Applicant: Teva Pharmaceuticals (Pty) Ltd	Product name: COPAXONE 40 mg/ml Solution for injection in pre-filled syringe or pen
Date of registration: 14 June 2022 Reg No: 48/34/0823	One pre-filled syringe or pen (1 ml) of solution for injection contains 40 mg glatiramer acetate, equivalent to 36 mg of glatiramer.

CURRENT APPROVED PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

COPAXONE 40 mg/ml, Solution for injection, pre-filled syringe.

COPAXONE 40 mg/ml, Solution for injection, pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

COPAXONE 40 mg/ml pre-filled syringe: 1 ml of solution for injection (1 pre-filled syringe) contains 40 mg glatiramer acetate*, equivalent to 36 mg of glatiramer.

COPAXONE 40 mg/ml pre-filled pen: 1 ml of solution for injection (1 pre-filled pen) 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.

COPAXONE 40 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 in pre-filled syringe or pen.

The solution is clear, colourless, and essentially 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 40 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 40 mg/ml 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 40 mg/ml is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration:

The initiation of COPAXONE 40 mg/ml treatment should be supervised by a neurologist or a medical practitioner experienced in the treatment of MS.

Posology:

The recommended dosage in adults is 40 mg of glatiramer acetate (one pre-filled syringe or one pre-filled pen), administered as a subcutaneous injection three times a week with at least 48 hours apart. 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 long term treatment should be made on an individual basis by the treating medical practitioner.

Renal impairment:

COPAXONE 40 mg/ml has not been specifically studied in patients with renal impairment (see **section 4.4**).

Elderly:

COPAXONE 40 mg/ml 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 in children and adolescents below 18 years of age. Therefore, COPAXONE 40 mg/ml should not be used in this population.

Method of administration:

COPAXONE 40 mg/ml is for subcutaneous use.

Patients should be instructed in self-injection techniques and should be supervised by a healthcare 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.

Before the patient begins the procedure to self-inject the COPAXONE 40 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.

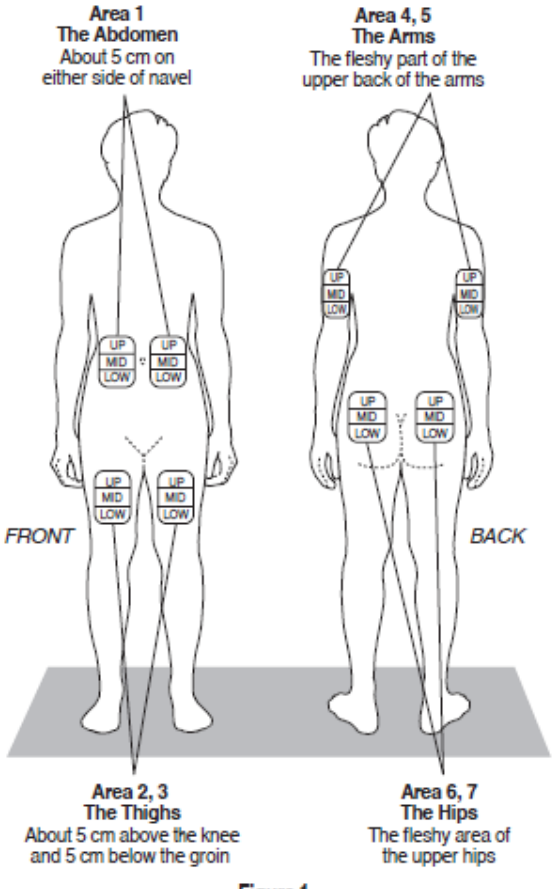


Figure 1

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.

Refer to the autoinjector leaflet for appropriate use with COPAXONE 40 mg/ml.

COPAXONE 40 mg/ml is for single use only.

4.3 Contraindications:

- Known hypersensitivity to glatiramer acetate or to any of the excipients listed in **section 6.1**.

4.4 Special warnings and precautions for use:

COPAXONE 40 mg/ml should only be administered subcutaneously.

