SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Copaxone 40 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 40 mg glatiramer acetate*, equivalent to 36 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 characterized, 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 (injection)

Clear solution free of visible particles.
The solution for injection has a pH of 5.5 - 7.0 and an osmolarity of about 300 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 40 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection three times a week with at least 48 hours apart.
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. There is not enough information available on the use of Copaxone 40 mg/ml TIW in children and adolescents below 18 years of age to make any recommendation for its use. Therefore, Copaxone 40 mg/ml TIW 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.

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.

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
Studies in animals have not shown reproductive toxicity (see section 5.3). Current data on the use of Copaxone 20 mg/ml in pregnant women indicate no malformative or feto/neonatal toxicity. Data on the use of Copaxone 40 mg/ml are consistent with these findings. To date, no relevant epidemiological data are available. As a precautionary measure, it is preferable to avoid the use of Copaxone during pregnancy unless the benefit to the mother outweighs the risk to the foetus.

Breastfeeding
It is unknown whether glatiramer acetate or its metabolites are excreted in human milk. In rats, no significant effects on offspring were observed except for a slight reduction in body weight gains in the offspring of mothers dosed during pregnancy and throughout lactation (see section 5.3).

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Copaxone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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.

All adverse reactions, which were more frequently reported in Copaxone 20 mg/ml 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 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)**
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

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
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
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

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
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. 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.

Rare (≥1/10,000 to <1/1,000) reports of anaphylactoid reactions were collected from MS patients treated with Copaxone in uncontrolled clinical trials and from post-marketing experience with Copaxone.

Copaxone 40 mg/ml (administered three times per week)

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

In general, the kind of adverse drug reactions seen in patients treated with Copaxone 40 mg/ml administered three times per week were those already known and 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 response was seen rarely (≥1/10,000, <1/1,000) in MS patients treated with Copaxone 20 mg/ml in uncontrolled clinical trials and from post-marketing experience. It was reported by 0.3% of the patients on Copaxone 40 mg/ml (Uncommon: ≥ 1/1,000 to < 1/100).
- No injection site necrosis was reported.
- Skin erythema and pain in extremity, not labelled for Copaxone 20 mg/ml, were reported each by 2.1% of the patients on Copaxone 40 mg/ml (Common: ≥ 1/100 to < 1/10).
- Drug-induced liver injury and toxic hepatitis, also seen rarely in MS patients treated with Copaxone 20 mg/ml in post marketing surveillance, were each reported by one patient (0.1%) on Copaxone 40 mg/ml (Uncommon: ≥ 1/1,000 to < 1/100).

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
Relapsing-Remitting Multiple Sclerosis

Evidence supporting the effectiveness of Copaxone 40 mg/ml injection administered subcutaneously three times a week in decreasing the frequency of relapses derives from one 12-month placebo-controlled study.

In the pivotal clinical trial Relapsing-Remitting Multiple Sclerosis was characterized by either at least one documented relapse in the last 12 months, or at least two documented relapses in the last 24 months, or one documented relapse between the last 12 and 24 months with at least one documented T1-gadolinium enhancing lesion on magnetic resonance imaging performed the last 12 months.
The primary outcome measure was the total number of confirmed relapses. Secondary MRI outcomes included the cumulative number of new/enlarging T2 lesions and the cumulative number of enhancing lesions on T1-weighted images, both measured at months 6 and 12.

A total of 1404 patients were randomized in a 2:1 ratio to receive either Copaxone 40 mg/ml (n=943) or placebo (n=461). Both treatment groups were comparable with respect to baseline demographics, MS disease characteristics and MRI parameters. Patients had a median of 2.0 relapses in the 2 years prior to screening.

Compared to placebo, patients treated with Copaxone 40 mg/ml three times per week had meaningful and statistically significant reductions in the primary and secondary outcome measures which are consistent with the treatment effect of Copaxone 20 mg/ml administered daily.
The following table presents the values for the primary and secondary outcome measures for the intent-to-treat population:

Outcome Measure	**Adjusted Mean Estimates**		**P-Value**
	Copaxone (40 mg/ml) (N=943)	**Placebo (N=461)**	
Annualized relapse rate (ARR)	0.331	0.505	p<0.0001
Absolute Risk Difference* (95% confidence intervals)	-0.174 [-0.2841 to -0.0639]		
Cumulative number of new/enlarging T2 lesions at months 6 and 12	3.650	5.592	p<0.0001
Rate ratio** (95% confidence intervals)	0.653 [0.546 to 0.780]		
Cumulative number of enhancing lesions on T1-weighted images at months 6 and 12	0.905	1.639	p<0.0001
Rate ratio** (95% confidence intervals)	0.552 [0.436 to 0.699]		

*Absolute risk difference is defined as the difference between the adjusted mean ARR of GA 40 mg TIW and adjusted mean ARR of Placebo.
** Rate ratio is defined as the ratio between GA 40 mg TIW and Placebo adjusted mean rates.

A direct comparison of the efficacy and 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 40 mg/mL: The proportion of patients with 3-month confirmed disability progression (CDP) was an exploratory endpoint in a 12-month placebo-controlled study (GALA). Three-month CDP was experienced by 3% and 3.5% of placebo- and Copaxone-treated patients, respectively (odds ratio, OR [95% CI]: 1.182 [0.661, 2.117] (p=0.5726)). Including the open-label extension of the study (up to 7 years), time to 6-month CDP was an exploratory endpoint. The hazard ratio (HR) [95% CI] for the intent

to treat cohort, comparing the early start Copaxone group to the delayed start group was 0.892 [0.688, 1.157] (p=0.3898).

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

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 SmPC. 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

2 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 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 40 mg/ml solution for injection consists of a 1 ml colourless type I glass syringe barrel with staked needle, a blue 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 40 mg/ml is available in packs containing 3 or 12 pre-filled syringes of 1 ml solution for injection or in a multipack containing 36 (3 packs of 12) 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]