Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methadone Mixture DTF (Sugar Free) 1 mg in 1 ml Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains methadone hydrochloride 1 mg.

Excipients:
Sunset yellow (E110) 0.008 mg/ml
Liquid maltitol (E965) 0.4 ml/ml

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
A clear, green solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Dosing and duration should be individualised based on a careful evaluation of subjective and patient data, bearing in mind clinical status, including hepatic or renal function of the patient.
Methadone should be administered with caution in patients with cardiac repolarisation disorders.
For oral administration only.

Addition:
Adults: Initially 10 – 20 mg per day, increasing by 10 - 20 mg per day until there are no signs of withdrawal or intoxication. The usual dose is 40-60mg per day.
The dose is adjusted according to the degree of dependence with the aim of gradual reduction.

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

Children: Not recommended for children.

4.3 Contraindications

- Respiratory depression, obstructive airways disease and during an acute asthma attack.
- Acute alcoholism (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).
- Head injury and raised intracranial pressure (further rise in intracranial pressure – *See section 4.8, Undesirable effects*: papillary response affected).
- Where these is a risk of paralytic ileus.
- Concurrent administration with MAOI drugs, including moclobemide, or for 2 weeks after stopping (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

- Use during labor (prolonged duration of action increases the risk of neonatal depression).
- Children (serious risk of toxicity).
- Phaeochromocytoma (risk of pressor response to histamine release).

4.4 Special warnings and precautions for use

Tolerance and dependence of the morphine type may occur. Methadone should be given with caution to patients with history of asthma (*See section 4.3, Contraindications*), convulsive disorders, depressed respiratory reserve, hypotension, shock, prostatic hyperplasia, adrenocortical insufficiency, inflammatory or obstructive bowel disorders, myasthenia gravis or hypothyroidism. In cases of hepatic or renal impairment the use of methadone should be avoided or given in reduced doses.

Cases of QT interval prolongation and torsade de pointes have been reported during treatment with methadone, particularly at high doses (>100 mg/d). Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:

- known history of QT prolongation
- advanced heart disease ,
- ischaemic heart disease & Liver disease,
- concomitant treatment with drugs that have a potential for QT-prolongation

4.5 Interaction with other medicinal products and other forms of interaction

- **Alcohol** – may induce serious respiratory depression and hypotension (*See section 4.3, Contraindications*).

- **Analgesics**
  - Buprenorphine and pentazocine – rapidly precipitate withdrawal symptoms in patients addicted to methadone.
  - Other opioid alalgesics – additive CNS depression, repiratory depression and/or hypotension.

- **Antiarrhythmics**
  - Mexiletine – methadone may delay mexiletine absorption.
  - See also *Drugs affecting cardiac conduction* below.

- **Antidepressants**
  - MAOIs including moclobemide (concurrent or within 2 weeks of discontinuation) are contra-indicated (*See section 4.3, Contraindications*) – risk of CNS excitation or depression.
  - Fluvoxamine – possible increase in plasma concentrations of methadone.
  - Tricyclics – additive CNS depression, respiratory depression and/or hypotension.

- **Antivirals**
  - Nevirapine – may decrease plasma concentrations of methadone by increasing its hepatic metabolism with subsequent withdrawal symptoms. Patients on methadone who start nevirapine should be monitored for withdrawal reactions and the methadone dose adjusted accordingly.
  - Efavirenz – similar reaction to nevirapine.
  - Nelfinavir, ritonavir and possibly abacavir – possibly reduction in plasma concentrations of methadone.
  - Zidovudine – methadone may increase the plasma concentrations of zidovudine.

- **Ciprofloxacin** – may increase methadone levels by inhibiting its metabolism.

- **Cytochrome P450 3A4 inhibitors** – methadone metabolism is mediated by the SYP 3A4 isoenzyme and therefore clearance is reduced when administered with drugs which inhibit SYP 3A4 activity such as:
  - Some anti-HIV agents (see Antivirals above).
  - Macrolide antibiotics.

- Cimetidine (also see Gastro-intestinal drugs below).
- Azole antifungal agents.

- **Drugs affecting cardiac conduction and electrolyte balance** – risk of cardiac events when taken concurrently with methadone.

- **Carbamazepine** – reduction in plasma concentrations of methadone.

- **CNS depressants** such as anaesthetics, antipsychotics, anxiolytics, major and minor tranquillisers and sedatives – additive CNS depressant, respiratory depression and/or hypotension.

