PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

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

RAMOLEP 40 mg/ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (mannitol 40 mg/ml).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.

Clear colourless to slightly yellow/brownish solution free from visible particles.

pH: 5,5 to 7,0 and osmolality of 300 mOsmol/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RAMOLEP is indicated for the reduction in frequency of relapses in ambulatory

patients with relapsing, remitting multiple sclerosis (MS) characterised by at least two attacks of neurological dysfunction over the preceding two-year period.

RAMOLEP is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration

Posology

The recommended dosage in adults is 20 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection once daily, or the recommended dosage in adults is 40 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection three times per week, at least 48 hours apart.

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

A decision concerning long term treatment should be made on an individual basis by the treating medical practitioner.

Special populations

Elderly

RAMOLEP has not been studied in the elderly.

Renal impairment

RAMOLEP has not been specifically studied in patients with renal impairment.

Paediatric population

RAMOLEP cannot be recommended for use in patients under 18 years as the safety and efficacy of glatiramer acetate in children and adolescents has not been established.

Method of administration

RAMOLEP 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 thereafter. 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.

4.3 Contraindications

- Hypersensitivity to glatiramer or to any of the excipients of RAMOLEP listed in section 6.1.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

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

Initiation of RAMOLEP treatment should be supervised by a neurologist or a medical practitioner experienced in the treatment of MS.

The treating medical practitioner should explain to the patient that a reaction associated with at least one of the following symptoms may occur within minutes of a RAMOLEP 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 RAMOLEP treatment and contact his/her medical practitioner or any emergency doctor. Symptomatic treatment may be instituted at the discretion of the medical

practitioner.

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 RAMOLEP to patients with pre-existing cardiac disorders. These patients should be followed up regularly during treatment.

Convulsions and/or anaphylactoid or allergic reactions may occur.

Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis or urticaria) may occur. If reactions are severe, appropriate treatment should be instituted and RAMOLEP should be discontinued.

Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with glatiramer. Maximal levels were attained after an average treatment duration of 3 to 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 RAMOLEP.

In patients with renal impairment, renal function should be monitored while they are treated with RAMOLEP. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

4.5 Interaction with other medicines and other forms of interaction

Interaction between RAMOLEP and other medicines have not been formally evaluated.

There is no data on interaction with interferon beta

An increased incidence of injection site reactions has been seen in RAMOLEP 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 RAMOLEP has, theoretically, the potential to affect the distribution of protein-bound medicines. Concomitant use of such medicines should be monitored carefully.

4.6 Fertility, pregnancy and lactation

Pregnancy

To date, no relevant epidemiological data are available. As a precautionary measure, RAMOLEP should not be used during pregnancy. A contraceptive cover should be considered whilst using RAMOLEP (see section 4.3).

Breastfeeding

It is unknown whether glatiramer acetate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from RAMOLEP 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.

Since RAMOLEP may cause confusion, visual disturbances and nausea, patients should be cautioned when driving or operating machines (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reaction is injection-site reactions, e.g. erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity and rare occurrences of lipoatrophy and skin necrosis.

Immediate post-injection reactions include vasodilatation (flushing), chest pain, dyspnoea, palpitation or tachycardia (see section 4.4). These reactions may occur within minutes of a RAMOLEP injection.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and Infestations	Frequent	Infection, influenza, bronchitis, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis.
	Less frequent	Abscess, cellulitis, furuncle, herpes zoster, pyelonephritis
Neoplasms benign, malignant and unspecified	Frequent	Benign neoplasm of skin, neoplasm
	Less frequent	Skin cancer

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Lymphadenopathy
	Less frequent	Leukocytosis, leukopenia, splenomegaly, thrombocytopenia, lymphocyte morphology abnormal
Immune system disorders	Frequent	Hypersensitivity
	Less frequent	Anaphylactic response
Endocrine disorders	Less frequent	Goitre, hyperthyroidism
Metabolism and nutrition disorders	Frequent	Anorexia, weight increased
	Less frequent	Alcohol intolerance, gout, hyperlipidaemia, blood sodium increased, serum ferritin decreased
Psychiatric disorders	Frequent	Anxiety, depression, nervousness
	Less frequent	Abnormal dreams, confusional state, euphoric mood, hallucination, hostility, mania, personality disorder, suicide attempt

