SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Copaxone 20 mg/ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

*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. Due to its compositional complexity, no specific polypeptide can be fully characterised, including in terms of amino acid sequence, although the final glatiramer acetate composition is not entirely random.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear solution free of visible particles
The solution for injection has a pH of 5.5 - 7.0 and an osmolarity of about 265 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Copaxone is indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see section 5.1 for important information on the population for which efficacy has been established).
Copaxone is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration

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

Posology

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.

Renal impairment

Copaxone has not been specifically studied in patients with renal impairment (see section 4.4).

Elderly

Copaxone has not been specifically studied in the elderly.

Paediatric population

The safety and efficacy of glatiramer acetate in children and adolescents has not been established.

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.

Method of administration

Copaxone is for subcutaneous use.

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 should be chosen for every injection, 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.

The CSYNC device is available should the patients want to make their injection with an injection device. The CSYNC device is an autoinjector to be used with Copaxone pre-filled syringes and it has not been tested with other pre-filled syringes. The CSYNC device should be used as recommended in the information provided by the device manufacturer.

4.3 Contraindications

Copaxone is contraindicated under the following conditions:

- Hypersensitivity to the active substance (glatiramer acetate) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Glatiramer acetate can cause post-injection reactions as well as anaphylactic reactions (see section 4.8):

Post-injection reactions
The treating physician should explain to the patient that a reaction associated with at least one of the following symptoms may occur within minutes of a Copaxone injection: vasodilatation (flushing), chest pain, dyspnoea, palpitations or tachycardia (see section 4.8). 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 for 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.

Anaphylactic reactions
Anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.8). Cases with fatal outcome have been reported. Some signs and symptoms of anaphylactic reactions may overlap with post-injection reactions.

All patients receiving treatment with Copaxone and caregivers should be informed about the signs and symptoms specific for anaphylactic reactions and that they should seek immediate emergency medical care in case of experiencing such symptoms (see section 4.8).

If an anaphylactic reaction occurs, treatment with Copaxone must be discontinued (see section 4.3).

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.

Rare cases of severe liver injury have been observed (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation). Liver injury occurred from days to years after initiating treatment with Copaxone. Most instances of severe liver injury resolved with discontinuation of treatment. In some cases, these reactions have occurred in the presence of excessive alcohol consumption, existing or history of liver injury and use of other potentially hepatotoxic medication. Patients should be regularly monitored for signs of hepatic injury and instructed to seek immediate medical attention in case of symptoms of liver injury. In case of clinically significant liver injury, discontinuation of Copaxone should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

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

Observations from existing clinical trials and post-marketing experience do not suggest any significant interactions of Copaxone with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days.

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.

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For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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Post-injection reactions

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There is no evidence to suggest that any particular patient groups are at special risk for 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.

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Anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.8). Cases with fatal outcome have been reported. Some signs and symptoms of anaphylactic reactions may overlap with post-injection reactions.
All patients receiving treatment with Copaxone and caregivers should be informed about the signs and symptoms specific for anaphylactic reactions and that they should seek immediate emergency medical care in case of experiencing such symptoms (see section 4.8).
If an anaphylactic reaction occurs, treatment with Copaxone must be discontinued (see section 4.3).

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.

Rare cases of severe liver injury have been observed (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation). Liver injury occurred from days to years after initiating treatment with Copaxone. Most instances of severe liver injury resolved with discontinuation of treatment. In some cases, these reactions have occurred in the presence of excessive alcohol consumption, existing or history of liver injury and use of other potentially hepatotoxic medication. Patients

should be regularly monitored for signs of hepatic injury and instructed to seek immediate medical attention in case of symptoms of liver injury. In case of clinically significant liver injury, discontinuation of Copaxone should be considered.

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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
A large amount of data on pregnant women (more than 1 000 exposed outcomes) indicate no malformative nor feto/neonatal toxicity.

Copaxone can be used during pregnancy, if clinically needed.

Breast-feeding
The physico-chemical properties and low oral absorption suggest that exposure of newborns/infants to glatiramer acetate via human breast milk is negligible. A non-interventional retrospective study in 60 breastfed infants of mothers exposed to glatiramer acetate compared to 60 breastfed infants of mothers not exposed to any disease modifying therapy and limited post-marketing human data showed no negative effects of glatiramer acetate.