COPAXONE 40 mg/ml should not be administered by intravenous or intramuscular routes.

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 COPAXONE 40 mg/ml 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 40 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 for these reactions. Nevertheless, caution should be exercised when administering COPAXONE 40 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 rarely. Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis or urticaria) may rarely occur. If reactions are severe, appropriate treatment should be instituted and COPAXONE 40 mg/ml should be discontinued.

Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with COPAXONE 40 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 40 mg/ml.

In patients with renal impairment, renal function should be monitored while they are treated with COPAXONE 40 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 have been observed (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation). Liver injury occurred from days to years after initiating treatment with COPAXONE 40 mg/ml. Most instances of severe liver injury resolved with discontinuation of treatment. In some cases, these reactions have occurred in the presence of excessive alcohol consumption, existing or history of liver injury and use of other potentially hepatotoxic medicines. Patients should be regularly monitored for signs of hepatic injury and instructed to seek immediate

medical attention in case of symptoms of liver injury. In case of clinically significant liver injury, discontinuation of COPAXONE 40mg/ml should be considered.

4.5 Interaction with other medicines and other forms of interaction:

Interaction between COPAXONE 40 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 40 mg/ml with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days.
An increased incidence of injection site reactions has been seen in COPAXONE 40 mg/ml patients receiving concurrent administration of corticosteroids.

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 40 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 the use of Copaxone 20 mg/ml in pregnant women indicate no malformative or foetal/neonatal toxicity. To date, no relevant epidemiological data are available.

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 40 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 40 mg/ml may cause syncope and motor dysfunction, and therefore may impair the ability to drive and use machines.

4.8 Undesirable effects:

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.

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

Infections and infestations	Infection, Influenza	Bronchitis, Gastroenteritis, Herpes Simplex, Otitis Media, Rhinitis, Tooth Abscess, Vaginal Candidiasis*	Abscess, Cellulitis, Furuncle, Herpes Zoster, Pyelonephritis		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Benign Neoplasm of Skin, Neoplasm	Skin Cancer		
Blood and lymphatic system disorders		Lymph-adenopathy*	Leukocytosis, Leukopenia, Splenomegaly, Thrombocytopenia, Lymphocyte Morphology Abnormal		
Immune system disorders		Hypersensitivity			

Endocrine disorders			Goitre, Hyperthyroidism		
Metabolism and nutrition disorders		Anorexia, Weight Increased*	Alcohol Intolerance, Gout, Hyperlipidaemia, Blood Sodium Increased, Serum Ferritin Decreased		
Psychiatric disorders	Anxiety*, Depression	Nervousness	Abnormal dreams, Confusional State, Euphoric Mood, Hallucination, Hostility, Mania, Personality Disorder, Suicide Attempt		
Nervous system disorders	Headache	Dysgeusia, Hypertonia, Migraine, Speech Disorder,	Carpal Tunnel Syndrome, Cognitive Disorder, Convulsion,		

		Syncope, Tremor*	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		
Hepato-biliary disorders		Liver Function Test Abnormal	Cholelithiasis, Hepatomegaly	Toxic hepatitis,	Hepatic failure#

				Liver injury	
Skin and subcutaneous tissue disorders	Rash*	Ecchymosis, Hyperhidrosis, Pruritus, Skin Disorder*, Urticaria	Angioedema, Dermatitis Contact, Erythema Nodosum, Skin Nodule		
Musculoskeletal and connective tissue disorders	Arthralgia, Back Pain*	Neck Pain	Arthritis, Bursitis, Flank Pain, Muscle Atrophy, Osteoarthritis		
Renal and urinary disorders		Micturition Urgency, Pollakiuria, Urinary Retention	Haematuria, Nephrolithiasis, Urinary Tract Disorder, Urine Abnormality		
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		

§ The term 'injection site reactions' (various kinds) comprises all adverse events occurring at the injection site excluding injection site atrophy and injection site necrosis, which are presented separately within the table.

♣ Includes terms which relate to localised lipoatrophy at the injection sites.

