

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pinadone Methadone DTF 1 mg/ml Oral Solution Sugar Free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 5 mg methadone hydrochloride
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
Clear, green, viscous, oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the relief of severe pain in conditions where morphine may be a reasonable alternative, such as severe cancer pain.

In the treatment of opioid addiction as substitution or maintenance therapy, within a broader treatment protocol/programme, accompanied by regular reviews and reassessment. This treatment must be supervised by specialist services.

4.2 Posology and method of administration

ANALGESIA

The usual initial dose is 5 to 10mg methadone which may be administered orally.
Since rigid adherence to a dosage schedule may provide inadequate analgesia, subsequent doses should be adjusted according to individual patient response. However, doses administered more frequently than six to eight hourly are liable to cause accumulation with increasing sedation and respiratory depression. In chronic use methadone should not be administered more than twice daily.

Pinadone Methadone DTF 1mg/ml Oral Solution Sugar Free may be used in combination with non-narcotic analgesics to provide additive analgesia.

OPIOID ADDICTION

Dosage should be titrated to the individual needs of patients.
The initial daily dose of methadone is the minimum dose required to eliminate the symptoms and signs of abstinence syndrome (withdrawal effects). Initial dosage regimen is 10-20 mg daily initially, increased by 10-20 mg daily until there are no signs of withdrawal or intoxication. The usual dose is 40-60 mg daily.

Providing a suitable dosage schedule is difficult and, currently, largely a subjective exercise, which involves balancing the addicts reported drug use with a clinical assessment of their dependence. Most clinicians adopt a cautious approach; low dose of methadone are prescribed initially.

These are followed by additional increments as judged appropriate, bearing in mind the hepatic and renal functions of the patient.

Hepatic impairment:

Caution should be exercised when Pinadone is used in patients with liver impairment. In patients with liver cirrhosis the metabolic breakdown of methadone is retarded and the first-pass effect is reduced. This may result in higher methadone plasma levels. Pinadone should be administered at a dose lower than usually recommended and the patient's response should be used as a guideline for further dosage requirements.

Renal impairment:

Caution should be exercised in the use of methadone in patients with renal impairment. The dose interval should be lengthened to a minimum of 8 hours if the glomerular filtration rate (GFR) is 10 – 50 ml/min and to a minimum of 12 hours if the GFR is lower than 10 ml/min.

Cardiac repolarisation disorder:

Methadone should be administered with caution to patients with cardiac repolarisation disorders (see section 4.4, Special warnings and precautions for use).

Dosage in Pregnancy:

Drug withdrawal needs to be achieved 4-6 weeks before delivery if neonatal abstinence syndrome is to be avoided, but abrupt withdrawal can cause intrauterine death. The prolonged duration of action of methadone can increase the risk of neonatal respiratory depression during labour. Detoxification to abstinence is least stressful to mother and foetus if undertaken during the mid-trimester.

Abstinence syndrome may not occur in the neonate for some days after birth. In the event that withdrawal is not possible prior to delivery, methadone administered to the mother may result in prolonged respiratory depression in the neonate and the administration of opioid antagonists may be required.

Children: Not recommended.

4.3 Contraindications

1. Respiratory depression, obstructive airways disease
2. Concurrent administration with M.A.O. inhibitors or within 2 weeks of discontinuation of treatment with them. Concurrent use of other central nervous system depressants.
3. Use during an acute asthma attack.
4. Obstetric use not recommended, because in labour the prolonged duration of action increases the risk of neonatal depression. Methadone is not suitable for children.
5. Hypersensitivity to methadone hydrochloride or any of the ingredients of the product.
6. Head injury and raised intracranial pressure.
7. Ulcerative colitis, as methadone administration may participate toxic dilatation or spasm of the colon.
8. Individuals with QT prolongation, including congenital long QT syndrome.
9. As with all narcotic analgesics, Pinadone Methadone DTF 1 mg/ml Oral Solution should not be administered to patients with severe hepatic impairment as it may not precipitate hepatic encephalopathy (see section 4.2, Posology and Method of Administration).