Copaxone can be used during breast-feeding.

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, in clinical trials and in post marketing experience, were erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity and rare occurrences of lipoatrophy and skin necrosis.

A reaction, associated with at least one or more of the following symptoms, has been described as the immediate post-injection reaction: vasodilatation(flushing), chest pain, dyspnoea, palpitation or tachycardia (see section 4.4). 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.

Adverse reactions identified from clinical trials and post marketing experience are presented in the table below. Data from clinical trials 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 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000**	**not knov (cannot estimate from th availab data)**
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	Anaphylactic reaction		
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		

System Organ Class (SOC)	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000**	**not know (cannot b estimate from th availabl data)**
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		
Respiratory, thoracic and mediastinal disorders	Dyspnoea*	Cough, Rhinitis Seasonal	Apnoea, Epistaxis, Hyperventilation, Laryngospasm, Lung Disorder, Choking Sensation		

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000	not know (cannot estimate from th availabl data)
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	Toxic hepatitis, Liver injury	Hepatic failure[#]
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		

Reproductive system and breast disorders			Breast Engorgement, Erectile Dysfunction, Pelvic Prolapse, Priapism, Prostatic Disorder, Smear Cervix Abnormal, Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder		
System Organ Class (SOC)	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000**	**not know (cannot estimate from th availabl data)**
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 PostInjection 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.

Few cases were reported with liver transplantation

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.

Description of selected adverse reactions

Anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9. Overdose

Symptoms
A few cases of overdose with Copaxone (up to 300 mg glatiramer acetate) have been reported. These cases were not associated with any adverse reactions other than those mentioned in section 4.8.

Management
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: Antineoplastic and immunomodulating agents, other immunostimulants ATC code: L03AX13

Mechanism of action
The mechanism by which glatiramer acetate exerts therapeutic effects in relapsing forms of MS is not fully elucidated but is presumed to involve modulation of immune processes. Studies in animals and MS patients suggest glatiramer acetate acts on innate immune cells, including monocytes, dendritic cells and B cells, which in turn modulate adaptive functions of B and T cells inducing anti-inflammatory and regulatory cytokine secretion. Whether the therapeutic effect is mediated by the cellular effects described above is not known because the pathophysiology of MS is only partially understood.

Clinical efficacy and safety
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 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 20 mg/mL: In the controlled study 9001/9001E, which enrolled 251 patients, who were followed for up to 35 months (including a blinded phase extension 9001E of the 9001 study), the cumulative percentage of patients who developed 3-month confirmed disability progression was 29.4% for placebo- and 23.2% for Copaxone-treated patients (p=0.199).

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 MS 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 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], pvalue=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%; $p=0.0209$).

5.2. 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, 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 cannot 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.
In rats, a slight but statistically significant reduction in body weight gain of offspring born to dams treated during pregnancy and throughout lactation was observed at subcutaneous doses ≥ 6mg/kg/day (2.83-times the maximum recommended human daily dose for a 60 kg adult based on mg/m2) in comparison to control. No other significant effects on offspring growth and behavioral development were observed.

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

3 years

6.4. Special precautions for storage

Keep the pre-filled syringes in the outer carton, in order to protect from light.

Store in a refrigerator (2 C – 8 C).

Do not freeze.

If the pre-filled syringes cannot be stored in a refrigerator, they can be stored between 15°C and 25°C, once for up to one 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 colourless type I glass syringe barrel with staked needle, a polypropylene (optional polystyrene) plunger rod, a rubber plunger stopper and a needle shield.

Each pre-filled syringe is packed separately in a PVC blister pack.

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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]
{Name and address}

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]

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

Most Copaxone safety data were accumulated for Copaxone 20 mg/ml administered as a subcutaneous injection once daily. This section presents accumulated safety data from four placebo-controlled trials with Copaxone 20 mg/ml administered once daily, and from one placebo-controlled trial with Copaxone 40 mg/ml administered three times a week.

A direct comparison of the safety between Copaxone 20 mg/ml (administered daily) and 40 mg/ml (administered three times per week) in the same study has not been performed.

Copaxone 20 mg/ml (administered once daily)
In all clinical trials with Copaxone 20 mg/ml, 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 20 mg/ml (70%) than placebo injections (37%). The most commonly reported injection-site reactions, which were more frequently reported in Copaxone 20 mg/ml 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, has been described as the immediate post-injection reaction: vasodilatation (flushing), chest pain, dyspnoea, palpitation or tachycardia (see section 4.4). 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 20 mg/ml compared to 13% of patients receiving placebo.

Adverse reactions identified from clinical trials and post marketing experience are presented in the table below. Data from clinical trials was derived from four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with Copaxone 20 mg/day 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 20 mg/day 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 20mg/day and 238 patients treated with placebo for up to 36 months.

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000	not known (cannot be estimated from the available data)
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	Anaphylactic reaction		
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		

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000	not known (cannot be estimated from the available data)
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		
Respiratory, thoracic and mediastinal disorders	Dyspnoea*	Cough, Rhinitis Seasonal	Apnoea, Epistaxis, Hyperventilation, Laryngospasm, Lung Disorder, Choking Sensation		

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000	not known (cannot be estimated from the available data)
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	Toxic hepatitis, Liver injury	Hepatic failure[#]
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		
Reproductive system and breast disorders			Breast Engorgement, Erectile Dysfunction, Pelvic Prolapse, Priapism, Prostatic Disorder, Smear Cervix Abnormal, Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder		

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000	not known (cannot be estimated from the available data)
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 localised lipoatrophy at the injection sites.

Few cases were reported with liver transplantation.

In the fourth trial noted above, an open-label treatment phase followed the placebo-controlled period. No change in the known risk profile of Copaxone 20 mg/ml was observed during the open-label follow-up period of up to 5 years.

<u>Copaxone 40 mg/ml (administered three times per week)</u>
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 labelled 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).

Injection site reactions were reported by 36% of the patients on Copaxone 40 mg/ml compared to 5% on placebo. Immediate post-injection reaction was reported by 8% of the patients on Copaxone 40 mg/ml compared to 2% on placebo.

A few specific adverse reactions are noted:

- Anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.4).

- 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, were each reported by one patient (0.1%) on Copaxone 40 mg/ml (Uncommon: ≥ 1/1,000 to < 1/100).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

A few cases of overdose with Copaxone (up to 300 mg glatiramer acetate) have been reported. These cases were not associated with any adverse reactions other than those mentioned in section 4.8.

Management

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: Antineoplastic and immunomodulating agents, other immunostimulants

ATC code: L03AX13

Mechanism of action
The mechanism by which glatiramer acetate exerts therapeutic effects in relapsing forms of MS is not fully elucidated but is presumed to involve modulation of immune processes. Studies in animals and MS patients suggest glatiramer acetate acts on innate immune cells, including monocytes, dendritic cells and B cells, which in turn modulate adaptive functions of B and T cells inducing anti-inflammatory and regulatory cytokine secretion. Whether the therapeutic effect is mediated by the cellular effects described above is not known because the pathophysiology of MS is only partially understood

Clinical efficacy and safety
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 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 20 mg/mL: In the controlled study 9001/9001E, which enrolled 251 patients, who were followed for up to 35 months (including a blinded phase extension 9001E of the 9001 study), the cumulative percentage of patients who developed 3-month confirmed disability progression was 29.4% for placebo and 23.2% for Copaxone-treated patients (p=0.199).

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 MS 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 randomised to Copaxone, 198 continued Copaxone treatment in the open-label phase. Of the 238 patients initially randomised 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 annualised 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).

5.2 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, 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 cannot 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.

In rats, a slight but statistically significant reduction in body weight gain of offspring born to dams treated during pregnancy and throughout lactation was observed at subcutaneous doses ≥ 6mg/kg/day (2.83-times the maximum recommended human daily dose for a 60 kg adult based on mg/m^2) in comparison to control. No other significant effects on offspring growth and behavioural development were observed.

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

3 years

6.4 Special precautions for storage

Keep the pre-filled syringes in the outer carton, in order to protect from light.
Store in a refrigerator (2°C – 8°C).
Do not freeze.
If the pre-filled syringes cannot be stored in a refrigerator, they can be stored between 15°C and 25°C, once for up to one 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 colourless type I glass syringe barrel with staked needle, a polypropylene (optional polystyrene) plunger rod, a rubber plunger stopper and a needle shield.

Each pre-filled syringe is packed separately in a PVC blister pack.

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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharmaceuticals Ltd.
Ridings Point
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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

30/10/2025