- **Gastro-intestinal drugs**
  - Cimetidine – potentiation of opioid activity due to displacement of methadone from protein binding sites.
  - Metoclopramide and domperidone – GI effects antagonised by methadone.

- **Naloxone** – antagonises the analgesic, CNS and respiratory depressant effects of methadone.

- **Naltrexone** – rapidly precipitates withdrawal symptoms in patients addicted to methadone.

- **Phenytoin** – potentiation of opioid activity due to displacement of methadone from protein binding sites.

- **Rifampicin and other rifamycins** – reduce opiate effects due to increased metabolism.

- **Urinary acidifiers** – increase the rate of methadone excretion thus decreasing plasma concentrations.

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 birthweight; increased stillbirth rates have also been reported. One study reported moderate to severe opioid abstinence syndrome in 75% of infants born to mothers maintained on methadone. These infants also exhibited reduced head circumference and increased systolic blood pressure. Another study, however, found no specific effect of methadone (or heroin) on either intra-uterine or post-natal growth.

There is some evidence that infants of mothers maintained on methadone are at increased risk of sudden infant death syndrome. Methadone is excreted in breast milk though it is unclear whether this contributes to any adverse effects on the nursing infant: the death of one 5-week old child of methadone maintained mother was attributed to methadone received via his mother's milk whilst others suggest that the amount capable of delivery by this route is unlikely to have any pharmacological effects on the infant.

4.7 Effects on ability to drive and use machines

The ability to drive or operate machinery may be severely affected during and after treatment with methadone. The time after which such activities can be safely resumed is extremely patient dependant and must be decided by the physician.

4.8 Undesirable effects

Nausea, vomiting and dizziness may occur. Methadone has the potential to increase intracranial pressure, particularly where it is already raised. It causes pain at the inection site: subcutaneous injection causes local tissue irritation and induration. In prolonged use it should not be administered more than twice daily to avoid the risk of accumulation and overdosage.

Other undesirable effects that may occur after taking methadone are hallucinations, confusion, vertigo, mood changes,

dysphoria, dependence, headache, drowsiness, sweating, postural hypotension, miosis, difficulty with micturition and hypothermia.

Bradycardia, palpitations, tachycardia, facial flushing, constipation, a dray mouth, ureteric or biliary spasm, an antidiuretic affect, decrease of libido or potency, urticaria, pruritis and rashes may also occur.

Cases of QT prolongation and torsade de pointes have been rarely reported.

4.9 Overdose

The signs and symptoms 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. Typically these are respiratory depression, extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment is supportive and use of a narcotic antagonist such as naloxone, nalorphine or levallophan 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 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 response of structurally and sterically specific opiate receptor sites in the brain, spinal cord and nervous system. In the treatment of Opioid addiction as an abstinence syndrome suppressant and/or by blockading the effects of other opiates ("narcotic blockade").

Methadone is rapidly absorbed after oral administration.

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 2ml/min/kg

Volume of distribution:

Approx 5L/kg

Half -Life:

Single dose = 10 - 25 hours

Repeated dose = 13 - 55 hours

Therapeutic concentration:

In plasma, usually in the range 0.05 - 2.0 mcg/ml. During Methadone maintenance treatment considerable fluctuations occur day to day.

Disposition in the Body:

Widely distributed in the tissues, 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 of 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 20-60% of a dose is excreted in the urine in 24hours, 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-dependant, 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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid maltitol (E965)
Sodium Benzoate (E211)
Green S (E142)
Sunset yellow (E110)
Quinoline yellow (E104)
Hydrochloric acid (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 year.
Use within 28 days of opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

30ml, 50ml, 100ml & 500ml of the oral solution in Type III amber glass bottles fitted with child-resistant closures.

Contact material: polyethylene

500ml and 1L HDPE bottle with tamper evident and child resistant cap. The material of construction of the closure is HDPE with an EP wad.

2.5L and 5L HDPE bottle with cap or tamper evidence will be provided with a tamper evident seal. The material of construction of the closures is HDPE with an EP wad.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Ltd
Bampton Road,
Harold Hill,
Romford,
RM3 8UG,
UK

8 MARKETING AUTHORISATION NUMBER

PA 0361/007/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 January 1996

Date of last renewal: 26 January 2006

10 DATE OF REVISION OF THE TEXT

March 2012