NEW ZEALAND DATA SHEET

1. PRODUCT NAME

COPAXONE® 20 mg/mL PRE-FILLED SYRINGE

COPAXONE® 40 mg/mL PRE-FILLED SYRINGE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Copaxone 20 mg/mL contains 20 mg of glatiramer acetate.

Copaxone 40 mg/mL contains 40 mg of glatiramer acetate.

Glatiramer acetate, the active ingredient in both Copaxone 20 mg/mL and Copaxone 40 mg/mL, is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction 0.141, 0.427, 0.095 and 0.338, respectively. The average molecular weight of glatiramer acetate is 5000 to 9000 Daltons.

For a full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Copaxone is a clear, colourless solution for injection, in a pre-filled syringe.

The pH of a 0.5% solution in water is in the range of 5.5 to 7.0 and an osmolarity of about 265 mOsmol/L and 300 mOsmol/L for the 20 mg/mL and 40 mg/mL, respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of the frequency of relapses in patients with Relapsing Remitting Multiple Sclerosis.

Treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent MRI lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded.

4.2 Dose and method of administration

The only recommended route of administration of Copaxone injection is by the subcutaneous route. Copaxone should not be administered by the intravenous or intramuscular routes.

Copaxone 20 mg/mL

The recommended dosage in adults is a once daily subcutaneous injection of 1 mL Copaxone 20 mg. This corresponds to one Copaxone 20 mg/mL pre-filled syringe.

Copaxone 40 mg/mL

The recommended dosage in adults is one subcutaneous injection of 1 mL Copaxone 40 mg administered three times a week and at least 48 hours apart. This corresponds to one Copaxone 40 mg/mL pre-filled syringe per administration.

Paediatric Use

No prospective, randomised, 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 studied specifically in elderly patients but safety data are reassuring for patients up to 65 years of age.

Use in Patients with Impaired Renal Function

Renal function should be monitored in patients with impaired renal function.

Method of Administration

Sites for self-injection include arms, abdomen, hips and thighs. A different site for injection should be used each day in order to reduce the likelihood of local irritation or pain as a result of the injection.

Patients should be instructed in self-injection techniques to assure the safe administration of Copaxone (see Copaxone Consumer Medicine Information).

Before injecting, the solution should be removed from refrigerated storage and left at room temperature for about 20 minutes to warm up.

Copaxone is intended for long-term treatment and its use should not be discontinued unless clearly indicated by a physician.

Copaxone pre-filled syringe contains no antimicrobial agent. It is for single use in one patient only. Discard any residue.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Immediate Post-Injection Reaction

In placebo-controlled studies of up to 2 years duration with COPAXONE 20 mg/mL, approximately 16% of patients given COPAXONE and 4% given placebo experienced a constellation of symptoms immediately after injection. In a 12-month, placebo-controlled study of COPAXONE 40 mg/mL, approximately 2% of patients given COPAXONE and none given placebo developed similar symptoms. Symptoms included: flushing, chest pain, palpitations, anxiety, dyspnoea, constriction of the throat, and urticaria. The symptoms were generally transient and self-limited and did not require specific treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care.

Whether an immunologic or non-immunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

The treating physician should explain to the patient that a reaction (Immediate Post Injection 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. 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.

Impaired Renal Function

The pharmacokinetics of Copaxone in patients with impaired renal function have not been determined. In patients with renal impairment, renal function should be monitored while they are treated with Copaxone. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded. This drug should be administrated with care in patients with renal dysfunction.

Liver injury

Very rare cases of severe liver injury, including liver failure, hepatitis with jaundice, and extremely rare cases of fulminant hepatitis leading to liver transplant, have been reported with Copaxone during postmarketing experience in patients with and without relevant risk factors in their medical history, such as history of drug induced liver events with other disease modifying therapies (DMTs) indicated for the treatment of multiple sclerosis, concomitant treatment with drugs with known Drug Induced Liver Injury (DILI) risk or medical history of liver impairment. Hepatic adverse events have occurred from days to

years after initiating treatment with Copaxone and with a similar profile with both dose regimens (20 mg/mL daily and 40 mg/mL TIW), suggesting idiosyncratic drug induced liver injury in most cases. Some cases, reported in patients who previously experienced liver injury during treatment with other immunomodulatory therapies used to treat multiple sclerosis, were suggestive of autoimmune hepatitis. Most events resolved with discontinuation of treatment and a relationship to Copaxone could not be excluded (see section 4.8 Adverse Effects (Undesirable effects), Post-marketing Experience).

