1.3.1.1.2 CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS **S6**

1 NAME OF THE MEDICINE

METHADONE ADCO 10 mg oral solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 10 mg methadone hydrochloride.

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

A clear pink-coloured liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

METHADONE ADCO 10 mg 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 METHADONE ADCO 10 mg assumes that the patient is taking part in a programme including drug-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 METHADONE ADCO 10 mg 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.

METHADONE ADCO 10 mg 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.

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 medicine is administered to elderly or ill patients.

Paediatric population

METHADONE ADCO 10 mg 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).

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 METHADONE ADCO 10 mg listed in section 6.1
- METHADONE ADCO 10 mg 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 with ulcerative colitis, since METHADONE ADCO 10 mg may precipitate toxic dilation or spasm of the colon
- Patients dependent on non-opioid medicines
- Patients with severe hepatic impairment as it may precipitate encephalopathy; dose adjustment may be necessary in cases of impaired hepatic function (see section 4.4)
- Patients with biliary and renal tract spasm.

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.

Great caution must be exercised in the following cases:

- Severe obstructive pulmonary disease, acute asthma attacks, cor pulmonale, lessened respiratory reserve, hypoxia and hypercapnia are relative contraindications; each case must be assessed individually
- A lower initial dose must be administered to patients with hypothyroidism, myxoedema (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 as METHADONE ADCO 10 mg is contraindicated in these group of patients and should be avoided
- METHADONE ADCO 10 mg 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

- In the case of elderly or ill patients, repeated doses should only be given with extreme caution.

Dependence may occur in chronic use.

The withdrawal period is longer for METHADONE ADCO 10 mg than for heroin because METHADONE ADCO 10 mg has a longer half-life.

METHADONE ADCO 10 mg should be given with caution to patients with:

- History of asthma (see section 4.3)
- Convulsive disorders
- Depressed respiratory reserve
- Adrenocortical insufficiency
- Inflammatory or obstructive bowel disorders
- Myasthenia gravis.

The precautions to be taken in the use of METHADONE ADCO 10 mg are the same as those applying to opiates in general.

Hepatic and renal impairment

Great caution must be exercised in patients with impaired hepatic and renal function. The metabolism of METHADONE ADCO 10 mg may be reduced in impaired hepatic function, and dose adjustment may be necessary.

Caution as METHADONE ADCO 10 mg may precipitate porto-systemic encephalopathy in patients with severe liver damage.

METHADONE ADCO 10 mg may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

QT prolongation

QT prolongation and *torsade de pointes* may occur with METHADONE ADCO 10 mg 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.

Opioid use disorder (abuse and dependence)

METHADONE ADCO 10 mg is an opioid analgesic and is highly addictive in its own right. METHADONE ADCO 10 mg 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 possibly death.

Exceeding the prescribed dose, together with prolonged and continuous use of this medicine, may lead to dependency and addiction.

- Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of METHADONE ADCO 10 mg may result in overdose and/or death.
- Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.
- Withdrawal symptoms, such as restlessness and irritability may occur once the medicine is stopped.
- There is an increased risk of addiction in patients with personal or family history of substance abuse or mental health 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).

Tolerance and dependence of the morphine type may occur.

METHADONE ADCO 10 mg can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Opioid-induced hyperalgesia (OIH) and allodynia

Opioid pain medicines have been associated with opioid-induced hyperalgesia (OIH), a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). Increases in pain typically occur following a dose increase and resolve quickly following proper diagnosis and management of the condition. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia).

Sleep-related breathing disorders

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

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with METHADONE ADCO 10 mg. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal.

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

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

If women take this medicine during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Respiratory depression

Due to the slow accumulation of METHADONE ADCO 10 mg in the tissues, respiratory depression may not be fully apparent for a week or two and may exacerbate asthma due to histamine release. Concomitant treatment with other medicines with CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5 Interactions).

Adrenal insufficiency

Opioid analgesics 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.

Decreased sex hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Hypoglycaemia

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

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

Concomitant use of METHADONE ADCO 10 mg 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 METHADONE ADCO 10 mg 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).

Narcotic antagonists or mixed agonist/antagonists

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 dependent patients.

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, METHADONE ADCO 10 mg is contraindicated in children (see section 4.3).

