Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methadone 10mg/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methadone Hydrochloride 10 mg in 1 ml.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clean colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methadone injection may be used as an analgesic for severe pain as an alternative to morphine.

4.2 Posology and method of administration

By intramuscular or subcutaneous injection.

Initially a single dose of 5-10 mg at six to eight hourly intervals, adjusted according to response.

Elderly: Repeated doses should only be given with extreme caution in the case of elderly or debilitated patients.

Children: Not suitable for use.

4.3 Contraindications

Respiratory depression or respiratory failure; airways obstruction. Use during an acute asthma attack is not advisable.

Methadone should not be administered to patients with head injuries or raised intracranial pressure as there is a risk of respiratory depression which may lead to a further elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
Monamine oxidase inhibitor drugs given concurrently or within two weeks of discontinuation.

Obstetric use is not recommended because of the increased risk of neonatal depression due to the long duration of action.

4.4 Special warnings and precautions for use

Methadone has a long half life and accumulation may occur with repeated doses, especially in elderly or debilitated patients.

Repeated administration of methadone may lead to dependence and tolerance development. Abrupt withdrawal in patients who have developed dependence may precipitate a withdrawal syndrome.

Even at low doses methadone is a **special hazard** to children if ingested accidentally.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of alcohol may induce serious respiratory depression and hypotension.

Monoamine oxidase inhibitors (MAOIs) may prolong and enhance the respiratory depressant effects of methadone and lead to CNS excitation or depression. Other agents with central nervous system depressant activity such as sedatives, hypnotics, anti-psychotics, anxiolytics and barbiturates may result in increased CNS depression, respiratory depression and hypotension. Hyperpyrexia and CNS toxicity has been reported when **selegiline** was co-administered with opioid analgesics.

Methadone is metabolised in the liver and interactions are likely with enzyme inhibitors or inducers; for example, **cimetidine** may enhance the effects of methadone, while **phenytoin** may increase its metabolism.

Similarly, reduced circulating levels of methadone and an increase in its urinary excretion have been reported with **rifampicin**.

Administration of **naltrexone** to a patient addicted to methadone will rapidly precipitate long term withdrawal symptoms.

Administration of **buprenophine** and **pentazocine** may precipitate withdrawal symptoms in the addicted patient.

Drugs that acidify or alkalinise the urine may affect methadone clearance which is increased at acidic pH.

4.6 Pregnancy and lactation

The narcotic analgesics are able to traverse the placenta and also are excreted in breast milk.
There is inadequate evidence of safety in human pregnancy.
Methadone should not be used during labour (see contraindications) or breast-feeding.

4.7 Effects on ability to drive and use machines

Methadone may severely impair the ability to drive and use machinery. The physician must decide the time after which activities may be safely resumed.

4.8 Undesirable effects

The most common side effects are nausea, vomiting, drowsiness, constipation, confusion and euphoria.

Other side effects which occur more commonly in ambulant patients, include pruritus, urticaria, dry mouth, urinary retention, vertigo, bradycardia, orthostatic hypotension, palpitations, sweating, facial flushing, hypothermia, restlessness, changes of mood, hallucinations and miosis. Raised intracranial pressure and muscle rigidity have been reported.

Methadone causes pain at injection sites. Local irritation has been observed at the injection site and induration may occur with repeated subcutaneous injection.

4.9 Overdose

a) Symptoms

Serious overdosage is characterised by respiratory depression and drowsiness which progress to coma or stupor, constricted pupils, cold clammy skin and occasionally bradycardia and hypotension.

b) Treatment

Treatment consists of the establishment of a patent airway and other supportive measures. Oxygen and assisted ventilation should be administered as necessary. Naloxone should be given if coma or bradycardia are present.

Administration of a narcotic antagonist will precipitate an acute withdrawal syndrome in a patient physically dependent upon narcotics. Use of the antagonist in such a person should be avoided if possible and should only be administered with great care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methadone is an opioid agonist with the general properties of morphine. It has analgesic properties and an extended duration of activity in suppressing withdrawal symptoms in physically dependant individuals. It is predominantly a central nervous depressant but it has stimulant actions resulting in nausea, vomiting and miosis.

5.2 Pharmacokinetic properties

Methadone is one of the more lipid soluble opioids and is well absorbed from the gastrointestinal tract but undergoes fairly extensive first pass metabolism. There is extensive binding to plasma and tissue proteins and fairly slow transfer between some parts of the tissue reservoir and the plasma. Methadone is distributed in skeletal muscle, kidney, lung, liver and spleen. Peak plasma concentration levels are reached in one hour with a half life of 6-8 hours for a single intramuscular dose, this figure reflecting distribution into tissue stores as well as renal and hepatic clearance. With regular doses the tissue reservoir is partially filled and the half life is extended to 13-47 hours reflecting only clearance.

Approx. 15-60% is recovered from the urine and as the dose is increased so a higher proportion of non-metabolised methadone is found there. Acidification of the urine can increase renal clearance by a factor of at least three and thus appreciably reduce the half life of elimination.

5.3 Preclinical safety data

The LD_{50} in rats is 95mg kg^{-1} and the intravenous LD_{50} in mice is 20mgkg^{-1}. Little detailed information on toxicology has been published.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium Hydroxide Solution
Water for injections

6.2 Incompatibilities

Physical incompatibility is judged by loss of clarity was reported when an intravenous solution of methadone hydrochloride was mixed with those of aminophylilne, ammonium chloride, amylobarbitone sodium, chlorothiazide sodium, heparin sodium, methicillin sodium, nitrofurantoin sodium, novobiocin sodium, pentobarbitone sodium, phenobarbitone sodium, phenytoin sodium, quinalbarbitone sodium, sodium bicarbonate, sodium iodide, sulphadiazine sodium, sulphafurazole diethanolamine or thiopentone sodium.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.
Keep container in the outer carton.

6.5 Nature and contents of container

Pack of 10 neutral glass ampoules. Each ampoule contains 1, 2, 3.5, 5, 7.5 or 10 ml of solution.

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

For single use only.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER

PA 0409/019/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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