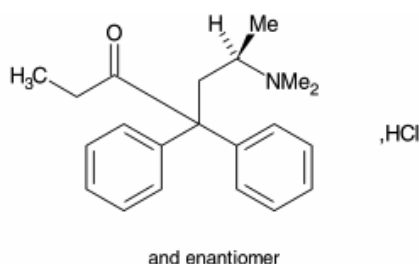


PRODUCT INFORMATION

METHADONE SYRUP

NAME OF THE MEDICINE: Methadone hydrochloride

The chemical name for methadone hydrochloride is (6*RS*)6-(Dimethylamino)-4,4-diphenylheptan-3-one hydrochloride, and the chemical structure is:



Molecular formula: $C_{21}H_{27}NO, HCl$

Relative molecular mass: 345.9

CAS Number: 1095-90-5

DESCRIPTION

Methadone hydrochloride is a synthetic opioid analgesic with the general properties of morphine. Methadone is a racemic mixture and levo-methadone is the active isomer. It occurs as odourless, colourless crystals or white crystalline powder. It is soluble in water, freely soluble in alcohol and chloroform; practically insoluble in ether and in glycerol.

Methadone Syrup is an oral solution of 5mg/mL methadone hydrochloride. Methadone Syrup also contains the following excipients: caramel, ethanol, glycerol, sodium benzoate, sorbitol solution (70%) (noncrystallising), water-purified and Flavour pharmaceutical 503978A.

PHARMACOLOGY

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.

Pharmacodynamic Effects

The combination of opioid agonism and N-methyl-D-aspartate (NMDA) antagonism by methadone produces an additive analgesic response while limiting opioid tolerance.

Pharmacokinetics

Absorption

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.

Distribution

Methadone undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with α_1 -acid glycoprotein being the main binding protein in plasma.

Metabolism

Methadone undergoes N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) with CYP3A4 being the main enzyme responsible. However, other CYP450 enzymes, including CYP2D6, are also likely to be involved in methadone's metabolism.

Elimination

Elimination of methadone occurs principally by metabolism, followed by urinary and faecal excretion of the metabolites, though there is some renal excretion of unchanged methadone. Marked interindividual variations 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.

Special Patient Populations

Elderly

Methadone clearance does not appear to be markedly affected by age, though a slight decrease has been observed over age 65.

Renal Impairment

Although methadone is mostly eliminated by metabolism, a significant proportion of the dose is excreted via the kidney.

INDICATIONS

Methadone Syrup is indicated for:

- the treatment of dependence on opioid drugs
- the treatment of severe pain.

CONTRAINDICATIONS

Methadone Syrup 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.

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 narcotic analgesics, methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (**see PRECAUTIONS**).

Methadone is contraindicated in biliary and renal tract spasm.

Methadone is contraindicated in individuals with existing QT prolongation, including those with congenital long QT syndrome (see **PRECAUTIONS**).

PRECAUTIONS

Deaths due to cardiac arrhythmias and respiratory depression may occur, particularly in patients receiving methadone for analgesia during treatment initiation or conversion from other opioids.

Respiratory Depression

Respiratory depression is the major hazard associated with methadone treatment. The peak depressive effects persist longer than peak analgesic effects, especially during the initial dosing period. Particular care should be taken during the dose initiation and adjustment period to minimise the risk of dose accumulation (see **DOSAGE AND ADMINISTRATION**).

Cardiac Repolarisation

In vivo and in vitro studies have demonstrated that methadone inhibits cardiac potassium channels and prolongs cardiac repolarisation (i.e. prolongs the QT interval). QT interval prolongation and serious arrhythmia (Torsade de Pointes) have been observed during treatment with methadone and appear to be more common with higher doses. Particular caution and careful monitoring is recommended in patients at risk of prolonged QT interval (e.g. cardiac hypertrophy, concomitant diuretic use, hypokalaemia, hypomagnesaemia), patients with a previous history of cardiac repolarisation prolongation, those taking medications affecting cardiac repolarisation or methadone metabolism, and in patients with an increased risk of arrhythmia (see **CONTRAINDICATIONS** and **Interactions with other medicines**). Patients developing QT prolongation while on methadone treatment should be evaluated for 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.

