PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE:

COPAXONE® 20 mg/ml (Solution for Injection, Pre-filled syringe)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each pre-filled syringe contains 20 mg glatiramer acetate* equivalent to 18 mg glatiramer base.

* 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.

COPAXONE 20 mg/ml contains sugar (mannitol) 40 mg, in a 1 ml sterile solution of water for injection.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Solution for injection (Pre-filled syringe).

A clear colourless solution essentially free of visible particles supplied in a 1 ml glass single use pre-filled syringe.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

COPAXONE 20 mg/ml is indicated for the treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (CDMS), (i.e. patients who have had a first clinical episode based on the McDonald criteria and have two or more gadolinium (Gd+) enhancing lesion(s) at 6 mm or more in diameter on MRI scanning).

COPAXONE is indicated for the reduction in frequency of relapses in ambulatory (i.e. who can walk unaided) patients with relapsing, remitting multiple sclerosis (MS) characterised by at least two attacks of neurological dysfunction over the preceding two-year period.

COPAXONE is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration:

Posology:

The recommended dosage in adults is 20 mg COPAXONE (one pre-filled syringe), administered as a subcutaneous injection once daily. For single use only. Any unused product or waste material must be discarded.

At the present time, it is not known for how long the patient should be treated.

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

Renal impairment:

COPAXONE 20 mg/ml has not been specifically studied in patients with renal impairment (see **section 4.4**).

Elderly:

COPAXONE 20 mg/ml has not been 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/ml subcutaneously every day was similar to that seen in adults. There is not enough information available on the use of COPAXONE 20 mg/ml in children below 12 years of age. Therefore, COPAXONE 20 mg/ml should not be used in this population.

Administration:

Patients should be instructed on self-injection techniques and should be supervised by a healthcare professional the first time they self-inject and for 30 minutes thereafter.

A different site for injection should be chosen every day as this will reduce the chances of any irritation or pain at the site of injection. Sites for self-injection include the abdomen, arms, hips and thighs.

Before the patient begins the procedure to self-inject the COPAXONE 20 mg/ml dose, the following points should be noted:

The patient should decide where to inject him/herself: There are seven injection areas on the body. Within each injection area there are multiple injection sites (Figure 1). The injection sites within an area should be rotated.