Caution is recommended when considering treatment with Copaxone in patients who have pre-existing liver disease or who have experienced liver injury previously during treatment with other drugs, including other disease modifying therapies (DMTs) for treatment of multiple sclerosis or with concomitant (DILI) risk drugs.

Prior to initiating treatment with COPAXONE, serum aminotransferase, alkaline phosphatase and total bilirubin levels should be obtained (within 6 months) for all patients. Patients should be monitored during treatment for signs of hepatic injury. Evaluation of transaminases is recommended during treatment, as clinically relevant. Patients should be advised to immediately report any signs or symptoms of hepatotoxicity (e.g., jaundice, dark urine, abdominal pain, nausea, vomiting, loss of appetite, weight loss, and unusual fatigue). Discontinue treatment if clinically significant liver injury induced by Copaxone is suspected.

Chest Pain

In placebo-controlled studies of up to 2 years with Copaxone 20 mg/mL approximately 13% of patients given COPAXONE and 6% given placebo experienced at least one episode of transient chest pain. In a 12-month, placebo-controlled study with Copaxone 40mg/mL approximately 2% of patients given COPAXONE and 1% given placebo experienced at least one episode of chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection was not always known. The pain was usually transient, often not associated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

Immune function

As Copaxone is an antigenic material, it is possible that its use may lead to the induction of antibodies (see section 5.1 Pharmacodynamic properties).

As with all immunogenic medicines, hypersensitivity reactions may rarely occur.

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

Copaxone has not been studied in patients with a history of severe anaphylactoid reactions or asthma, nor in patients under treatment for asthma. Particular caution is therefore advised regarding the use of Copaxone in such patients.

Although Copaxone is intended to minimise the autoimmune response to myelin, there is the possibility that chronic treatment with Copaxone might result in alteration of normal immune responses.

Injection site lipoatrophy and skin necrosis

At injection sites, localised lipoatrophy and, rarely, injection site skin necrosis may occur. Skin necrosis has only been observed in the post-marketing setting. Localised lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites with each injection.

Effects on laboratory tests

None known.

4.5 Interaction with other medicines and other forms of interaction

Results from clinical trials do not suggest any significant interactions of Copaxone with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids. Copaxone has not been formally evaluated in combination with Interferon beta-1b.
However, 10 patients who switched from therapy with Interferon beta-1b to Copaxone have not reported any serious or unexpected adverse events thought to be related to treatment.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No evidence of reproductive toxicity was observed. In a fertility and reproductive study in rats, glatiramer acetate had no adverse effects on reproductive parameters at subcutaneous doses of up to 36 mg/kg/day, which is 15 times the daily therapeutic dose in humans expressed in terms of mg/m^2.

Use in Pregnancy

Pregnancy Category B1.

No adverse effects on embryofoetal development occurred in reproduction studies in rats and rabbits receiving subcutaneous doses up to 37.5 mg/kg of glatiramer acetate during the period of organogenesis (15 and 28 times the daily human dose of 20 mg on a mg/m^2 basis respectively). In a perinatal/postnatal study, in which rats received subcutaneous glatiramer acetate at doses up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

To date, post-market information was received on more than 8,000 pregnancies, out of which 2000 were prospectively reported pregnancies with known outcome in patients exposed to conventional dose regimens of Copaxone. In this cohort, the reported rate of fetal loss was below 14% while congenital anomalies or disorders occurred in less than 3% of the pregnancies. These prevalence rates are within the range found in a normal population. However, since there are no adequate and well controlled studies in pregnant women, and because animal reproduction studies are not always predictive of human response, Copaxone should be used during pregnancy only if the benefits to the mother outweigh the potential risks to the fetus.

