SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

Eptadone 10 mg/mL, oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains methadone hydrochloride 10 mg.

Sugar free.

Excipient(s) with known effect:

Contains sodium benzoate 0,05 % *w/v* (preservative).

Contains sweetener (xylitol 100 mg/mL).

Contains glycerol 100 mg/mL.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, blue coloured syrup liquid with cherry taste.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eptadone is indicated as substitution treatment in opiate dependence in conjunction with medical, psychological and social therapy.

4.2 Posology and method of administration

Posology

Treatment with Eptadone assumes that the patient is taking part in a programme including medicine-assisted rehabilitation for narcotics abuse, approved by a relevant authority.

The dose must be tailored for each individual patient.

Adults

The standard initial dose is 20 mg once daily.

The dose is increased in steps of 10 mg at a time over a period of three weeks, usually to 70 or 80 mg. After a recommended stabilisation period of four weeks, the dose is adjusted until the patient feels well, does not feel a need for intoxication and is without clinical signs of psychomotor function effects or abstinence symptoms. The normal dose is 60 to 120 mg of Eptadone per 24 hours, but some individuals may require higher doses.

Dosage must be determined on the basis of a clinical assessment supported by serum level monitoring. The recommended serum level is 600 to 1 200 nmol/litre (200 to 400 ng/mL). Great importance is attached to the clinical assessment.

Eptadone is normally administered once daily.

More frequent administration carries a risk of accumulation and overdose.

Certain patients develop auto-induction, which leads to the medicine being metabolised more rapidly in the body. In such cases, the dose must be adjusted upwards once or more to maintain the optimum effect.

Treatment withdrawal

Treatment must be stopped if it is insufficiently effective or if the patient cannot tolerate it. The effect must be evaluated in accordance with national guidelines. If treatment must be stopped, this must be done by gradual dose reduction. The dose may be reduced relatively rapidly to start with, but reduction must be slow

in the final phase (from 20 mg daily and downwards) (see section 4.4).

Special populations

Elderly: Caution must be exercised when this medicine is administered to elderly or ill patients (see section 4.4).

Hepatic impairment: Where not contraindicated dose adjustment may be necessary (see section 4.3 and 4.4).

Hypothyroidism or prostatic hypertrophy: Must receive a lower initial dose (see section 4.4).

Paediatric population

Eptadone is contraindicated in children (see section 4.3).

Method of administration

For oral administration only.

The correct dosage should be extracted from the bottle by using a dispenser, measuring cylinder or syringe.

4.3 Contraindications

- Hypersensitivity to methadone or to any of the excipients of Eptadone (listed in section 6.1);
- Eptadone is contraindicated in children;
- Respiratory depression, obstructive airways disease and during an acute asthma attack;
- Acute alcoholism (see section 4.5);
- Head injury and raised intracranial pressure (further rise in intracranial pressure);
- Concurrent administration of MAOI medicines, including moclobemide, or for 2 weeks after stopping (see section 4.5);
- Use during labour (prolonged duration of action increases the risk of neonatal depression);
- Patients dependent on non-opioid medicines;
- Patients with severe hepatic impairment as it may precipitate encephalopathy. Dose adjustment may

be necessary in cases of mild or moderate impaired hepatic function (see section 4.2 and 4.4);

- Patients with ulcerative colitis, since Eptadone may precipitate toxic dilation or spasm of the colon;
- Patients with biliary and renal tract spasm;
- Risk of paralytic ileus (including medicine induced gastrointestinal hypotonia);
- Phaeochromocytoma.

4.4 Special warnings and precautions for use

At the beginning of the dose increase period the patient must be observed after administration to record any abnormal/untoward reactions. The patient will have increased serum levels for up to two hours, and it is important that any overdose reactions or other dangerous/severe reactions can be recorded.

The precautions to be taken in the use of Eptadone are the same as those applying to opiates in general.

Opioid Use Disorder (OUD) (abuse and dependence)

Eptadone is an opioid analgesic and is highly addictive in its own right.