Children are more sensitive than adults which is why poisoning may occur at very low doses. To avoid unintentional intake of METHADONE ADCO 10 mg by children, METHADONE ADCO 10 mg should in cases when it is taken home, be kept in a safe place where children cannot reach it.

4.5 Interactions with other medicines and other forms of interaction

METHADONE ADCO 10 mg 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 METHADONE ADCO 10 mg 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 METHADONE ADCO 10 mg. A 40 - 100 % increase of the quote between the serum levels and the METHADONE ADCO 10 mg dose has been shown with concomitant fluvoxamine treatment. If these medicines are prescribed to patients on METHADONE ADCO 10 mg 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 METHADONE ADCO 10 mg 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 METHADONE ADCO 10 mg has begun. Abstinence symptoms have been reported following such interactions and hence, it may be necessary to increase the METHADONE ADCO 10 mg dose. If treatment with a CYP3A4 inducer is interrupted, the METHADONE ADCO 10 mg dose should be reduced.

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 METHADONE ADCO 10 mg may also increase because of increased blood brain barrier passage.

CNS depressants:

Alcohol, anaesthetics, hypnotics and sedatives, barbiturates, phenothiazines, some other major tranquillisers and tricyclic antidepressants may increase the general depressant effects of METHADONE ADCO 10 mg when used concomitantly.

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

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 METHADONE ADCO 10 mg treatment, the slowly eliminated substance methadone, gives 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 METHADONE ADCO 10 mg 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 antidysrhythmic (sotalol, amiodarone, flecainide), antipsychotics (thioridazine, haloperidol, sertindole, phenothiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

Histamine H_2 antagonists:

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

MAOIs:

The concurrent use of MAOIs is contraindicated as they may prolong and enhance the respiratory depressant effects of METHADONE ADCO 10 mg. METHADONE ADCO 10 mg should not be given for two weeks after treatment with MAOIs (see section 4.3).

pH of urine:

Medicines that acidify or alkalinise the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH. Patients that are treated with

METHADONE ADCO 10 mg are recommended to avoid medicines containing ammonium chloride.

Opioid agonist analgesics:

Additive CNS depression, respiratory depression and hypotension.

Opioid antagonists:

Naloxone and naltrexone antagonise the analgesic, CNS and respiratory depressant effects of METHADONE ADCO 10 mg and can rapidly precipitate withdrawal symptoms. Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

Antiretroviral medicines such as nevirapine, efavirenz, nelfinavir, ritonavir:

Based on the known metabolism of methadone, these medicines may decrease plasma concentrations of methadone by increasing its hepatic metabolism.

Narcotic withdrawal syndrome has been reported in patients treated with some retroviral medicines and METHADONE ADCO 10 mg concomitantly.

METHADONE ADCO 10 mg maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and METHADONE ADCO 10 mg dose should be adjusted accordingly.

Some protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of METHADONE ADCO 10 mg. When ritonavir is administered alone, a two-fold AUC of methadone has been observed.

Methadone may increase the plasma concentration of zidovudine. During treatment with METHADONE ADCO 10 mg, patients must be carefully monitored for signs of toxicity caused by zidovudine, hence it may be necessary to reduce the dose of zidovudine. Because of mutual interactions between zidovudine and METHADONE ADCO 10 mg (zidovudine is a CYP3A4 inducer), typical opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

METHADONE ADCO 10 mg delays the absorption and increases the first pass metabolism of stavudine and didanosine which results in a decreased bioavailability of stavudine and didanosine.

Ciprofloxacin:

Concomitant use may lead to sedation, confusion and respiratory depression.

Pregnancy tests:

METHADONE ADCO 10 mg may interfere with the urine testing for pregnancy.

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).

Gabapentinoids:

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

Serotonergic medicines:

Serotonergic syndrome may occur with concomitant administration of METHADONE ADCO 10 mg with pethidine, monoamine oxidase (MAO) inhibitors and serotonin medicines such as Selective Serotonin Re-uptake Inhibitors (SSRIs), Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

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 METHADONE ADCO 10 mg treatment during pregnancy. METHADONE ADCO 10 mg should not be administered during pregnancy.

Breastfeeding

METHADONE ADCO 10 mg is distributed into breast milk and should not be used during lactation.

Fertility

No data on male and female fertility is available.