Use in Lactation

There are no data on the effects of Glatiramer acetate on milk production or on the presence of Glatiramer acetate in human milk. The physico-chemical properties and low oral absorption suggest that exposure of newborns/infants to glatiramer acetate via human breast milk is negligible.
Limited data in humans showed no negative effects of glatiramer acetate on breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Glatiramer acetate and any potential adverse effects on the breastfed infant from Glatiramer acetate or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

Based on current data, no special caution is required for patients operating a car or using complex machinery.

4.8 Undesirable effects

Copaxone 20 mg/mL Administered Once Daily

The adverse event data in this section are derived from 5 pivotal, double-blind, placebo-controlled clinical trials which were conducted during pre-marketing and post-marketing periods in a total of 563 patients treated with Copaxone and 564 patients treated with placebo for up to 36 months. Three trials were conducted in RRMS and one trial in secondary progressive MS (SPMS). The fifth trial was in patients presenting with a first clinical event and MRI features suggestive of MS and included 243 patients treated with Copaxone and 238 patients treated with placebo.

In the 5 placebo-controlled clinical trials the most commonly observed adverse events occurring at an incidence of at least 10% with the use of Copaxone and at least 1.5 times higher than among placebo-treated patients were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Approximately 5% of the subjects receiving Copaxone discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were: injection site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity.

Controlled Clinical Trials Experience

The following table (Table 1) lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with Copaxone 20 mg/mL in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with Copaxone than in patients treated with placebo. Adverse events were usually mild in intensity.

Table 1: Controlled Trials: Incidence of Copaxone (20 mg/mL Daily) Adverse Events ≥2% and More Frequent than Placebo

MedDRA Version 10.0		Copaxone 20 mg (N=563)		Placebo (N=564)	
		No. of Patients	% of Patients	No. of Patients	% of Patients
Blood And Lymphatic System Disorders	Lymphadenopathy	39	7	15	3
Cardiac Disorders	Palpitations	53	9	23	4
	Tachycardia	28	5	9	2
Eye Disorders	Eye Disorder	17	3	6	1
	Diplopia	15	3	10	2
Gastrointestinal Disorders	Nausea	82	15	61	11
	Vomiting	38	7	23	4
	Dysphagia	12	2	6	1
General Disorders And Administration Site Conditions	Injection Site Erythema	242	43	55	10
	Injection Site Pain	227	40	111	20
	Injection Site Pruritus	154	27	21	4
	Injection Site Mass	146	26	33	6
	Asthenia	124	22	118	21
	Pain	112	20	96	17
	Injection Site Oedema	109	19	23	4
	Chest Pain	74	13	34	6
	Injection Site Inflammation	49	9	8	1
	Oedema	46	8	11	2
	Injection Site Reaction	45	8	7	1
	Pyrexia	35	6	31	5
	Injection Site Hypersensitivity	22	4	0	0
	Local Reaction	19	3	7	1
	Chills	18	3	4	1
	Face Oedema	18	3	3	1
	Oedema Peripheral	17	3	13	2
	Injection Site Fibrosis	11	2	3	1
	Injection Site Atrophy*	10	2	0	0

MedDRA Version 10.0		Copaxone 20 mg (N=563)		Placebo (N=564)	
		No. of Patients	% of Patients	No. of Patients	% of Patients
Immune System Disorders	Hypersensitivity	17	3	9	2
Infections And Infestations	Infection	167	30	158	28
	Influenza	79	14	75	13
	Rhinitis	38	7	31	5
	Bronchitis	33	6	29	5
	Gastroenteritis	32	6	22	4
	Vaginal Candidiasis	25	4	13	2
Metabolism And Nutrition Disorders	Weight Increased	15	3	4	1
Musculoskeletal And Connective Tissue Disorders	Back Pain	69	12	59	10
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Neoplasm of Skin	9	2	3	1
Nervous System Disorders	Tremor	22	4	9	2
	Migraine	20	4	12	2
	Syncope	18	3	10	2
	Speech Disorder	9	2	3	1
Psychiatric Disorders	Anxiety	73	13	56	10
	Nervousness	13	2	5	1
Renal And Urinary Disorders	Micturition Urgency	26	5	22	4
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	80	14	21	4
	Cough	34	6	27	5
	Laryngospasm	14	2	7	1
Skin And Subcutaneous Tissue Disorders	Rash	109	19	63	11
	Hyperhidrosis	42	7	29	5
	Pruritus	29	5	25	4
	Urticaria	19	3	8	1
	Skin Disorder	18	3	5	1
Vascular Disorders	Vasodilatation	110	20	31	5

*Injection site atrophy comprises terms relating to localised lipoatrophy at injection site

The overall frequency of adverse events and the frequencies of individual adverse events were higher in patients treated with Copaxone for RRMS or SPMS, and lower in patients treated with Copaxone for a first clinical episode of MS.