Dependence

In common with all opioids, prolonged use of methadone has the potential to produce dependence of the morphine type. The possibility of addiction cannot be excluded and patients should be reminded of the necessity of adhering to the prescribed dosage. However, when used for pain relief in terminal care, the risk of dependence is of limited concern. Discontinuation of therapy with methadone should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see **ADVERSE EFFECTS**).

Phaeochromocytoma

Extreme caution should be exercised when administering methadone to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.

Ambulatory patients

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

Methadone should be used with caution in the presence of:

hypothyroidism
adrenocortical insufficiency
hypopituitarism
prostatic hypertrophy
shock
diabetes mellitus.

Methadone Syrup is not suitable for administration by injection.

Methadone Syrup is for oral use only.

Mutagenic Potential

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 between 1 and 6 mg/kg was associated with increased pre-implantation deaths and chromosomal aberrations of sperm cells when compared with controls.

Carcinogenic Potential

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

Teratogenic Potential

No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given methadone at doses from ten to fifty 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 programs 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 but this reflected the lack of dilution from seminal secretions. A reduction in libido has been reported as well as impotence, delayed, and/or failed ejaculation.

Use in Pregnancy (Category C)

There is insufficient evidence on which to determine the safety profile of methadone in pregnancy, therefore it should only be used if the potential benefit outweighs the potential risk.

Narcotic analgesics may cause respiratory depression in the newborn infant. During the last 2-3 hours before expected delivery, narcotic analgesics should therefore only be used after weighing the needs of the mother against the risk to the foetus. Methadone is not recommended for use during labour because its prolonged duration of action increases the risk of respiratory depression in the neonate.

Like other opiates, methadone crosses the placenta during pregnancy, and most neonates born to mothers on methadone maintenance will suffer from withdrawal if left untreated.

Withdrawal symptoms may be observed in infants born to mothers receiving methadone maintenance consisting of central nervous system, gastrointestinal, and respiratory disturbances. Abstinence syndrome may not occur in the neonate for some days after birth. Therefore, in addition to initial monitoring of respiratory depression, neonates should undergo prolonged monitoring for signs and symptoms of withdrawal.

Infants born to mothers on methadone maintenance have been reported to have smaller birth weights when compared to infants of non-drug exposed mothers. The infants born to mothers on methadone maintenance were not small for gestational age, and by six months of age, these infants did not exhibit any general development sequelae.

Use in Lactation

Methadone is distributed into breast milk, with a mean ratio of milk to plasma concentration of 0.44. However, doses of methadone to the infant via breast milk are low, estimated at 3% of maternal doses, on average, and insufficient to prevent neonatal abstinence syndrome in infants born to mothers on methadone maintenance.

Breast feeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation.

Interactions with Other Medicines

Methadone is metabolised by various cytochrome P450 (CYP450) enzymes. Therefore, co-administration of drugs known to interfere with CYP450 enzymes may affect its clinical activity. (see **PHARMACOLOGY**)

Some compounds may increase the metabolism of methadone, e.g. **rifampicin, phenytoin, carbamazepine, St John's Wort**, and antiretroviral agents used in the treatment of HIV infection (particularly **nevirapine, efavirenz and some protease inhibitors**). This has the potential to result in withdrawal symptoms.

Patients on methadone maintenance who are also taking enzyme inducers such as **carbamazepine**, may require higher than typical doses of methadone.

Some compounds may decrease the metabolism of methadone e.g. **fluconazole** and some selective serotonin re-uptake inhibitors (SSRIs), particularly **fluvoxamine**. This may increase the likelihood of methadone toxicity.

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 **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 **mineralocorticoid hormones**.

Methadone can also affect the metabolism of other drugs. Plasma concentrations of some drugs may be increased, e.g. **nelfinavir, zidovudine, fluconazole** and **desipramine**, whereas concentrations of others may be decreased, e.g. **abacavir** and **amprenavir**.

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

Central nervous system depressants: The general depressant effects of methadone may be enhanced by other centrally-acting agents such as alcohol, barbiturates, neuromuscular blocking agents, phenothiazines and tranquilisers. 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.

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 patient with renal dysfunction. The dosage interval should be increased to a minimum of 8-hourly when the glomerular filtration rate (GFR) is 10 to 50 mL/minute and to a minimum of 12-hourly when the GFR is below 10 mL/minute.

Cardiac Repolarisation Disorders

Methadone should be administered with particular caution to patients at risk for development of prolonged QT interval (see **PRECAUTIONS** and **CONTRAINDICATIONS**).