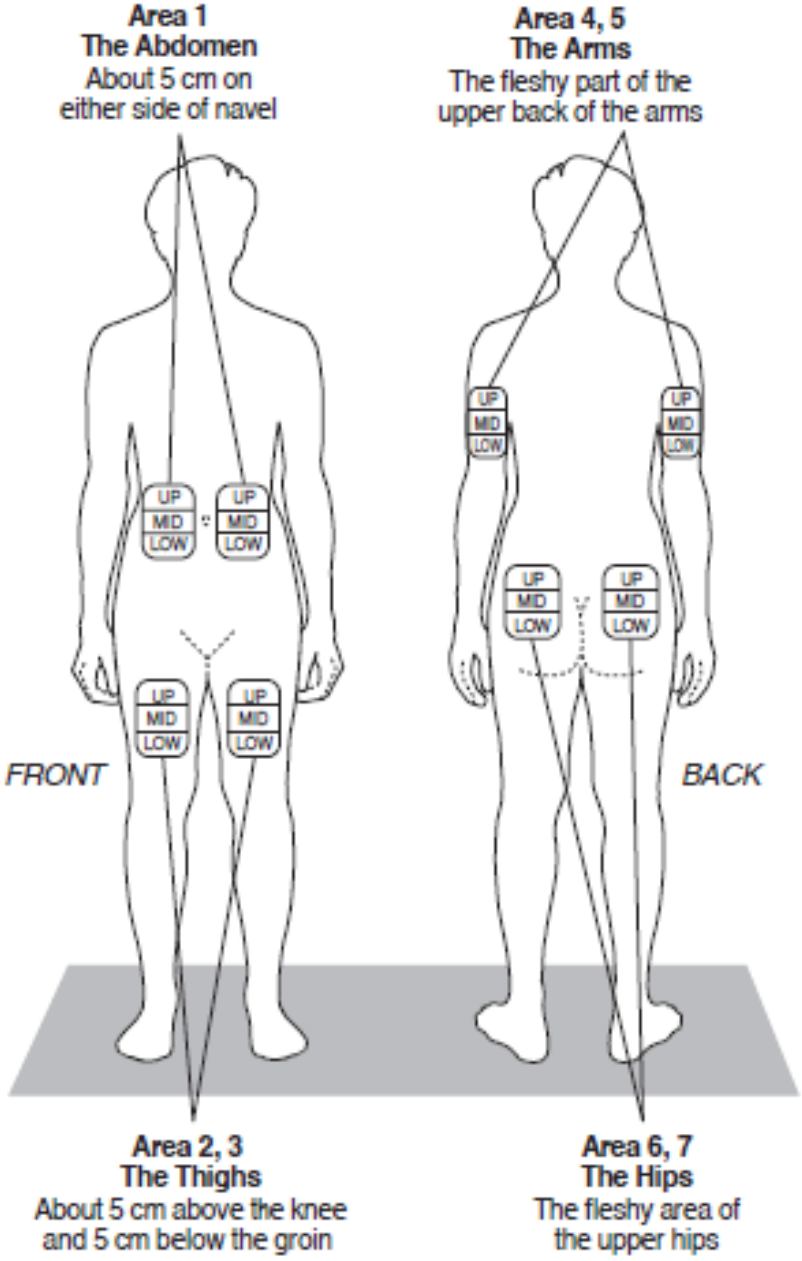
Area 1
The Abdomen
About 5 cm on either side of navel
Area 4, 5
The Arms
The fleshy part of the upper back of the arms
UP
MID
LOW
FRONT
BACK
Area 2, 3
The Thighs
About 5 cm above the knee and 5 cm below the groin
Area 6, 7
The Hips
The fleshy area of the upper hips

Figure 1

Each site should not be used more than once each week. Marking a calendar may help the patient keep track of the sites used each day.

The patient should administer the injection consistently, at the same time each day (when the patient feels strongest).

The patient may find it beneficial to have a friend attend the injection training as his/her assistant, and to have the friend be present for the first injection.

If the injection needs to be delayed, the blister should be returned to the package and stored in the refrigerator.

1. The syringe should be removed from its protective blister by peeling back the paper label.
2. The patient should pick up the pre-filled syringe as he/she would pick up a pencil, using the hand he/she writes with. The plastic cover should be removed from the needle.
3. Advise the patient to pinch a fold of about 5 cm of skin between the thumb and the index finger (Figure 2).

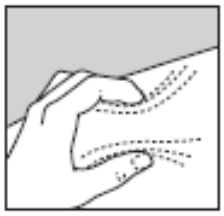

Figure 2

4. The needle should be inserted into the 5 cm fold of skin. Advise the patient that it may help to steady his/her hand by resting the heel of the hand against the body (Figure 3).

Figure 3

5. The fold of skin should be released when the needle is all the way in.
6. Advise the patient to inject the medication by holding the syringe steady while pushing down on the plunger until the syringe is empty. The injection should take just a few seconds.

4.3 Contraindications:

COPAXONE 20 mg/ml is contraindicated under the following conditions:

- Patients known to be hypersensitive to glatiramer acetate or to any of the excipients listed in **section 6.1**.

4.4 Special warnings and precautions for use:

COPAXONE 20 mg/ml should only be administered subcutaneously. COPAXONE 20 mg/ml should not be administered by the intravenous or intramuscular route.

The initiation of COPAXONE 20 mg/ml treatment should be supervised by 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: vasodilatation (flushing), chest pain, dyspnoea, palpitations or tachycardia (see section 4.8), may occur within minutes of a COPAXONE 20 mg/ml injection.

