SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

EQUITY METHADONE, 2 mg/ml (oral solution).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg methadone hydrochloride.

Contains sodium benzoate 0,12 % *m/v* as preservative.

Contains sunset yellow (E110) 0,008 mg/ml.

Contains sweetener (Saccharine sodium 0,25 mg/ml and sodium cyclamate 2,5 mg/ml).

EQUITY METHADONE IS A SUGAR FREE ORAL SOLUTION.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear pale orange solution, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment in opiate dependence in conjunction with medical, psychological and social therapy.

4.2 Posology and method of administration

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

For oral administration only. 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 stabilization 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 methadone 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/l (200 to 400 ng/ml). Great importance is attached to the clinical assessment.

EQUITY METHADONE is normally administered once daily. More frequent administration carries a risk of accumulation and overdose.

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

Dose adjustment may be necessary in cases of impaired hepatic function (see section 4.4). Patients with hypothyroidism or prostatic hypertrophy must receive a lower initial dose.

Elderly

Caution must be exercised when this medication is administered to elderly or ill patients.

Children

EQUITY METHADONE must not be administered to children.

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).

4.3 Contraindications

- Hypersensitivity to methadone or to any of the excipients listed in section 6.1.
- Respiratory depression.
- Acute obstructive airway disease.
- Concomitant administration of MAO-inhibitors or administration within two weeks after finished MAO inhibitor treatment.
- Contraindicated in children.

4.4 Special warnings and precautions for use

QT prolongation and torsade de pointes have been reported with EQUITY METHADONE 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.

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.

Children are more sensitive than adults that is why poisoning may occur at very low doses. To avoid unintentional intake of methadone by children, EQUITY METHADONE should in cases when it is taken home,

be kept in a safe place where children cannot reach it.

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

Opioid Use Disorder (abuse and dependence)

EQUITY METHADONE is an opioid analgesic and is highly addictive in its own right. It 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.

As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of EQUITY METHADONE.

Abuse or intentional misuse of EQUITY METHADONE may result in overdose and/or death. The risk of developing Opioid Use Disorder (OUD) 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).

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.

Dependence may occur in chronic use.

The withdrawal period is longer for EQUITY METHADONE than for heroin because methadone has a longer half-life.

Sleep-related breathing disorders

Opioids 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.

Severe obstructive pulmonary disease, acute asthma attacks, cor pulmonale, lessened respiratory reserve, hypoxia, hypercapnia is a relative contraindication. Each case must be assessed individually.

Concurrent administration of other opiates, alcohol, barbiturates, benzodiazepines and other strong sedative psychoactive medicines may potentiate the effects and side effects of EQUITY METHADONE and should be avoided.

Concurrent treatment with narcotic antagonists or mixed agonist/antagonists should be avoided (with the exception of treatment of overdose) as it may precipitate withdrawal symptoms in physically dependant patients.

Great caution must be exercised in the following cases:

- Patients with impaired hepatic and renal function. The metabolism of EQUITY METHADONE may be reduced in impaired hepatic function, and dose adjustment may be necessary.
- A lower initial dose must be administered to patients with hypothyroidism, myxedema, (it can increase the risk of respiratory depression and prolonged CNS depression), renal (increased risk of convulsions) and hepatic impairment (opioids metabolised in liver), asthma or decreased lung volume (it may decrease respiratory drive and increase airway resistance) urethral stricture or prostatic hypertrophy (it may cause urinary retention) (see section 4.2).
- Patients with possible head injury or conditions involving increased intracranial pressure.
- EQUITY METHADONE should not be used in patients with intestinal pseudo-obstruction, acute abdomen and inflammatory bowel disease.
- In patients with kidney calculi and in patients with gallstones it may be necessary to administer atropine or other spasmolytic prophylactically.
- Elderly patients and patients suffering from cardiovascular diseases. They are at increased risk of hypotension and syncope.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines:

Concomitant use of EQUITY METHADONE oral solution 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 EQUITY METHADONE 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).

Excipients

EQUITY METHADONE contains sunset yellow (E110), which may cause allergic reactions and blood orange flavour (including propylene glycol) which may cause alcohol-like symptoms.