(Please refer to section 4.5)

4.7 Effects on ability to drive and use machines

METHADONE ADCO 10 mg 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

a. Summary of the safety profile

The side effects of METHADONE ADCO 10 mg treatment are in general the same as those in treatment with other opiates.

The most serious side effect of methadone as contained in METHADONE ADCO 10 mg is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest may occur.

b. Tabulated list of adverse reactions

The following side effects have been reported and may occur with METHADONE ADCO 10 mg:

System Organ Class	**Frequency**	**Adverse Event**
Blood and lymphatic system disorders	Frequency unknown	Reversible thrombocytopenia has been reported in opioid patients with chronic hepatitis
Endocrine disorders	Less frequent	Hypothyroidism
	Frequency unknown	Raised prolactin levels with long-term administration.
Metabolism and nutrition disorders	Frequent	Fluid retention
	Less frequent	Anorexia
	Frequency unknown	Hypokalaemia, hypomagnesemia, hypoglycaemia
Psychiatric disorders	Frequent	Euphoria, hallucinations
	Less frequent	Dysphoria, agitation, insomnia, disorientation
	Frequency unknown	Dependence, confusion particularly at the start of the treatment, changes of mood

Nervous system disorders	Frequent	Dizziness, sedation, confusion, headache, sleep disturbances, sweating
	Less frequent	Visual disturbances, syncope
	Frequency unknown	METHADONE ADCO 10 mg has the potential to increase intracranial pressure, particularly in circumstances where it is already raised
Eye disorders	Frequent	Miosis, blurred vision
	Frequency unknown	Dry eyes
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*.
Vascular disorders	Less frequent	Orthostatic hypotension, facial flushing
Respiratory, thoracic and	Less frequent	Respiratory depression (at high doses), pulmonary oedema

mediastinal disorders	Frequency unknown	Exacerbation of existing asthma, dry nose, central sleep apnoea syndrome
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation (obstipation)
	Less frequent	Dry mouth (xerostomia), glossitis, acute pancreatitis*
Hepatobiliary disorders	Less frequent	Bile duct dyskinesia
Skin and subcutaneous tissue disorders	Frequent	Transient rash, sweating
	Less frequent	Pruritus, urticaria, other rash, bleeding urticaria, tendency to oedema
Renal and urinary disorders	Less frequent	Urinary retention and antidiuretic effect, micturition
Reproductive system and breast disorders	Frequent	Reduced libido
	Less frequent	Reduced potency and amenorrhea

	Frequency unknown	Galactorrhoea, dysmenorrhoea
General disorders and administration site conditions	Frequent	Fatigue
	Less frequent	Oedema of the lower extremities, asthenia, oedema
	Frequency unknown	Hypothermia, drug withdrawal syndrome
Investigations	Frequent	Weight increase

*__Post-marketing experience:__

Less frequent increased risk of abdominal pain, including pancreatitis has been reported.

c. Description of selected adverse reactions

In long term use of METHADONE ADCO 10 mg, 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 METHADONE ADCO 10 mg 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. 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.

For reporting of side effects directly to the Holder of Certificate of Registration, contact +27 635 0134 or email Adcock.aereports@adcock.com.

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 METHADONE ADCO 10 mg 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in addictive disorders (Drugs used in opioid dependence).

ATC code: N07BC02

Category and class A.2.9 Other Analgesics

Pharmacodynamic effects

METHADONE ADCO 10 mg 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 δ and k-receptors. METHADONE ADCO 10 mg operates in a similar way to morphine but has a less sedative effect. The use of METHADONE ADCO 10 mg 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 varies 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

FD & C Red Dye E123 (Amaranth/Permicol Red), sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the bottle in the outer carton to protect from light.

6.5 Nature and contents of container

METHADONE ADCO 10 mg is packed in:

- A 1 litre amber coloured round high-density polyethylene (HDPE) bottle with a white HDPE screw cap which is then packed in a printed E-fluted carton, or

- A 1 litre white coloured round high-density polyethylene (HDPE) bottle with a white polypropylene (PP) screw cap which is then packed in a printed E-fluted carton, or
- A 100 mL white coloured round high-density polyethylene (HDPE) bottle with a white HDPE child resistant (CR) cap which is then packed in a printed E-fluted carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road

Aeroton

Johannesburg

2013

Tel: +27 11 494 8000

8 REGISTRATION NUMBER(S)

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