The majority of these symptoms are short-lived and resolve spontaneously without any sequelae. Should a severe adverse event occur, the patient must immediately stop COPAXONE 20 mg/ml 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 from these reactions. Nevertheless, caution should be exercised when administering COPAXONE 20 mg/ml 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. Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis or urticaria) may occur. If reactions are severe, appropriate treatment should be instituted and COPAXONE 20 mg/ml should be discontinued.

Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with

COPAXONE 20 mg/ml. 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 20 mg/ml.

In patients with renal impairment, renal function should be monitored while they are treated with COPAXONE 20 mg/ml. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

Rare cases of severe liver injury (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation) have been reported with COPAXONE 20 mg/ml in post-marketing experience (see **section 4.8**). Liver injury occurred from days to years after initiating treatment with COPAXONE 20 mg/ml. Concomitant conditions reported in these cases included excessive alcohol consumption, existing or history of liver injury and use of other potentially hepatotoxic medicines. In case of clinically significant liver injury, discontinuation of COPAXONE 20 mg/ml should be considered.

4.5 Interaction with other medicines and other forms of interaction:

Interaction between COPAXONE 20 mg/ml and other medicines have not been formally evaluated.

There are no data on interaction with interferon beta.

Observations from existing clinical trials and post-marketing experience do not suggest any significant interactions of COPAXONE 20 mg/ml with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days.

In vitro data 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 20 mg/ml has, theoretically, the potential to affect the distribution of protein bound substances concomitant use of such medicines 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 pregnant women indicate no malformative or feto/neonatal toxicity of COPAXONE 20 mg/ml. To date, no relevant epidemiological data are available.

As a precautionary measure, it is preferable to avoid the use of COPAXONE 20 mg/ml during pregnancy unless the benefit to the mother outweighs the risk to the fetus.

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 breastfeeding or to discontinue/abstain from COPAXONE 20 mg/ml therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines:

COPAXONE 20 mg/ml may cause syncope and motor dysfunction, and therefore may impair the ability to drive and use machines.

However, no studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects:

In clinical trials, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving COPAXONE 20 mg/ml. 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, in clinical trials and 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(s) may occur within minutes of a COPAXONE 20 mg/ml 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. This

data was derived from four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with COPAXONE 20 mg/ml 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/ml 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 20 mg/ml and 238 patients treated with placebo for up to 36 months.

SYSTEM ORGAN CLASS (SOC)	**VERY COMMON (≥1/10)**	**COMMON (≥1/100, <1/10)**	**UNCOMMON (≥1/1000, <1/100)**
Infections and infestations:	Infection, influenza	Bronchitis, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis*	Abscess, cellulitis, furuncle, herpes zoster, pyelonephritis
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps):		Benign neoplasm of skin, neoplasm	Skin cancer
Blood and lymphatic system disorders:		Lymphadenopathy*	Leukocytosis, leukopenia, splenomegaly, thrombocytopaenia, lymphocyte morphology abnormalities, ecchymosis, lymphadenopathy
Immune system disorders:		Hypersensitivity	
Endocrine system:			Goitre, hyperthyroidism
Metabolism and nutrition disorders:		Anorexia, weight increased*	Alcohol intolerance, gout, hyperlipidaemia, blood

			sodium increases, serum ferritin decreases
Psychiatric disorders:	Anxiety*, depression	Nervousness	Abnormal dreams, confused state, euphoric mood, hallucinations, 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:		Tachycardia*, palpitations*	Extrasystoles, sinus bradycardia, tachycardia paroxysmal
Vascular disorders:	Vasodilation*		Varicose vein
Respiratory, thoracic and mediastinal disorders:	Dyspnoea*	Cough, rhinitis seasonal	Apnoea, choking sensation, epistaxis, hyperventilation,