Eptadone has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death. Tolerance, physical, and/or psychological dependence may develop upon repeated administration of Eptadone.

Abuse or intentional misuse of Eptadone may result in overdose and/or death.

The risk of developing Opioid Use Disorder is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Eptadone can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use. Toxic doses are highly variable.

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This

includes the review of concomitant opioids and psycho-active medicines (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Withdrawal

Abrupt cessation of treatment can lead to withdrawal symptoms which, although similar to those with morphine, are less intense but more prolonged. Withdrawal of treatment should therefore be gradual (see section 4.2). The withdrawal period is longer for Eptadone than for heroin because Eptadone has a longer half-life. Babies born to mothers receiving Eptadone may suffer withdrawal symptoms.

The opioid medicine withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations.

Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heartrate.

Respiratory depression/disorders

Due to the slow accumulation of Eptadone in the tissues, respiratory depression may not be fully apparent for a week or two and may exacerbate asthma due to histamine release.

Eptadone should be given with caution to patients with a history of asthma (see section 4.3) and in patients with depressed respiratory reserve.

Sleep-related breathing disorders

Opioids, as contained in Eptadone, can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Hepatic and renal impairment

Great caution must be exercised in patients with impaired hepatic and renal function. The metabolism of Eptadone may be reduced in impaired hepatic function, and dose adjustment may be necessary where not contraindicated (see section 4.3).

Caution as Eptadone may precipitate porto-systemic encephalopathy in patients with severe liver damage (see section 4.3).

Eptadone may cause troublesome constipation, which is particularly dangerous in patients with hepatic impairment, and measures to avoid constipation should be initiated early;

Hypothyroidism or prostatic hypertrophy

In patients with hypothyroidism or prostatic hypertrophy a lower, initial dose must be administered (see section 4.2);

Elderly patients

Great caution must be exercised in elderly patients. They are at increased risk of hypotension and syncope. In the case of elderly or ill patients, repeated doses should only be given with extreme caution.

QT prolongation

QT prolongation and torsade de pointes may occur with Eptadone use, particularly at doses above 100 mg daily.

It should be given with caution to patients at risk of developing prolongation of the QT interval including those with:

- known history of QT prolongation or family history of sudden death;
- advanced heart disease;
- hepatic disease;
- hypokalaemia or other electrolyte imbalance;
- concomitant treatment with medicines that have a potential for QT-prolongation.

It should also be used with caution in patients who are taking other potentially dysrhythmogenic medicines, medicines likely to cause electrolyte imbalance, or medicines that inhibit the cytochrome P450 isoenzyme CYP3A4 (see section 4.5).

ECG monitoring is recommended before starting treatment in patients with risk factors for QT prolongation, with a further test at dose stabilisation. ECG monitoring is also recommended before and at 7 days after dose titration above 100 mg daily in patients without recognised risk factors.

Adrenal insufficiency

Eptadone should be given with caution to patients with adrenocortical insufficiency. Eptadone may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Hypoglycaemia

Hypoglycaemia has been observed in the context of methadone, such as contained in Eptadone, overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9).

Concomitant use of sedative medicines

Concomitant use of Eptadone and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Eptadone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these

symptoms (see section 4.5).

Eptadone should also be given with caution to patients with:

- Cardiovascular disease;
- Convulsive disorders;
- Inflammatory or obstructive bowel disorders where not contraindicated (see section 4.3);
- Myasthenia gravis.

Eptadone contains sodium benzoate

Sodium benzoate:

Sodium content: This medicine contains less than 1 mmol sodium (23 mg) per 1 mL, that is to say essentially 'sodium-free'.

Benzoate: Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

Paediatric population

As there is a risk of greater respiratory depression in neonates and because there are currently insufficient published data on the use in children, Eptadone is contraindicated in children (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

MAOI's

The concurrent use of MAOl's is contraindicated as they may prolong and enhance the respiratory depressant effects of Eptadone (see section 4.3).

