

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pinadone Methadone Mixture DTF 1 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 1mg methadone hydrochloride.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Oral solution

A clear, viscous, green oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

The subject formulation contains 2.5 times the concentration of methadone found in methadone linctus and is suitable ONLY for use as substitution or maintenance therapy of narcotic dependence.

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 is usually 10 mg to 20 mg daily, increasing 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 doses of methadone are prescribed initially. These are followed by additional increments as judged appropriate, bearing in mind the hepatic and renal function of the patient.

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, concurrent administration with M.A.O.(monoamine oxidase) inhibitors or within 2 weeks of discontinuation of treatment with them. Concurrent use of other central nervous system depressants.
2. Use during an acute asthma attack.
3. Obstetric use not recommended, because in labour the prolonged duration of action increases the risk of neonatal depression.
Methadone is not suitable for children.

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 doses 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 (adrenocorticotropin) 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.

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. As might be expected, interactions occur with enzyme inducers and inhibitors; abstinence syndrome has been precipitated by

phenytoin and rifampicin whilst co-administration of cimetidine has precipitated toxicity.

2. 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.

3. 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.

4.6 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 contra-indications.

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.

4.8 Undesirable effects

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

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 the 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 a 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. 5 L/kg.

Half-life:

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

Therapeutic concentration:

In plasma, usually in the range 0.05-1.0 µg/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

Glycerol
 Sucrose
 Citric acid
 Sodium benzoate (E211)
 Sunset yellow (E110)
 Green S (E142)
 Purified water

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

500ml Amber glass bottle:	24 months.
20ml, 25ml, 30ml and 500ml HDPE bottle:	6 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

500ml type III amber glass bottle with aluminium pilfer proof cap or polypropylene tamper evident cap with an LDPE liner.

20ml, 25ml, 30ml and 500ml HDPE bottle with aluminium pilfer proof cap or polypropylene tamper evident cap with an LDPE liner.

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

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 281/61/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 January 1998

Date of last renewal: 23 January 2003

10 DATE OF REVISION OF THE TEXT

June 2004