4.4 Special warnings and precautions for use

1. The symptoms and signs of overdosage and toxicity of methadone are essentially those for morphine, though it is said that methadone has a greater respiratory depressive effect and a lesser sedative effect than an equi-analgesic dose of morphine. Toxic dose are highly variable, regular usage giving tolerance. Pulmonary oedema is a frequent corollary of overdosage whilst the dose-related histamine-releasing property of methadone may account for at least some of the urticaria and pruritis associated with methadone administration. Methadone may lead to an increase in intracranial pressure.
2. Adverse effects occurring more rarely in patients being treated for opioid addiction are as follows:
 - (a) A number of heroin addicts have been reported to die within a few days of starting a methadone maintenance programme. Evidence of chronic persistent hepatitis was detected in ten heroin addicts, who died within 2-6 days of starting methadone treatment. The mean prescribed dose at the time of death was about 60mg. It has been suggested that these sudden deaths may have arisen as a result of accumulation of methadone over several days resulting in death from complications such as cardiac arrhythmias or cardiovascular collapse as methadone, like dextropropoxyphene, has membrane stabilising activity and can block nerve conduction.

In view of the possibility of reduced clearance and raised plasma levels it is recommended that liver function tests and urine tests be carried out prior to maintenance and that lower starting doses of methadone be used.

- (b) Evidence of hypoadrenalism has been found in chronic methadone addicts. Findings consistent with both deficient ACTH production and subsequent secondary hypoadrenalism and methadone induced primary adrenal cortical hypofunction have been reported.
 - (c) Choreic movements involving the upper limbs, torso and speech mechanisms have been reported in a 25-year-old man receiving methadone hydrochloride maintenance therapy (45-60 mg/day) for 2 years. Discontinuation of methadone resulted in complete alleviation of the abnormal movements with no recurrence during the subsequent eight months.
 - (d) The function of the secondary sex organs was found to be markedly impaired in 29 male participants in a methadone maintenance programme. The ejaculate volume and seminal vesicular and prostatic secretions in subjects maintained on methadone (mean daily dose 66.9 mg) were reduced by over 50% compared to 16 heroin addicts and 43 narcotic-free controls. Serum testosterone levels were also approximately 43% lower in those on methadone. Whilst the sperm counts of the methadone users were more than twice the control level, reflecting a lack of sperm dilution by secondary sex organ secretion, the sperm motility of these subjects was markedly lower than normal.
3. Caution is advised in patients with pheochromocytomas as administration of methadone may precipitate a hypertensive crisis.
4. Cases of QT-interval prolongation and torsades de pointes have been reported during treatment with methadone, particularly at high doses (>>100mg/d). Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of: advanced heart disease or ischaemic heart disease, known history of QT prolongation, liver disease, concomitant treatment with drugs that have a potential for QT-prolongation.
5. Sunset Yellow may cause allergic reactions.
6. This product contains maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

1. Methadone is metabolised in the liver to inactive metabolites via the mixed-function oxidase system (primarily the cytochrome P-450 isoenzymes CYP3A4). As might be expected, interactions occur with enzyme inducers and inhibitors. Inducers of this isoenzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone, St. John's Wort, some protease inhibitors) may increase the metabolism of methadone. Withdrawal symptoms as a consequence of such interactions have been reported. In inhibition of CYP3A4 clearance of methadone will fall. Co-administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, cimetidine, erythromycin, fluconazole, selective serotonin reuptake inhibitors, itraconazole, ketoconazole, and telithromycin) may result in increased plasma concentration of methadone. If these drugs are prescribed for methadone maintenance patients an awareness of the risk of overdose is needed.
2. In addition to compounds that may decrease the metabolism of methadone, extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone (see Warnings and Precautions). Interactions may occur with methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. Caution should also be exercised when prescribing concomitant drugs capable of inducing electrolyte disturbances that may prolong the QT interval (hypomagnesaemia, hypokalaemia). These include diuretics, laxatives and in rare cases mineral or corticoid hormones.
3. Urinary clearance of methadone is increased by acidic urine and decreased in alkaline urine. Drugs and preparations altering urinary pH may thus affect methadone pharmacokinetics. It should be noted that vegetarians tend to produce alkaline urine, and dietary habits may thus be relevant to methadone dosage.
4. The subject formulation contains colouring additives that are permitted colour additives for foods within the EC. These colours are synthetic azo dyes and are recognised to produce sensitisation manifest as bronchospasm, rhinitis and skin rashes. Persons already sensitised to aspirin may react adversely when exposed to these dyes.
5. The general depressant effects of methadone may be enhanced by other centrally-acting agents such as, alcohol, barbiturates, neuromuscular blocking agents, phenothiazines and tranquillisers. Some psychotropic drugs, however, may potentiate the analgesic effects of methadone.
6. Concurrent use of opioid drugs may increase the risk of respiratory depression.
7. Opioid antagonists may precipitate withdrawal symptoms.
8. Concurrent administration with MAO-inhibitors may result in enhanced dampening of the CNS, severe hypotension and/or respiratory arrest.

4.6 Fertility, pregnancy and lactation

Methadone administered to pregnant women for the management of opioid addiction has the potential for several adverse effects on the foetus and neonate. A careful benefit/risk assessment must be made. Apart from the risk of prolonged respiratory depression in the neonate, the immediate problems are neonatal withdrawal syndrome and low birth weight; increased stillbirth rates have also been reported.

The effects of methadone itself on pregnancy and infants born to methadone-treated mothers are difficult to assess in view of the complicating factors such as poor prenatal care, poor maternal nutrition, smoking, poor environmental and social conditions. Most studies have associated methadone with a low birth weight but methadone has not convincingly been associated with congenital malformations.

It should not be used during labour (see section 4.3 contraindications).

Methadone is excreted in breast milk, though it is unclear whether this contributes to adverse effects on the nursing infant.

4.7 Effects on ability to drive and use machines

Methadone may cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink as blurred vision, dizziness, or nausea may occur which may affect the ability to drive or operate machinery.

4.8 Undesirable effects

The most common side effects include nausea, vomiting, constipation and drowsiness. Larger doses cause respiratory depression and hypotension.

Gastrointestinal disorders:

Common: Nausea, vomiting, dry mouth, constipation, biliary spasm

Nervous system disorders:

Very common: dizziness, drowsiness, light-headedness.

Psychiatric disorders:

Dependence miosis, hallucinations, mood changes

Respiratory, thoracic and mediastinal disorders:

Respiratory depression

Vascular disorders

Postural hypotension and facial flushing.

Rare: Hypotension and collapse.

Cardiac disorders:

Bradycardia and palpitations.

Rare cases of QT prolongation and torsades de pointes have been reported.

Renal and urinary disorders

Common: Urinary retention or hesitancy.

Methadone in common with other opioids may cause spasm of the renal tracts (see Contraindications).

Skin and subcutaneous tissue disorders

Urticaria, pruritis

General disorders

Hypothermia, sweating, weight gain

Reproductive system and breast disorders

Prolonged use of methadone in men has been reported to be associated with the development of gynaecomastia and impaired fertility (see Pregnancy and Lactation).

Withdrawal (abstinence) syndrome: Chronic use of opioid analgesics may be associated with the development of physical dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered. Withdrawal symptoms that may be observed after discontinuation of opioid use include:

Body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRa Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

The symptoms and signs of overdosage and toxicity of methadone are essentially those for morphine, though respiratory depression may be more profound and prolonged than for an equivalent dose of morphine. Treatment is supportive and use of a narcotic antagonist such as naloxone, malorphine or levallorphan should be limited to those patients with demonstrated respiratory or cardiovascular depression due to methadone.

Naloxone is the preferred antagonist as there is less likelihood of further respiratory depression from the effects of the narcotic antagonist. Use of a narcotic antagonist may need to be continued for up to 48 hours due to the duration of action of methadone, and for this reason respiratory and cardiovascular monitoring is mandatory. Dialysis, CNS stimulation and respiratory stimulants are contraindicated. Acidification of the urine will increase the renal clearance of the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methadone is a narcotic analgesic in the manner of morphine and like morphine is highly addictive drug in its own right. It has a less sedative effect than morphine. It acts on the CNS system and smooth muscle. This action is caused by the response of structurally and sterically specific opiate receptor sites in the brain, spinal cord and nervous system.

5.2 Pharmacokinetic properties

Protein-binding: Up to 90% but considerable inter-subject variation. About 15% is bound to immunoglobulin, the remainder to albumin.

Distribution in blood: Plasma: Whole blood ratio, about 1:3.

Clearance: Plasma clearance about 2 ml/min/kg.

Volume of distribution: Approx. 5L/kg.

Half-life: a) single dose 10-25 hours.
b) repeated doses 13-55 hours.

Therapeutic concentration: In plasma, usually in the range 0.05-1.0m/ml.

During Methadone maintenance treatment, considerable fluctuations occur day to day.

Disposition in the body: Widely distributed in the tissue, with higher concentrations in the liver, lungs and kidneys than in the blood. The main metabolic reaction is N-demethylation resulting in a substance which spontaneously cyclises to form the major metabolites, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP), neither of which are active.

Hydroxylation to methadol followed by N-demethylation to Normethadol also occurs to some extent. Other metabolic reactions occur and there are at least eight known metabolites.

In subjects on Methadone maintenance, about 20 to 60% of a dose is excreted in the urine in 24 hours, with up to about 33% of the dose as unchanged drug and up to about 43% as EDDP; EMDP accounts for about 5 to 10% of the dose.

The ratio of EDDP to unchanged Methadone is usually very much higher in the urine of patients on Methadone maintenance treatment than in simple overdose cases. Urinary excretion of unchanged drug is pH dependent, being increased in acid urine. Up to 30% of a dose may be eliminated in the faeces, but this appears to decrease with increasing dosage. About 75 % of the total excreted material is unconjugated.

5.3 Preclinical safety data

Not appropriate

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Benzoic acid
Sodium hydroxide
Maltitol Liquid (E965)
Hydroxyethylcellulose
Purified water
Sunset yellow (E110)
Green (E142).

6.2 Incompatibilities

Syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing as physical incompatibility with methadone hydrochloride has been reported.

6.3 Shelf life

20ml, 25ml, 30ml, 35ml, 40ml, 45ml, 50ml, 55ml, 60ml HDPE bottles:	6 months
100ml, 500ml, 5L HDPE bottle:	2 years
100ml Amber glass bottle:	3 years
500ml and 1L Amber glass bottle:	2 years
In-use shelf life for Amber Glass Bottles only:	3 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Type III amber glass bottle with tamper evident polypropylene cap and a LDPE liner containing 100ml, 500 ml or 1L.

Jaycare Pharma HDPE bottle with tamper evident polypropylene cap and a LDPE liner containing 500 ml.

BXL Cascelloid HDPE bottle with tamper evident polypropylene cap and a LDPE liner containing 20 ml, 25ml, 30ml, 35ml, 40ml, 45ml, 50ml, 55 ml, 60ml and 100ml.

5L HDPE container with tamper evident HDPE cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Methadone hydrochloride is a controlled drug under the Misuse of Drugs Act SI 12 of 1977.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
T/A Pinewood Healthcare
Ballymacarbry
Clonmel
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/061/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 1995
Date of last renewal: 15 November 2005

10 DATE OF REVISION OF THE TEXT

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