EQUITY METHADONE contains 1,20 mg Sodium benzoate in each 1 ml solution, which is equivalent to 0,12 % *m/v*. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

EQUITY METHADONE contains less than 1 mmol sodium (23 mg) per 1 ml solution, i.e, essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

P-glycoprotein inhibitors: Methadone is a substrate of p-glycoprotein; all medicines that inhibit P-glycoprotein (e.g. quinidine, verapamil, ciclosporin), may therefore raise the serum concentration of methadone. The pharmacodynamic effect of EQUITY METHADONE may also increase because of increased blood brain barrier passage.

EQUITY METHADONE is metabolised in the liver via the cytochrome P450 isoenzymes. Consequently, use

with other medicines that induce or inhibit these isoenzymes may result in changes in plasma concentration of EQUITY METHADONE and, possibly, adverse reactions.

Medicines inhibiting isoenzyme activity: Methadone is a substrate of CYP3A4 (see section 5.2). By inhibition of CYP3A4 clearance of methadone is lowered. Concomitant administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, delavirdine, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, fluoxetine, fluvoxamine, nefazodone and telithromycin) may result in increased plasma concentrations of EQUITY METHADONE. A 40-100 % increase of the quote between the serum levels and the EQUITY METHADONE dose has been shown with concomitant fluvoxamine treatment. If these medicines are prescribed to patients on EQUITY METHADONE maintenance treatment, one should be aware of the risk of overdose.

Medicines inducing isoenzyme activity: Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase and the plasma levels of EQUITY METHADONE decrease. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone, *Hypericum perforatum* (St John´s Wort)), may induce hepatic metabolism.

The consequences of enzyme induction are more marked if the inducer is administered after treatment with EQUITY METHADONE has begun. Abstinence symptoms have been reported following such interactions and hence, it may be necessary to increase the EQUITY METHADONE dose. If treatment with a CYP3A4 inducer is interrupted, the EQUITY METHADONE dose should be reduced.

Products that affect the acidity of the urine: Acidification of the urine increases the elimination of EQUITY METHADONE. Patients that are treated with EQUITY METHADONE are recommended to avoid products containing ammonium chloride.

Concomitant HIV infection treatment: Some protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of EQUITY METHADONE. When ritonavir is administered alone, a two-fold AUC of methadone has been observed. The plasma levels of zidovudine (a

nucleoside analogue) increase with EQUITY METHADONE use after both oral and intravenous administration of zidovudine. This is more notifiable after oral than after intravenous use of zidovudine. These observations are likely caused by inhibition of zidovudine glucuronidation, and therefore decreased clearance of zidovudine. During treatment with EQUITY METHADONE, patients must be carefully monitored for signs of toxicity caused by zidovudine, why it may be necessary to reduce the dose of zidovudine. Because of mutual interactions between zidovudine and EQUITY METHADONE (zidovudine is a CYP3A4 inducer), typical opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

Didanosine and stavudine: EQUITY METHADONE delays the absorption and increases the first pass metabolism of stavudine and didanosine which results in a decreased bioavailability of stavudine and didanosine.

EQUITY METHADONE may double the serum levels of desipramine.

Pharmacodynamic interactions

Administration of naloxone, naltrexone, buprenorphine or pentazocine to a patient on EQUITY METHADONE treatment will rapidly produce abstinence symptoms.

CNS depressants: Medicines with a sedative effect on the central nervous system may result in increased respiratory depression, hypotension, strong sedation or coma, therefore it may be necessary to reduce the dose of one or both of the medicines. With EQUITY METHADONE treatment, the slowly eliminated substance methadone, give rise to a slow tolerance development and every dose increase may after 1-2 weeks give rise to symptoms of respiratory depression. The dose adjustments must therefore be made with caution and the dose increased gradually with careful observation.

Peristalsis inhibition: Concomitant use of EQUITY METHADONE and peristalsis inhibiting medicines (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in long-term use.

QT-prolongation: Cardiac events may occur in cases of co-administration with medicines affecting cardiac conduction (prolong QT interval) or electrolyte balance such as antidysrhytmics (sotalol, amiodarone, flecainide), antipsychotics (thioridazine, haloperidol, sertindole, phenothiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

MAO-inhibitors: Caution must be exercised in concomitant administration of MAO inhibitors which may result in reinforced CNS-inhibition, serious hypotonia and/or apnoea. EQUITY METHADONE should not be combined with MAO-inhibitors and for two weeks after treatment (see section 4.3).