Central nervous system depressants

Anaesthetics, hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole), anxiolytics,

sedatives, barbiturates, phenothiazines, some other major tranquillizers and tricyclic antidepressants may increase the general depressant effects of Eptadone when used concomitantly (see section 4.4). Antipsychotics may enhance the sedative effects and hypotensive effects of Eptadone.

Eptadone may increase desimipramine levels by up to a factor of two.

There are reports that antidepressant medicines (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone contained in Eptadone.

Alcohol may enhance the sedative and hypotensive effects of Eptadone and increase respiratory depression.

The concomitant use of Eptadone with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Gabapentinoids

The concomitant use of opioids, as contained in Eptadone, and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.

Serotonergic medicine

Serotonergic syndrome may occur with concomitant administration of Eptadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

Histamine H2 Antagonists

Histamine H2 antagonists such as cimetidine, can reduce the protein binding of methadone, such as contained in Eptadone, resulting in increased opiate action.

Antibacterials

Rifampicin: Reduced plasma levels and increased urinary excretion of methadone, such as contained in Eptadone can occur with concurrent administration of rifampicin. Adjustment of the dose of Eptadone may be necessary.

Ciprofloxacin: Plasma levels of methadone, contained in Eptadone, may increase with concurrent administration of ciprofloxacin due to inhibition of CYP 1A2 and CYP 3A4. Reduced serum concentrations of ciprofloxacin may occur. Concomitant use may lead to sedation, confusion and respiratory depression.

Erythromycin: Theoretically this may increase Eptadone levels due to decreased methadone metabolism.

Antifungals

Fluconazole, voricanozole and ketoconazole: May raise Eptadone levels, due to decreased methadone metabolism.

Anticonvulsants (phenytoin, phenobarbitone, carbamazepine and primidone)

Induces the metabolism of methadone, such as contained in Eptadone, and there may be a risk of precipitating withdrawal syndrome. Adjustment of the dose of Eptadone should be considered.

pH of urine

Medicines that acidify or alkalinise the urine may have an effect on clearance of methadone, such as contained in Eptadone, as it is increased at acidic pH and decreased at alkaline pH.

Opioid agonist analgesics

Additive CNS depression, respiratory depression and hypotension.

Opioid antagonists

Naloxone and naltrexone antagonises the analgesic, CNS and respiratory depressant effects of Eptadone and

can rapidly precipitate withdrawal symptom (see section 4.4). Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

Antiretroviral medicines such as nevirapine, efavirenz, nelfinavir, ritonavir

Based on the known metabolism of methadone, such as contained in Eptadone, these medicines may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Methadone may increase the plasma concentration of zidovudine. Narcotic withdrawal syndrome has been reported in patients treated with some retroviral medicines and methadone, such as contained in Eptadone concomitantly.

Eptadone maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and Eptadone dose should be adjusted accordingly.

Cyclizine and other sedating antihistamines

May have additive psychoactive effects; antimuscarinic effects at high doses.

QT interval prolongation

In patients taking medicine affecting cardiac conduction, or medicine which may affect electrolyte balance there is a risk of cardiac events when Eptadone is taken concurrently (see section 4.4).

Cytochrome P450 3A4 inhibitors

Methadone, such as contained in Eptadone, clearance is decreased when co-administered with medicines which inhibit CYP3A4 activity. These include some anti-HIV medicines, macrolide antibiotics, cimetidine and azole antifungal medicines (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme).

St. John's wort

May lower plasma concentrations of methadone, such as contained in Eptadone.

Metamizole

Co-administration of Eptadone with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of methadone with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and Eptadone are administered concurrently; clinical response and/or medicine levels should be monitored as appropriate.

Centrally acting alpha-adrenergic blocker

There is an increased risk of hypotension, cognitive effects and ECG changes (including PR interval and QT interval prolongation) when Eptadone is co-administered with centrally acting alpha-adrenergic blockers (lofexidine and clonidine).

Antiarrhythmics

Eptadone delays the absorption of mexiletine.