Few cases were reported with liver transplantation.

Rare (≥1/10 000 to <1/1 000) reports of anaphylactoid reactions were collected from MS patients treated with COPAXONE 40 mg/ml in uncontrolled clinical trials and from post-marketing experience with COPAXONE 40 mg/ml.

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. Immediate post-injection reaction was reported by 8 % of the patients on COPAXONE 40 mg/ml.

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 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:

Symptoms:

A few cases of overdose with COPAXONE 40 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**.

Management:

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 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 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:

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 characterised 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 in 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 1 404 patients were randomised in a 2:1 ratio to receive either COPAXONE 40 mg/ml (n=943) or placebo (n=461).

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.

A direct comparison of the efficacy and safety between 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 3,5 % of COPAXONE 40 mg/ml-treated patients, (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 40 mg/ml 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 Professional Information. Due to the lack of pharmacokinetic data in humans, margins of exposure between humans and animals cannot be established.

Immune complex deposition in the glomeruli of the kidney was reported in a small number of rats and monkeys treated for at least 6 months. In a 2 years rat study, no indication of immune complex deposition in the glomeruli of the kidney was seen.

Anaphylaxis after administration to sensitised animals (guinea pigs or mice) was reported. The relevance of these data for humans is unknown.

Toxicity at the injection site was a common finding after repeated administration in animals.

In rats, a slight but statistically significant reduction in body weight gain of offspring born to dams treated during pregnancy and throughout lactation was observed at subcutaneous doses ≥ 6mg/kg/day (2,83-times the maximum recommended human daily dose for a 60 kg adult based on mg/m^2) in comparison to control. No other significant effects on offspring growth and behavioural development were observed.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Mannitol

Water for injections

6.2 Incompatibilities:

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

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Keep the pre-filled syringes or pre-filled pens 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/pre-filled pens cannot be stored in a refrigerator, they can be stored between 15 °C and 25 °C, for up to one month.

After this one month period, if the COPAXONE 40 mg/ml pre-filled syringes/ pre-filled pens 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:

COPAXONE 40 mg/ml pre-filled syringe:

A pre-filled syringe containing COPAXONE 40 mg/ml solution for injection consists of a 1 ml colourless type I glass syringe barrel with 27G½ staked needle or 29G½ thin wall staked needle, a blue polypropylene (optional polystyrene) plunger rod, a grey rubber plunger stopper and a needle shield.
The pre-filled syringe is packed in a PVC blister closed with either a printed paper lid form or a transparent lid film, one syringe per blister, packed in carton boxes. COPAXONE 40 mg/ml pre-filled syringe 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 in an outer carton. Not all pack sizes may be marketed.

COPAXONE 40 mg/ml pre-filled pen:

Pre-filled pen consisting of a single use, disposable, spring-powered injector with needle safety shield integrating a pre-filled syringe which contains 1 ml solution for injection. The syringe inside the pen consists of a colourless type I glass syringe barrel, a stainless steel 29 gauge needle and a bromobutyl rubber plunger stopper and a needle shield.
COPAXONE 40 mg/ml pre-filled pen is available in packs containing 3 or 12 pre-filled pens of 1 ml solution for injection or in a multipack containing 36 (3 packs of 12) pre-filled pens of 1 ml solution for injection in an outer carton. Not all pack sizes may be marketed.
The assembled pens are packed directly into plastic trays holding three pens each. Four trays are then stacked on top of each other for packages holding 12 pens.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

Instructions for use:

The instructions for use provided at the end of the patient information leaflet must be followed step-by-step carefully.

The pre-filled syringe and the pre-filled pen are for single use only.

COPAXONE 40 mg/ml should not be used if the solution is cloudy or discoloured or contains particles.

COPAXONE 40 mg/ml should not be used if the solution has been frozen.

The pre-filled syringe and the pre-filled pen should not be shaken.

Any unused medicine 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

8. REGISTRATION NUMBER(S):

48/34/0823

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

14 June 2022

10. DATE OF REVISION OF THE TEXT: