

# DATA SHEET

## METHATABS

### Methadone Hydrochloride 5mg BP

## PRESENTATION

Tablet 5mg - white 7.0mm normal convex tablet

## USES

**Actions** Methadone hydrochloride is a synthetic opioid analgesic. Methadone is a racemic mixture and levomethadone is the active isomer.

The pharmacological actions of methadone are qualitatively similar to those of morphine. Significant quantitative differences are its effective analgesic activity after administration by the oral route and its tendency to show persistent effects with repeated administration.

**Pharmacokinetics** Methadone hydrochloride is readily absorbed after administration by mouth and has high oral bioavailability. Peak plasma concentrations have been reported 1 to 5 hours after oral administration of a single dose in tablet form. It undergoes considerable tissue distribution, and protein binding is reported to be 60 to 90% with  $\alpha$ -acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenyl-5 – methypyrrolidine, both of them inactive, occurs in the liver. The metabolites are excreted in the faeces and urine together with unchanged methadone. Other metabolites, including methanol and nor-methadol (reported to be pharmacologically active), have also been described, but account for a small proportion of the dose. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver and released again mainly unchanged.

Marked interindividual variation in kinetics have been observed with methadone. Elimination half-lives vary considerably (a range of 15-to 60 hours has been reported) and careful adjustment of dosage is necessary with repeated administration.

Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. Declining concentrations have been reported during methadone maintenance suggesting that tolerance occurs, possibly as a result of auto-induction of hepatic microsomal enzymes.

## **INDICATIONS**

Methadone is indicated for relief of severe pain. Epidural or intrathecal administration of small doses of opioid analgesics may provide prolonged pain relief. Although administration via these routes may decrease the risk of some side/adverse effects respiratory depression may occur.

Methadone is sometimes used as an antitussive when severe pain is present and coughing cannot be relieved by other means.

Methadone is indicated as a suppressant to permit detoxification. Oral methadone is also indicated as maintenance therapy to discourage addicts from returning to illicit use of other opioid drugs.

Methadone is not recommended for obstetric analgesia because its long duration of action increases the risk of neonatal respiratory depression.

## **DOSAGE AND ADMINISTRATION**

A dose of 10 to 20mg by mouth may be given initially and increased as necessary by 5 to 10mg daily. The dose must not be increased by more than 5 to 10mg daily, and by nor more than 30mg in any 7-day period. After stabilisation, which can often be achieved with a dose of 30 to 50mg daily (up to a maximum of 80mg daily), the dose of methadone is gradually decreased until total withdrawal is achieved. Some treatment schedules for opioid dependence involved prolonged maintenance therapy with methadone where the daily dose is adjusted carefully for the individual.

## **CONTRAINDICATIONS**

Methadone is contraindicated in individuals who are hypersensitive to methadone or other components in METHADONE Syrup:

Like other opioids, methadone is contraindicated in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.

Methadone should not be given during an attack of bronchial asthma.

Methadone is contraindicated in the presence of acute alcoholism, head injury and raised intracranial pressure.

Methadone is contraindicated in individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment (see Interactions).

As with other opioids, methadone is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon.

As with all narcotics, methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (see Warnings and Precautions)

Methadone is contraindicated in biliary and renal tract spasm.

## **WARNINGS AND PRECAUTIONS**

In common with all opioids, prolonged use of methadone has the potential to produce dependence of the morphine type. Methadone should be used with caution in the presence of hypothyroidism, adrenocortical insufficiency, hypopituitarism, prostatic hypertrophy, shock, diabetes mellitus. Extreme caution should be exercised when administering methadone to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.

In common with other opioids, methadone may produce orthostatic hypotension and drowsiness in ambulatory patients. They should be cautioned, therefore, against driving a vehicle operating machinery or other activities requiring vigilance.

### **Cardiac Conduction Effects:**

Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia ( torsades de pointes ) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment ( > 200mg/day ). Most cases involve patients being treated for pain with large, multiple daily doses of methadone although cases have been reported in patients receiving doses commonly used for maintenance of opioid addiction.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval ( eg cardiac hypertrophy, concomitant diuretic use, hypokalaemia, hypomagnesaemia ). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increase risk if dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. For use of methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighted against the benefit of adequate pain management and the availability of alternative therapies.

### **Mutagenicity:**

Methadone did not exhibit demonstrable mutagenic activity in a wide range of standard in vitro and in vivo mutagenicity assays. However, in a Dominant Lethal assay in mice, treatment with methadone at doses of 1 to 6 mg/kg was associated with increased pre-implantation deaths and chromosomal aberrations of sperm cells, when compared with controls.