Events which occurred only in 4-5 more subjects in the Copaxone group than in the placebo group (less than 1% difference), but for which a relationship to Copaxone could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for Copaxone. Clinically significant laboratory values for haematology, chemistry, and urinalysis were similar for both Copaxone and placebo groups in blinded clinical trials. No patient receiving Copaxone withdrew from any placebo-controlled trial because of abnormal laboratory findings which were assessed as possibly related to Copaxone. In one of the placebo-controlled trials, a transient elevation in eosinophils was shown after three months of Copaxone treatment in up to 7% of the patients which gradually declined while on treatment.

Data on adverse events occurring in the controlled clinical trials were analysed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. This percentage is indicative of the higher representation of Caucasians in the MS population, even though it does not reflect the exact world racial distribution among MS patients. In addition, the vast majority of patients treated with Copaxone were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse event incidence related to clinically relevant age subgroups.

Pre-marketing Clinical Trials Experience with Copaxone 20 mg/mL

During the pre-marketing period, clinical trials were conducted in RRMS and SPMS, only some of which were placebo-controlled. At that time, Copaxone was administered to approximately 900 individuals who received at least one dose.

Similar types of events were grouped into standardised categories using COSTART dictionary terminology. All reported events occurring at least twice and potentially important events occurring once are listed below, except those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Additional adverse events reported during the post-marketing period are also included.

Events are further classified within body system categories and listed in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring in less than 1/1000 patients.

Body as a Whole:

Frequent: Injection site oedema, injection site atrophy, abscess, injection site hypersensitivity.

Infrequent: Injection site haematoma, injection site fibrosis, moon face, cellulitis, generalised oedema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, photosensitivity reaction and injection site necrosis.

Cardiovascular:

Frequent: Hypertension.

Infrequent: Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum haemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal haemorrhage, tenesmus, tongue discolouration, and duodenal ulcer.

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

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

Haemic and Lymphatic:

Infrequent: Leukopenia, anaemia, cyanosis, eosinophilia, hematemesis, lymphoedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

Infrequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paraesthesia, depersonalisation, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation, hay fever.

Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

Frequent: Visual field defect.

Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

Frequent: Amenorrhea, haematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary

frequency and vaginal hemorrhage.

Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

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 involving a total of 943 patients treated with Copaxone 40 mg/mL three times per week, and 461 patients treated with placebo for 12 months. Approximately 3% of patients treated with Copaxone 40mg/mL discontinued treatment because of an adverse event.

Adverse drug reactions seen in patients treated with Copaxone 40 mg/mL were those already known and labelled for Copaxone 20 mg/mL daily and mostly reported at a similar frequency.

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 from an integrated safety analysis consisting of three studies that involved Copaxone 20 mg/mL once daily compared to Copaxone 40 mg/mL daily (two studies), and Copaxone 40 mg/mL 3-times-a-week compared to placebo. There was no direct comparison performed in a study between Copaxone 20 mg/mL daily with Copaxone 40 mg/mL 3-times-a-week. Only adverse events reported for the Copaxone 20 mg/mL daily, Copaxone 40 mg/mL 3-times-a-week and placebo groups are presented below:

- During the double blind phase of the trials the incidence in subjects of hypersensitivity/anaphylaxis was 0.6% on 20 mg/mL once daily, 0.7% on 40 mg/mL 3 times-a-week and 0.4% on placebo.
- No injection site necrosis was reported with the 40 mg/mL 3-times-a-week. Injection Site Atrophy occurred in 1.1% of patients on 20 mg/mL daily, 0.5% on 40 mg/mL 3-times-a-week and 0% on placebo.
- During the double blind phase of the trials the incidence in subjects of skin erythema was 3.3% on 20 mg/mL once daily, 2.1% on 40 mg/mL 3-times-a-week and 0% on placebo, while for pain in extremity it was 5.2% on 20 mg/mL daily, 2.1% on 40 mg/mL 3-times-a-week and 1.7% on placebo.
- During the double blind phase of the trials the incidence in subjects of drug-induced liver injury was 0.2% on 20 mg/mL once daily, 0.1% on 40 mg/mL 3-times-a-week and 0% on placebo, while for toxic hepatitis it was 0% on 20 mg/mL daily, 0.1% on 40 mg/mL 3-times-a-week and 0% on placebo: Hepatic Steatosis had an incidence 0.2% in both Copaxone groups and 0% on placebo.

Controlled Clinical Trial Experience

The following table (Table 2) lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with Copaxone 40 mg/mL in the blinded, placebo-controlled trial. These signs and symptoms were numerically more common in patients treated with Copaxone 40 mg/mL than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 2: Adverse reactions in a controlled clinical trial with an incidence ≥2% of patients and more frequent with COPAXONE 40 mg/mL 3- times-a-week than with placebo

		COPAXONE 40 mg/mL (n=943)	Placebo (n=461)
General Disorders And Administration Site Conditions	Injection Site Erythema	22%	2%
	Injection Site Pain	10%	2%
	Injection Site Mass	6%	0%
	Injection Site Pruritus	6%	0%
	Injection Site Oedema	6%	0%
	Pyrexia	2%	1%
	Influenza-like Illness	3%	2%
	Injection Site Inflammation	2%	0%
	Chills	2%	0%
	Chest Pain	2%	1%
Infections And Infestations	Nasopharyngitis	11%	9%
	Respiratory Tract Infection Viral	3%	2%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	3%	0%
Vascular Disorders	Vasodilatation	3%	0%
Gastrointestinal Disorders	Nausea	2%	1%
Skin And Subcutaneous Tissue Disorders	Erythema	2%	0%
	Rash	2%	1%

Post-marketing Experience

Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse events occurring under treatment with Copaxone Injection 20 mg/mL not mentioned above that have been received since market introduction and that may or may not have causal relationship to the drug are listed below. As these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; LE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue oedema; stomach ulcer; haemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Haemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukaemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain oedema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung; hay fever

Special Senses: glaucoma; blindness; visual field defect

Urogenital System: *urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency*

Rare cases of severe liver injury (including liver failure and hepatitis with jaundice and fulminant hepatitis leading to liver transplant) have been reported with Copaxone in post-marketing experience. Most instances of severe liver injury resolved with discontinuation of treatment. Hepatic events have occurred from days to years after initiating treatment with Copaxone.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (https://pophealth.my.site.com/carmreportnz/s/).

4.9 Overdose

There are 13 reports to date of overdose with Copaxone which were confirmed by health care professionals. Most cases concern 2 or 3 injections given on the same day. The largest dose of Copaxone that has been administered is 300mg on a single occasion. No adverse reactions occurred and the patient continued treatment.

There is no specific antidote. Treatment of overdose consists of discontinuation of Copaxone, along with monitoring the patient for at least 10 hours and the institution of appropriate symptomatic and supportive therapy. Contact the Poisons Information Centre for advice on the management of overdosage.

In New Zealand, call the New Zealand Poisons Centre on 0800 POISON or 0800 764 766 for advice on overdosage management

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glatiramer acetate is a white to slightly yellowish lyophilised material which is sparingly soluble in water and insoluble in acetone.

The structural formula of glatiramer acetate is shown below:

Poly [L-Glu$^{13\text{-}15}$, L-Ala$^{39\text{-}46}$, L-Tyr$^{8.6\text{-}10}$, L-Lys$^{30\text{-}37}$].n (CH_3CO_2H)

n = 15 to 24 units per 100 amino acid residues.

The superscripts in the formula above represent the molar fraction percent range of the amino acid residues comprising the various polypeptide species in glatiramer acetate where the sequence of the amino acid residues varies among the individual species.

CAS Registry Number: 147245-92-9

CAS Registry Number of the free base: 28704-27-0

The precise mechanism by which glatiramer acetate exerts its effects in patients with multiple sclerosis (MS) is unknown. It is thought to act by modifying immune processes that are currently held to be responsible for the pathogenesis of MS. This view of glatiramer acetate derives from knowledge that it reduces the incidence and severity of experimental allergic encephalomyelitis (EAE) - a condition induced in several animal species through immunisation with CNS-derived material containing myelin and often used as an experimental animal model of MS.

Relapsing Remitting Multiple Sclerosis

Copaxone 20 mg/mL Administered Once Daily

Evidence supporting the effectiveness of Copaxone 20 mg/mL for decreasing the frequency of relapses in patients with relapsing-remitting multiple sclerosis (RRMS) derives from two placebo controlled trials, both of which used a Copaxone dose of 20 mg/day.

One trial enrolled 50 patients who were randomised to receive daily doses of Copaxone 20 mg or placebo subcutaneously. Patients were diagnosed with RRMS by standard criteria and had at least two exacerbations during the two years immediately preceding enrolment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 6 is defined as one at which a patient is still ambulatory with assistance: a score of 7 means the patient must use a wheelchair.

Patients were reviewed every 3 months for two years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g. the persistence of the lesion for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the two year trial, but two other important outcomes were also specified as endpoints: the frequency of relapses during the trial and the change in number of relapses compared to the previous two years.

The following table (Table 3) presents the results of analyses of the three outcomes described above, as well as several other secondary measures. These analyses are based on the intent-to-treat population (i.e. all patients who received at least one dose of treatment and who had at least one on-treatment assessment).

Table 3: Primary and secondary efficacy outcomes from the two year study that investigated Copaxone 20 mg/mL in patients with relapsing-remitting multiple sclerosis

Outcome	**Copaxone (n=25)**	**Placebo (n=25)**
% relapse free	56%	28%
Mean relapse frequency in 2 years	0.6	2.4
Mean reduction in relapse rate compared to previous 2 years	3.2	1.6
Median time to first relapse (days)	> 700	150
% of patients progression free *	80%	52%

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

The second trial was of similar design to the first study. A total of 251 patients were enrolled. The primary outcome measure was the mean 2 year relapse rate. The table (Table 4) below presents the results of the analysis of this outcome for the intent-to-treat population, as well as other secondary measures:

Table 4: Primary and secondary efficacy outcomes from the second two year study that investigated Copaxone 20 mg/mL in patients with relapsing-remitting multiple sclerosis

Outcome	**Copaxone (n=125)**	**Placebo (n=126)**
Mean relapse rate in 2 years	1.19	1.68
% relapse free	34%	27%
Medium time to first relapse (days)	287	198
% of patients progression free	78%	75%
Mean change in EDSS *	-0.05	+0.21

***** EDSS = Expanded DSS, using a 0.5 unit scale

Results also showed that glatiramer acetate reactive antibodies were present in all treated patient's sera, with maximal levels attained after a duration of 3-4 months. Thereafter antibody levels slowly declined and stabilised at a level slightly higher than baseline.

The antibody profile in patients who experienced relapses was similar to that observed in all patients and the occurrence of relapses was independent of glatiramer acetate antibody production. The occurrence

of systemic reactions had no correlation to glatiramer acetate antibody production. Analysis of glatiramer acetate antibody type revealed that specific IgG and not IgE antibodies were produced following chronic treatment with Copaxone. The ability of glatiramer acetate antibodies to neutralise the biological activity of glatiramer acetate was investigated in several *in-vitro* and *in-vivo* systems. No neutralising activity was exhibited by a variety of monoclonal and polyclonal glatiramer acetate antibodies, including those formed during long-term administration to MS patients.

Thus antibody formation is unlikely to be associated with either short or long term safety issues and is unlikely to affect the clinical efficacy or the biological activity of Copaxone.

In both studies, Copaxone exhibited a clear beneficial and statistically significant effect on relapse rate and it is on this basis that Copaxone is considered effective. Response rates were apparently better for those patients where therapy was initiated early in the course of the disease. A correlation between reduction in relapse frequency alone and a decreased risk of future disability remains to be established.

Copaxone 40 mg/mL Administered Three Times per Week

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. The primary outcome measure was the total number of confirmed relapses. The effect of Copaxone on several magnetic resonance imaging (MRI) variables including number of new or enlarging T2 lesions and number of enhancing lesions on T1-weighted images was also 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.

The following table (Table 5) presents the values for the primary and secondary outcome measures for the intent-to-treat population.

Table 5: Primary and secondary efficacy outcomes from the 1 year study that investigated Copaxone 40 mg/mL in patients with relapsing-remitting multiple sclerosis

Outcome Measure	Adjusted Mean Estimates		P-Value
	Copaxone (40 mg/mL) (N=943)	Placebo (N=461)	
Total number of confirmed relapses during the placebo-controlled treatment phase	0.331	0.505	
Risk ratio (95% confidence intervals)	0.656 (0.539 to 0.799)		<0.0001
Relative risk reduction	34.4%		
Cumulative number of new/enlarging T2 lesions at Months 6 and 12	3.650	5.592	<0.0001
Rate ratio (95% confidence intervals)	0.653 (0.546 to 0.780)		
Relative risk reduction	34.7%		

Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12	0.905	1.639	<0.0001
Rate ratio (95% confidence intervals)	0.552 (0.436 to 0.699)		
Relative risk reduction	44.8%		
Brain atrophy as defined by the percent brain volume change from baseline to month 12*	-0.706	-0.645	0.2058
Adjusted mean difference (95% confidence intervals)	-0.061 (-0.154 to 0.033)		

***** Short term studies of change in brain volume after initiating glatiramer acetate in RRMS may be complicated by pseudoatrophy.

Single clinical event suggestive of Multiple Sclerosis

Copaxone 20 mg/mL Administered Once Daily

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.

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). Copaxone prolonged the time to CDMS by 386 (115%) days, from 336 days in the placebo group to 722 days in the Copaxone group (based on the 25th percentile; Kaplan-Meier estimates). The robustness of the results was confirmed in the Completers and Per-Protocol cohorts.

The favourable effect of treatment with Copaxone over placebo was also demonstrated in two secondary MRI endpoints. The first, number of new T2 lesions at last observed value (LOV) of the placebo-controlled phase was statistically significantly (p-value<0.0001) lower for patients on Copaxone, demonstrating a treatment effect of 58% for Copaxone over placebo. The mean (SD) number of new T2 lesions was 0.7 (1.7) in the Copaxone group and 1.8 (3.6) in the placebo group. The second MRI endpoint, baseline-adjusted T2 lesion volume at LOV of the placebo-controlled phase, showed a statistically significant (p-value=0.0002) reduction of 25% in T2 lesion volume. The mean (SD) change from baseline in total T2 lesion volume was 1.2 (2.6) mL in the Copaxone group and 2.6 (3.9) mL in the placebo group. The clinical secondary endpoint showed that the proportion of patients who converted to CDMS (43% of the placebo patients compared to 25% of the Copaxone patients) was statistically significantly (p-value<0.0001) lower for patients on Copaxone, demonstrating a treatment effect of 59% in favour of Copaxone.

Subgroup analyses of the risk in three years for progression to CDMS according to baseline factors demonstrated evidence of efficacy in all subgroups evaluated. A significant risk reduction of 39% and 54% was obtained for patients with and without corticosteroid treatment for the initial attack, respectively, and 66% risk reduction was demonstrated for patients with a unifocal optic manifestation at the initial attack. A significant risk reduction of 71% for patients with baseline T1 gadolinium enhancement and 58% for patients with 9 or more T2 lesions at baseline was obtained. Copaxone was also effective in patients with no enhancement at baseline who demonstrated a significant risk reduction of 44%.

5.2 Pharmacokinetic properties

Pharmacokinetics

There is no information regarding the absorption, distribution, metabolism or excretion profile of glatiramer acetate in humans as there is currently no direct and sensitive analytical method for measuring glatiramer acetate in biological fluids. Therefore all pharmacokinetic studies have been conducted in animals using radiolabelled glatiramer acetate. The methodology is limited because the radiolabel dissociates rapidly from glatiramer acetate and re-associates with other macromolecules. However the studies indicate that glatiramer acetate is readily absorbed; repetitive dosing has no effect on absorption; C_{max} and AUC are linearly dependent across the administered glatiramer acetate dose range and there is no evidence of any tissue accumulation of glatiramer acetate.

Results from studies with human tissues reveal rapid hydrolysis of glatiramer acetate by both subcutaneous and muscle tissues. In contrast, plasma has a “stabilising” effect on glatiramer acetate, which may be explained by the observation that it is 97.5% bound to plasma proteins *in vitro*. Based on results of animal studies and on the hydrolysis of glatiramer acetate by human tissues, it may be concluded that glatiramer acetate is extensively degraded at the site of subcutaneous injection. It has not been possible to determine the excretory fate of glatiramer acetate or its metabolites as they cannot be distinguished from naturally occurring amino acids or peptides.

Although the concentration of glatiramer acetate in blood cannot be determined directly, three lines of evidence support it being bioavailable to the immune system, which is the site of its therapeutic activity:

1. Clinical efficacy in patients with relapsing-remitting multiple sclerosis.
2. Formation of antibodies to glatiramer acetate in treated patients.
3. Decline in the peripheral blood mononuclear cell proliferative response to glatiramer acetate following chronic exposure.

5.3 Preclinical safety data

Genotoxicity

Glatiramer acetate was not mutagenic *in vitro*, but a clastogenic effect was observed in two separate *in vitro* assays in human lymphocytes. There was no evidence of clastogenicity in a mouse bone marrow micronucleus assay *in vivo*.

Carcinogenicity

In a 2-year carcinogenicity study, repeated subcutaneous administration of glatiramer acetate to male mice at doses 12 times the daily human therapeutic dose on a mg/m^2 basis was associated with the development of skin and subcutis sarcomas. This effect may have been associated with persistent tissue damage at injection sites, which tended to be more common and was of greater severity in males. The incidence of skin sarcoma was not increased in female mice at doses up to 12 times the daily human therapeutic dose on a mg/m^2 basis. In a 2-year carcinogenicity study in rats, subcutaneous administration of glatiramer acetate at 12 times the daily therapeutic human dose on a mg/m^2 basis was associated with an increased incidence of benign adrenal phaeochromocytomas in males only; this effect was not seen at 6 times the daily human dose and was within the historical control values for the testing laboratory. The possible relevance of these findings to humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Both solutions for injection contain 40 mg of mannitol, and water for injections.

6.2 Incompatibilities

No data available.

6.3 Shelf life

Copaxone 20 mg/mL: 24 months

Copaxone 40 mg/mL: 36 months

6.4 Special precautions for storage

Store Copaxone at 2°C to 8°C. Refrigerate, do not freeze. In the event of refrigeration being unavailable, Copaxone may be stored below 25ºC on one occasion 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). Keep the pre-filled syringe in the outer carton when not injecting, in order to protect from light.

6.5 Nature and contents of container

Copaxone 20 mg/mL

Copaxone 20 mg/mL is supplied in packs of 28 pre-filled syringes for subcutaneous injection.

Copaxone 20 mg/mL is supplied as a sterile pre-filled syringe fitted with staked ½ inch needle containing 20 mg glatiramer acetate, 40 mg mannitol, and water for injections.

Copaxone 40 mg/mL

Copaxone 40 mg/mL is supplied in packs of 12 pre-filled syringes for subcutaneous injection.

Copaxone 40 mg/mL is supplied as a sterile pre-filled syringe fitted with staked ½ inch needle containing 40 mg glatiramer acetate, 40 mg mannitol, and water for injections.

6.6 Special precautions for disposal

Copaxone pre-filled syringes contain no antimicrobial agent. It is for single use in one patient only. Discard any residue.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Teva Pharma New Zealand Ltd.

PO Box 128244 Remuera

Auckland 1541

New Zealand

Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

Copaxone 20 mg/mL:

Date of Medsafe Consent: 6 August 2009

Copaxone 40 mg/mL:

Date of Medsafe Consent: 9 November 2017

10. DATE OF REVISION OF THE TEXT

24 November 2023

Summary table of changes

Section Changed	Summary of New Information
4.6	Benefit-risk assessment in breastfeeding updated
4.8	Updated link to New Zealand Adverse Reactions Reporting Form

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