Opioid analgesics delay gastric emptying, thereby invalidating test results. Delivery of technetium Tc 99m disofenin to the small bowel may be prevented and plasma amylase and plasma lipase activity may be increase because opioid analgesics may cause constriction of the sphincter of Oddi and increased biliary tract pressure; these actions result in delayed visualisation and thus resemble obstruction of the common bile duct. The diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been given. Cerebrospinal fluid pressure (CSF) may be increased; effect is secondary to respiratory depression – induced carbon dioxide retention.

Sedative medicines such as benzodiazepines or related medicines:
The concomitant use of opioids 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).

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Neonatal abstinence syndrome, respiratory depression and low birth weight have been reported in neonates after EQUITY METHADONE treatment during pregnancy. EQUITY METHADONE should not be administered during pregnancy.

Breastfeeding:

EQUITY METHADONE is distributed into breast milk and should not be used during lactation.

Fertility:

No fertility data are available.

4.7 Effects on ability to drive and use machines

EQUITY METHADONE 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 side effects of EQUITY METHADONE treatment are in general the same as those in treatment with other opiates.

The most serious side effect of methadone as contained in EQUITY METHADONE is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest have occurred.

Tabulated summary of adverse reactions

System organ class **MedDRA**	**Frequency**	**Adverse event**

Endocrine disorders	*Less frequent*	Hypothyroidism
Investigations	*Frequent*	Weight increase
Metabolism and nutrition disorders	*Frequent*	Fluid retention
	Less frequent	Anorexia
	Frequency unknown	Hypokalaemia, hypomagnesemia
Blood and lymphatic system disorders	*Frequency unknown*	Reversible thrombocytopenia has been reported in opioid patients with chronic hepatitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Respiratory depression (at high doses), pulmonary oedema
	Frequency unknown	Central sleep apnoea syndrome
Gastrointestinal disorders	*Frequent*	Nausea, vomiting, constipation (obstipation)
	Less frequent	Dry mouth (xerostomia), glossitis
Psychiatric disorders	*Frequent*	Euphoria, hallucinations
	Less frequent	Dysphoria, agitation, insomnia, disorientation
	Frequency unknown	Dependence
Ear and labyrinth disorders	*Frequent*	Vertigo
Eye disorders	*Frequent*	Blurred vision, miosis
Nervous system disorders	*Frequent*	Sedation, headache, dizziness, confusion, sleep disturbances
	Less frequent	Visual disturbances, syncope
Skin and subcutaneous tissue disorders	*Frequent*	Transient rash, sweating
	Less frequent	Pruritus, urticaria, other rash and in very uncommon cases bleeding

		urticaria
Hepatobiliary disorders	*Less frequent*	Bile duct dyskinesia
Vascular disorders	*Less frequent*	Facial flush, hypotension
Cardiac disorders	*Less frequent*	Bradycardia, palpitations, cases of prolonged QT intervals and "torsade de pointes" have been reported in treatment with EQUITY METHADONE, especially with high doses
Renal and urinary disorders	*Less frequent*	Urinary retention and antidiuretic effect
Reproductive system and breast disorders	*Frequent*	Reduced libido
	Less frequent	Reduced potency and amenorrhea
General disorders and administration site conditions	*Frequent*	Fatigue
	Less frequent	Oedema of the lower extremities, asthenia, oedema

Description of selected adverse reactions

In long term use of EQUITY METHADONE, as for maintenance treatment, the undesirable effects diminish successively and progressively during a period of several weeks. However, obstipation and perspiration often remain.

Long-term use of EQUITY METHADONE may lead to morphine-like dependence. The abstinence syndromes are similar to the ones observed with morphine and heroine, however less intense, but more long-lasting.

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 Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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.

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 EQUITY METHADONE 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs in opioid dependency.

ATC code: N07BC02.

Methadone 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 σ- and κ-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.

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 N-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

Blood orange flavouring

Purified water

Sunset yellow FCF (E110)

Saccharine sodium (sweetener)

Sodium benzoate (preservative)

Sodium cyclamate (sweetener)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 3 years

Opened: 1 month

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle in the outer carton to protect it against light.

6.5 Nature and contents of container

Type III amber glass bottle with a ribbed white polypropylene child-proof cap, with opaque tamper evident polyethylene band, clean printed black text on top.

Pack sizes: 60 ml and 500 ml

6.6 Special precautions for disposal and other handling

500 ml pack size is a dispensing pack and is only to be used by healthcare professionals.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

0157

8. REGISTRATION NUMBER(S)

43/2.9/0539

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 04 December 2009

10. DATE OF REVISION OF THE TEXT

21 January 2024