**Carcinogenicity:**

Long term carcinogenicity tests in rodents did not reveal any evidence of methadone-related neoplasia.

**Teratogenicity:**

No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given methadone at doses from 10 to 50 times the average daily human maintenance dose. Developmental abnormalities of the central nervous system have been reported in hamsters and mice given high doses in early pregnancy.

**Fertility:**

Methadone does not appear to impair human female fertility. Studies in men on methadone maintenance programmes have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls, reflecting the lack of dilution through reduced seminal secretions.

**Use in Pregnancy and Lactation:**

There is inadequate evidence of the safety of methadone in human pregnancy although it has been in selected use for many years without apparent ill consequence. Autopsies on five infants who died in utero did not reveal any abnormality attributable to methadone use by their dependent mothers. Nevertheless, the use of methadone in pregnancy should be avoided unless there is no safer alternative.

Narcotics may cause respiratory depression in the newborn infant. During the last 2 to 3 hours before expected delivery, narcotics should therefore only be used after weighing the needs of the mother against the risk to the fetus.

Breast feeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation. Withdrawal symptoms can occur in the infant. Assays of breast milk from methadone-maintained mothers showed methadone concentrations of 0.17 to 5.6 mcg/ml

**Use in Children:**

Methadone is not recommended for use in children less than 18 years of age since documented clinical experience has been insufficient to establish a suitable dosage regimen; furthermore, children are particularly sensitive to the respiratory and central nervous system effects of methadone.

**Use in the Elderly:**

Methadone has a long plasma half life which may lead to accumulation, particularly if renal function is impaired (see Renal Impairment). In common with other opioids, methadone may cause confusion in this age group, therefore careful monitoring is advised.

### **Hepatic Impairment**

Particular care should be taken when methadone is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated, methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications).

### **Renal Impairment**

Methadone should be used with caution in patients with renal dysfunction.

## **ADVERSE EFFECTS**

The major side effect of methadone is respiratory depression. Other reported events include nausea, vomiting, dizziness, drowsiness, light-headedness, dry mouth, sweating and confusion. These effects appear to be more common in ambulatory patients and in those receiving oral therapy. Euphoria has been reported at higher doses in tolerant patients.

Hypotension and collapse have occasionally been reported.

Methadone, in common with other opioids, may cause spasm of the biliary and renal tracts (see Contraindications). It also possesses antidiuretic properties.

Prolonged use of methadone in men has been reported to be associated with the development of gynaecomastia.

## **INTERACTIONS**

Monoamine oxidase inhibitors (MAOI's) may prolong and enhance the respiratory depressant effects of methadone. Opioids and MAOI's used together may cause fatal hypotension and coma.

Rifampicin has been reported to reduce circulating levels of methadone and increase its urinary excretion in these patients. The resulting lowered plasma concentrations of methadone may induce withdrawal symptoms.

Phenytoin has been reported to enhance the metabolism of methadone with resulting withdrawal symptoms in the patients.

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.

Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals. Although the significance of this finding is not known for man, caution should be exercised when such drugs are co-administered.

## **OVERDOSAGE**

### **Signs and Symptoms:**

The symptoms and signs of overdosage with methadone parallel those for other opioids, namely profound respiratory depression, pin-point pupils, hypotension, circulatory failure and pulmonary oedema and coma.

Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pin-point pupils and apnoea have been reported in children.

### **Treatment:**

General supportive measures should be employed as required. The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and the restoration of spontaneous respiration. A dose of 0.4 to 2mg is given by intravenous injection repeated at intervals of 2 to 3 minutes if necessary, up to 10mg. Naloxone may also be given by subcutaneous or intramuscular injection or intravenous infusion.

Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse, since the duration of action of the antagonist may be substantially shorter than that of methadone.

The use of other respiratory or central stimulants is not recommended.

Acidification of the urine will enhance urinary excretion of methadone.

Methadone is not dialysable by either peritoneal dialysis or haemodialysis.

## **PHARMACEUTICAL PRECAUTIONS**

Store below 25°C

Shelf life is 60 months from date of manufacture.

## **MEDICINE CLASSIFICATION**

Controlled Drug B3.

## **PACKAGE QUANTITIES**

Pack of 100 tablets in glass bottles.

## **FURTHER INFORMATION**

Nil

**NAME AND ADDRESS**

PSM Healthcare Ltd t/a Healthcare Manufacturing Group  
PO Box 76 401  
Manukau City  
Auckland  
Phone 09-279-7979

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