			laryngospasm, lung disorder
Gastrointestinal disorders:	Nausea*	Anorectal disorder, constipation, dysphagia, dental caries, dyspepsia, Fecal incontinence, vomiting*	Colitis, colonic polyp, enterocolitis, eructation, oesophageal ulcer, periodontitis, rectal haemorrhage, salivary gland enlargement
Hepatobiliary disorders:		Liver function test abnormalities	Cholelithiasis, hepatomegaly
Skin and subcutaneous tissue disorders:	Rash*	Ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria	Angioedema, contact dermatitis, erythema nodosum, skin nodule
Musculoskeletal and connective tissue disorders:	Arthralgia, back pain*	Neck pain	Arthritis, bursitis, flank pain, muscle atrophy, osteoarthritis
Renal and urinary disorders:		Micturition urgency, pollakiuria, urinary retention	Haematuria, nephrolithiasis, urinary tract disorder, urine abnormality
Pregnancy, puerperium and perinatal conditions:			Abortion
Reproductive system and breast disorders:			Breast engorgement, erectile dysfunction, pelvic prolapse, priapism, prostatic disorders, cervix smear abnormalities, 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*, peripheral oedema, oedema, pyrexia	Cyst, veisalgia, hypothermia, immediate post-injection reaction, inflammation injection site necrosis, mucous membrane disorders
Injury, poisoning and procedural complications:			Post vaccination syndrome

* More than 2 % (> 2/100) higher incidence in the COPAXONE 20 mg/ml 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.

Post-marketing data:

The following adverse reaction reports were collected from MS patients treated with COPAXONE 20 mg/ml in uncontrolled clinical trials and from post-marketing experience with COPAXONE 20 mg/ml: hypersensitivity reactions (including rare occurrence of anaphylaxis, > 1/10000, < 1/1000.

Rare cases of severe liver injury (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation) have been reported with COPAXONE 20 mg/ml in post-marketing experience. Most instances of severe liver injury resolved with discontinuation of treatment. Hepatic events occurred from days to years after initiating treatment with COPAXONE 20 mg/ml. In case of clinically significant liver injury, discontinuation of COPAXONE 20 mg/ml should be considered.

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. Healthcare 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:

A few cases of overdosage with COPAXONE 20 mg/ml (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**.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and Class: A 34. Other

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, other immunostimulants. ATC code: L03AX13

Mechanism of action:

The mechanism(s) by which glatiramer acetate exerts therapeutic effects in relapsing forms of multiple sclerosis (MS) is not fully elucidated but is presumed to involve modulation of immune processes. Studies in animals and MS patients suggest that 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:

In clinical trials in MS patients receiving COPAXONE 20 mg/ml, 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 20 mg/ml.

COPAXONE 20 mg/ml 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 20 mg/ml treatment has an effect on relapse duration or severity.

There is currently no evidence for the use of COPAXONE 20 mg/ml in patients with primary or secondary progressive disease.

Single clinical event suggestive of MS:

During the placebo-controlled period of up to three years, COPAXONE 20 mg/ml 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 20 mg/ml over placebo was also demonstrated in two secondary MRI endpoints, i.e. number of new T2 lesions and T2 lesion volume.

No appreciable differences between the Early Start and Delayed Start cohorts were observed for either hypo-intense 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 glatiramer acetate (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 PI. 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 year 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 ≥ 6 mg/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

6.2 Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicines.

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Store at 2 - 8 ºC and protect from light. DO NOT FREEZE.

If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15 ºC to 25 ºC) for up to 1 month.

After this one month period, if the COPAXONE 20 mg/ml pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2 °C to 8 °C).

6.5 Nature and contents of container:

A single-dose 1 ml pre-filled syringe consisting of a colourless glass barrel, a plastic plunger rod and a grey rubber stopper.

Pack size: 28 x 1 ml pre-filled syringe.

6.6 Special precautions for disposal and other handling:

For single use only.

Any unused medicines or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park, Magwa Crescent West,

Waterfall City, Midrand,

Gauteng,

2090,

South Africa.

8. REGISTRATION NUMBER(S):

A40/34/0258

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

1 December 2006

10. DATE OF REVISION OF THE TEXT:

20 May 2022