disorder, Choking sensation
Gastrointestinal Disorders	Nausea*	Anorectal Disorder, Constipation, Dental Caries, Dyspepsia, Dysphagia, Faecal Incontinence, Vomiting*	Colitis, Colonic Polyp, Enterocolitis, Eructation, Oesophageal Ulcer, Periodontitis Rectal Haemorrhage, Salivary Gland Enlargement
Hepatobiliary Disorders		Liver Function Test Abnormal	Cholelithiasis, Hepatomegaly
Skin And Subcutaneous Tissue Disorders	Rash*	Ecchymosis, Hyperhidrosis, Pruritus, Skin Disorder*, Urticaria	Angioedema, Dermatitis Contact, Erythema Nodosum, Skin Nodule
Musculoskeletal And Connective Tissue Disorders	Arthralgia, Back Pain*	Neck Pain	Arthritis, Bursitis, Flank Pain, Muscle Atrophy, Osteoarthritis
Renal And Urinary Disorders		Micturition Urgency, Pollakiuria, Urinary Retention	Haematuria, Nephrolithiasis, Urinary Tract Disorder, Urine Abnormality
Pregnancy, Puerperium And Perinatal Conditions			Abortion
Reproductive System And Breast Disorders			Breast Engorgement, Erectile Dysfunction, Pelvic Prolapse, Priapism, Prostatic Disorder, Smear Cervix Abnormal, Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder
General Disorders And Administration Site Conditions	Asthenia, Chest Pain*, Injection Site Reactions*§, Pain*	Chills*, Face Oedema*, Injection Site Atrophy♣, Local Reaction*, Oedema Peripheral, Oedema, Pyrexia	Cyst, Hangover, Hypothermia, Immediate Post-Injection Reaction, Inflammation, Injection Site Necrosis, 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. Adverse reaction without the * symbol represents a difference of less than or equal to 2%.
§ The term 'Injection site reactions' (various kinds) comprises all adverse events occurring at the injection site excluding injection site atrophy and injection site necrosis, which are presented separately within the table.
♣ Includes terms which relate to localized lipoatrophy at the injection sites.

In the fourth trial noted above, an open-label treatment phase followed the placebo-controlled period (see Section 5.1). No change in the known risk profile of Copaxone was observed during the open-label follow-up period of up to 5 years.

Rare (>1/10000, <1/1000) reports of anaphylactoid reactions were collected from MS patients treated with Copaxone in uncontrolled clinical trials and from post-marketing experience with Copaxone.

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.

RRMS:
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 included 251 patients treated for up to 35 months (Copaxone n=125, placebo n=126) and 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.

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. An open-label treatment phase followed the placebo-controlled period: following conversion to clinically definite multiple sclerosis (CDMS) or after three years of treatment, or upon proof of overwhelming effect, whichever came first, all patients 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 three 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 favourable 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 analysis of cumulative number of lesions until end of each year in new T1 Gd-enhancing lesions, new T2 lesions and new T1 hypointense lesions. An effect in reductions in favor of early versus delayed treatment was observed for the total number of new T1 Gd-enhancing lesions, T1 Gd-enhancing lesions volume, as well as the total number of new T1 hypointense lesions measured over the entire study period.

No appreciable differences between the Early Start and Delayed Start cohorts were observed for either hypointense T1 lesions volume or brain atrophy over 5 years. However, analysis of brain atrophy at LOV (adjusted to treatment exposure) showed a reduction in favour of early treatment with GA.

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 one 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 container

A pre-filled syringe containing Copaxone solution for injection consists of a 1 ml long colourless type I glass syringe barrel with staked needle, a plastic plunger rod, a rubber plunger stopper and a needle shield.

Copaxone is available in packs containing 7, 28 or 30 pre-filled syringes of 1 ml solution for injection or a multipack containing 90 (3 packs of 30) pre-filled syringes of 1 ml solution for injection.

Not all pack sizes may be marketed.

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
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Whistler Drive
Castleford
West Yorkshire
WF10 5HX United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 10921/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 7 April 2003

10 DATE OF REVISION OF THE TEXT

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