1.3.1.1 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 content: Sugar free oral solution

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

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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.

Dharmisha Bhaga

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);

Dharmisha Bhaga

- 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 is a relative contraindication; each case must be assessed individually;
- Patients with hypothyroidism or prostatic hypertrophy. A lower, initial dose must be administered;
- Patients with possible head injury or conditions involving increased intracranial pressure as METHADONE ADCO 10 mg is contraindicated in these group of patients

Dharmisha Bhaga

and should be avoided;

- 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.

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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.

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Addiction/Tolerance/Dependence

METHADONE ADCO 10 mg is a medicine of addiction. 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.

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.

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.

Babies born to mothers receiving METHADONE ADCO 10 mg may suffer withdrawal symptoms.

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.

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).

4.5 Interactions with other medicines and other forms of interaction

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CNS depressants:

Alcohol, anaesthetics, hypnotics and sedatives, barbiturates, phenothiazines, some other major tranquillizers 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.

Histamine H_2 antagonists:

Histamine H_2 antagonists such as cimetidine, can reduce the protein binding of methadone resulting in increased opiate action.

Rifampicin:

Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of METHADONE ADCO 10 mg may be necessary.

Anticonvulsants (phenytoin, phenobarbitone, parbamazepine and primidone):

Induce the metabolism of methadone and there may be a risk of precipitating withdrawal syndrome. Adjustment of the dose of METHADONE ADCO 10 mg should be considered.

MAOIs:

The concurrent use of MAOIs is contraindicated as they may prolong and enhance the respiratory depressant effects of METHADONE ADCO 10 mg.

pH of urine:

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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.

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 symptom. Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

Antiretroviral agents 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. Methadone may increase the plasma concentration of zidovudine. 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.

Ciprofloxacin:

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

Other medicines:

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METHADONE ADCO 10 mg may have an effect on other medicines as a consequence of reduced gastrointestinal motility.

Pregnancy tests:

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

Cytochrome P450 3A4 inhibitors:

Methadone clearance is decreased when co-administered with medicines which inhibit CYP3A4 activity, such as 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.

In patients taking medicines affecting cardiac conduction, or medicines which may affect electrolyte balance there is a risk of cardiac events when METHADONE ADCO 10 mg is taken concurrently.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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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.

b. Tabulated summary of adverse reactions

Endocrine disorders

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Less frequent: Hypothyroidism

Frequency unknown: Raised prolactin levels with long-term administration.

Psychiatric disorders

Frequency unknown: Dependence, confusion particularly at the start of the treatment, changes of mood, including euphoria, and hallucinations.

Nervous system disorders

Frequent: Dizziness, euphoria, sedation, confusion, headache, sleep disturbances, sweating.

Frequency unknown: METHADONE ADCO 10 mg has the potential to increase intracranial pressure, particularly in circumstances where it is already raised.

Eye disorders

Less frequent: Miosis, visual disturbances

Frequency unknown: Dry eyes

Ear and labyrinth disorders

Frequency unknown: Vertigo

Cardiac disorders

Less frequent: Bradycardia, drop in blood pressure (at high doses), QT prolongation and torsade de pointes.

Frequency unknown: Palpitations.

Vascular disorders

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Frequency unknown: Orthostatic hypotension, facial flushing.

Respiratory, thoracic and mediastinal disorders

Less frequent: Respiratory depression (at high doses)

Frequency unknown: Exacerbation of existing asthma, dry nose.

Gastrointestinal disorders

Less frequent: Dry mouth

Frequent: Nausea, vomiting, constipation.

Skin and subcutaneous tissue disorders

Less frequent: Skin itching, tendency to oedema

Renal and urinary disorders

Less frequent: Urinary retention.

Reproductive system and breast disorders

Frequent: Reduced libido

Frequency unknown: Galactorrhoea, dysmenorrhoea, amenorrhoea

General disorders and administration site conditions

Frequency unknown: Hypothermia

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

Dharmisha Bhaga

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.

For reporting of side effects directly to the HCR, 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.

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

ATC code: N07BC02

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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 o- 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.

Metabolism

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-

Dharmisha Bhaga

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

Dharmisha Bhaga

6.4 Special precautions for storage

Store at or below 30 ºC.

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 or white 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.

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8. REGISTRATION NUMBER(S)

54/2.9/0839

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 09 November 2021

10. DATE OF REVISION OF THE TEXT

24 July 2024

Dharmisha Bhaga