Medicine affecting gastric emptying

Domperidone and metoclopramide may increase the speed of onset but not the extent of methadone, such as contained in Eptadone, absorption by reversing the delayed gastric emptying associated with opioids. Conversely, Eptadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity.

Other medicines

Eptadone may have an effect on other medicines as a consequence of reduced gastro-intestinal motility.

Grapefruit juice

There are several anecdotal reports of raised methadone, such as contained in Eptadone, levels due to decreased methadone metabolism.

Pregnancy tests

Eptadone may interfere with the urine testing for pregnancy.

Cannabidiol

Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Eptadone should not be administered during pregnancy.

Neonatal abstinence syndrome, respiratory depression and low birth weight have been reported in neonates after treatment with methadone, such as contained in Eptadone, during pregnancy.

Breastfeeding

Methadone, such as contained in Eptadone is distributed into breast milk and therefore Eptadone should not be used during lactation.

Fertility

No data on male and female fertility is available (see section 4.5).

4.7 Effects on ability to drive and use machines

Eptadone will affect the psychomotor functions until the patient has been stabilised at a suitable level, so he/she should not drive or use machines until stabilisation has been achieved and there have been no symptoms of abuse for six months. When driving and use of machines can be resumed is largely dependent

on the individual patient and must be determined by the medical practitioner.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse effect of Eptadone is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest have occurred.

The most frequent adverse effects observed were nausea and vomiting.

The adverse effects of Eptadone treatment are in general the same as those in treatment with other opiates.

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Frequency unknown	Reversible thrombocytopenia has been reported in opioid-dependent patients with chronic hepatitis
Endocrine disorders	Less frequent	Hypothyroidism
	Frequency unknown	Raised prolactin levels with long-term administration, hypoadrenalism, hypogonadism
Metabolism and nutrition disorders	Frequent	Fluid retention
	Frequency unknown	Anorexia, hypokalaemia, hypomagnesaemia, hypoglycaemia
Psychiatric disorders	Frequent	Euphoria, hallucinations
	Less frequent	Dysphoria, dependence, agitation, insomnia, disorientation
	Frequency unknown	Drug dependence (see section 4.4), confusion particularity at the start of the treatment

Nervous system disorders	Frequent	Dizziness, sedation, confusion, headache, sleep disturbances, sweating
	Less frequent	Syncope
	Frequency unknown	Eptadone has the potential to increase intracranial pressure, particularly in circumstances where it is already raised
Eye disorders	Frequent	Blurred vision, miosis, dry eyes
	Less frequent	Visual disturbances
	Frequency unknown	Nystagmus, strabismus, visual acuity reduced
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Less frequent	Bradycardia, palpitations, drop in blood pressure (at high doses), QT prolongation and torsade de pointes (at high doses)
Vascular disorders	Less frequent	Orthostatic hypotension, facial flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory depression (at high doses), pulmonary oedema, exacerbation of asthma, dry nose
	Frequency unknown	Central sleep apnoea syndrome
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation
	Less frequent	Xerostomia, glossitis
Hepatobiliary disorders	Less frequent	Bile duct dyskinesia
Skin and subcutaneous tissue disorders	Frequent	Transient rash
	Less frequent	Tendency to oedema, pruritus, urticaria, other rash and in less frequent cases bleeding urticaria
Renal and urinary disorders	Less frequent	Urinary retention, anti-diuretic effect

Reproductive system and breast disorders	Frequent	Reduced libido
	Less frequent	Reduced potency, galactorrhoea, dysmenorrhoea and amenorrhoea
General disorders and administration site conditions	Frequent	Fatigue, drowsiness
	Less frequent	Oedema of the lower extremities, asthenia, oedema, hypothermia, medicine withdrawal syndrome
Investigations	Frequent	Weight increase

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms:

Severe overdose is characterised by respiratory failure, extreme drowsiness that develops into stupor or coma, maximum miosis, slack musculature, cold and clammy skin and occasionally bradycardia and hypotension. Apnoea, cardiovascular failure, cardiac arrest and death may occur in cases of severe overdose. Hypoglycaemia has been reported.

Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment:

Secure the airways by assisted or controlled ventilation. It may prove necessary to use opioid antagonists, but since the effect of Eptadone is long-lasting (36 to 48 hours) and that of antagonists is only 1 to 3 hours, antagonist treatment must be repeated as necessary. Antagonists must not be used if there is any sign of respiratory failure or loss of consciousness. If the patient is physically dependent on narcotics, administration of an antagonist may lead to acute abstinence symptoms. If possible the use of antagonists should be avoided in such patients, but if it nevertheless proves necessary to administer antagonists because of severe respiratory depression, great caution must be exercised. In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8). Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.2.9 Other analgesics.

Pharmacotherapeutic group: Nervous system, other nervous system medicines, medicines used in addictive disorders, methadone.

ATC code: N07BC02

Mechanism of action

Methadone, such as contained in Eptadone is a narcotic analgesic that belongs to the same group as morphine. This substance has an agonist effect on the opiate receptors in the brain, bone marrow and nervous system; high affinity with the μ-receptors and some affinity with the o-and K-receptors. Methadone operates in a similar way to morphine, but has a less sedative effect. The use of methadone can reduce or eliminate the effect of other opiates. Methadone enters mast cells and releases histamine by a non-immunological mechanism. It causes a dependence syndrome of the morphine type.

5.2 Pharmacokinetic properties

Absorption

Methadone is rapidly absorbed following oral administration and has high oral bioavailability. Methadone undergoes considerable first-pass metabolism.

Distribution

Methadone is widely distributed in the tissue with higher concentrations in the liver, lungs and kidneys than in the blood. It diffuses across the placenta and is distributed into breast milk. It is extensively protein bound (60 to 90 %), but with great individual differences. Methadone binds to albumin and other plasma and tissue proteins.

Biotransformation

Methadone is metabolised in the liver, mainly by N-demethylation and cyclisation. Metabolism is primarily catalysed by CYP3A4, although other cytochrome P450 isoenzymes are also involved. Methadone is metabolised to the major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and the minor metabolite 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), both of them inactive. Hydroxylation to methadol succeeded by demethylisation to normethadol also occurs to some degree. Other metabolic reactions also occur and at least eight other metabolites are known.

Elimination

Elimination half-life vary considerably after single (10 to 25 hours) and repeated doses (13 to 55 hours). Plasma clearance is around 2 mL/min/kg. About 20 to 60 % of the dose is eliminated in urine over 24 hours (about 33 % in unmodified form; about 43 % as EDDP and about 5 to 10 % as EMDP).

The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment than in normal overdoses. Elimination of unmodified methadone in urine is pH-

dependent and increases with greater urinary acidity. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xylitol

Glycerol

Sodium benzoate

Citric acid monohydrate

Cherry flavour

Hydroxyethylcellulose

Brilliant blue FCF (E133)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 36 months

In-use stability: Up to 365 days after first opening.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging to protect from light.

6.5 Nature and contents of container

100 mL

An amber transparent glass bottle, closed with a child resistant, tamper evident polyethylene (LDPE/HDPE) screw cap, with a polyethylene (LDPE) insert. A measuring pipette is provided in the final package of the 100 mL bottle.

500 mL

An amber non-plasticised PVC (Poly Vinyl Chloride) 500 mL bottle with 28 mm treaded neck, closed with a polypropylene child-proof screw cap fitted with a polyethylene (EPE) liner. A graduated measuring cup is provided in the final package.

1 000 mL

An amber non-plasticised PVC (Poly Vinyl Chloride) 1000 mL bottle with brim-full capacity of 1375 ± 30 mL, closed with a polypropylene child-proof screw cap fitted with a polyethylene (EPE) liner and a one-piece top tabbed multistrate induction inner seal. A graduated measuring cup is provided in the final package.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

0157

8. REGISTRATION NUMBER(S)

57/2.9/0630

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 June 2025

10. DATE OF REVISION OF THE TEXT

24 June 2025