MedDRA system organ class	**Frequency**	**Adverse reactions**
Nervous system disorders	Frequent	Headache, dysgeusia, hypertonia, migraine, speech disorder, syncope, tremor
	Less frequent	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	Frequent	Diplopia, eye disorder
	Less frequent	Cataract, corneal lesion, dry eye, eye haemorrhage, eyelid ptosis, mydriasis, optic atrophy
Ear and labyrinth disorders	Frequent	Ear disorder
Cardiac disorders	Frequent	Palpitations, tachycardia
	Less frequent	Extra-systoles, sinus bradycardia, tachycardia paroxysmal
Vascular	Frequent	Vasodilatation

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders	Less frequent	Varicose vein
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, cough, rhinitis seasonal
	Less frequent	Apnoea, epistaxis, hyperventilation, laryngospasm, lung disorder, choking sensation
Gastrointestinal disorders	Frequent	Nausea, anorectal disorder, constipation, dental caries, dyspepsia, dysphagia, fecal incontinence, vomiting
	Less frequent	Colitis, colonic polyp, enterocolitis, eructation, oesophageal ulcer, periodontitis, rectal haemorrhage, salivary gland enlargement
Hepato-biliary disorders	Frequent	Liver function test abnormal
	Less frequent	Cholelithiasis, hepatomegaly, medicine-induced liver injury, toxic hepatitis

MedDRA system organ class	**Frequency**	**Adverse reactions**
Skin and subcutaneous tissue disorders	Frequent	Rash, ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria, erythema
	Less frequent	Angioedema, dermatitis contact, erythema nodosum, skin nodule
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, back pain, neck pain, pain in extremity
	Less frequent	Arthritis, bursitis, flank pain, muscle atrophy, osteoarthritis
Renal and urinary disorders	Frequent	Micturition urgency, pollakiuria, urinary retention
	Less frequent	Hematuria, nephrolithiasis, urinary tract disorder, urine abnormality
Pregnancy, puerperium and perinatal conditions	Less frequent	Abortion
Reproductive system and breast disorders	Less frequent	Breast engorgement, erectile dysfunction, pelvic prolapse, priapism, prostatic disorder, smear cervix abnormal, testicular disorder, vaginal

MedDRA system organ class	**Frequency**	**Adverse reactions**
		haemorrhage, vulvovaginal disorder
General disorders and administration site conditions	Frequent	Asthenia, chest pain, injection site reactions*, pain, chills, face edema, injection site atrophy**, local reaction, edema peripheral, edema, pyrexia
	Less frequent	Cyst, hangover, hypothermia, immediate post-injection reaction, inflammation, injection site necrosis, mucous membrane disorder
Injury, poisoning and procedural complications	Less frequent	Post vaccination syndrome

* 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

In cases of overdose, adverse reactions as mentioned in section 4.8 can be expected.

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 34 Other

Pharmacotherapeutic group: Immunostimulants, Other immunostimulants

ATC code: L03AX13

Mechanism of action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunisation against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in MS patients suggest that upon its

administration, glatiramer acetate-specific suppressor T cells are induced and activated in the periphery.

Relapsing-Remitting Multiple Sclerosis

Glatiramer acetate has no beneficial effect on progression of disability in relapsing-remitting MS patients.

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

There is currently no evidence for the use of glatiramer acetate 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, RAMOLEP must not be mixed with other medicines.

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 to 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 RAMOLEP 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

The container closure system consists of a single use glass syringe barrel with an integrated needle. A rubber stopper (bromobutyl, type 1) is fitted in the barrel for closure and acts as a piston during injection. A driving rod is screwed in the rubber stopper. The needle is covered with a needle shield.

The pre-filled syringe is packed in a PVC tray that is closed with a paper lidding foil. Each tray holds 1 syringe. Trays holding the pre-filled syringes are packed in a carton box.

The volume of solution in the syringe is 1,0 ml.

RAMOLEP 20 mg/ml:

7 pre-filled syringes

28 pre-filled syringes

30 pre-filled syringes

90 (3x30) pre-filled syringes

RAMOLEP 40 mg/ml

3 pre-filled syringes

12 pre-filled syringes

36 (3x12) pre-filled syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Single use only, any unused solution should be discarded.

There are no special requirements for the disposal of unused product or waste material.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106, 16th Road

Midrand

8 REGISTRATION NUMBERS

RAMOLEP 20 mg/ml: 54/26/0697

RAMOLEP 40 mg/ml: 54/26/0698

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date on the medicine registration certificate.

10 DATE OF REVISION OF THE TEXT