ADVERSE EFFECTS

Respiratory

The major side effect of methadone is respiratory depression.

Gastrointestinal

Reported events include nausea*, vomiting*, dry mouth*, and constipation. Methadone, in common with other opioids may cause spasm of the biliary tract (see **CONTRAINDICATIONS**).

Neurological

Reported events include dizziness*, drowsiness*, light-headedness*, sweating* and confusion*. Euphoria has been reported at higher doses in tolerant patients.

Cardiovascular

Hypotension, collapse, and generalised oedema have occasionally been reported. ECG changes including QT prolongation and Torsade de Pointes have occurred very rarely, usually in patients with risk factors or receiving high doses of methadone (see **PRECAUTIONS**).

Renal

Methadone, in common with other opioids may cause spasm of the renal tract (see **CONTRAINDICATIONS**). It also possesses antidiuretic properties, and urinary retention or hesitancy has been reported.

Endocrine

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

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.

In known drug addicts, methadone has produced withdrawal symptoms but these are mild. Tolerance and dependence of the morphine type may occur.

* These adverse reactions appear to be more common in ambulatory patients and in those receiving oral therapy.

DOSAGE AND ADMINISTRATION

Methadone Syrup must not be used parenterally.

Dose initiation, titration and duration should be individualised, taking into account the pharmacodynamic and pharmacokinetic properties of methadone and the need for close observation of the patient for cumulative toxicity. This should be based on a careful evaluation of subjective and objective patient data, bearing in mind clinical status, including hepatic or renal function of the patient.

Care needs to be taken with methadone to avoid toxicity because the time to reach steady-state concentrations following a change in dosage may be up to 12 days. Dose conversion ratios from other opioids are not static, but are a function of previous opioid exposure. Incomplete cross-tolerance between μ -opioid agonists makes determination of dosing during opioid conversion complex.

It is recommended that use of this drug should only be undertaken by prescribers familiar with its use.

Treatment of dependence on opioid drugs:

A dose of 10 to 20 mg by mouth may be given initially and increased as necessary by 5 to 10 mg daily. The dose must not be increased by more than 5 to 10 mg daily, and by no more than 30 mg in any seven day period. After stabilisation, which can often be achieved with a daily dose of 30 to 50 mg daily (up to a maximum of 80 mg 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.

Treatment of severe pain:

Adults: Usual single dose 5-10 mg by mouth.

Owing to its long plasma half-life, caution with repeated dosage should be observed in all patients, particularly in the very ill or elderly. The usual initial dose should be 5-10 mg 6-8 hourly, later adjusted to the degree of pain relief obtained. Doses administered more frequently than 6- to 8-hourly are liable to cause accumulation with increasing sedation and respiratory depression. In chronic use, methadone should not be administered more than twice daily.

Methadone may be used in combination with non-narcotic analgesics to provide additive analgesia.

Where the drug is given orally for longer duration, it is wise to restrict the dose to the smallest amount which controls the symptoms.

Children and adolescents aged less than 18 years

Methadone is not recommended for use in this age group, 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 depressant effects of methadone.

Elderly

Methadone has a long plasma half life which may lead to accumulation, particularly if renal function is impaired (see **PRECAUTIONS** and **PHARMACOLOGY**).

In common with other opioids, methadone may cause confusion in this age group therefore, careful monitoring is advised.

Renal impairment

Methadone should be used with caution in patients with renal dysfunction; the dosage interval should be increased to a minimum of eight hourly when the glomerular filtration rate (GFR) is 10 to 50 ml/minute and to a minimum of 12-hourly when the GFR is below 10 ml/minute.

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**).

Cardiac repolarisation disorders

Methadone should be administered with particular caution to patients at risk of development of prolonged QT interval (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

OVERDOSAGE

Symptoms and Signs

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

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

Treatment

General supportive measures, including ECG monitoring, should be employed as required. Lavage, dialysis and CNS stimulation are contraindicated. The specific opioid antagonist naloxone can be used for the reversal of coma and the restoration of spontaneous respiration. Intravenous infusion is the preferred route of administration in the management of methadone overdose because of the short half-life of naloxone relative to the long half-life of methadone, continuous infusion reduces the possibility of prolonged respiratory depression and the risk of relapse, which can occur suddenly. It should be noted that QT prolongation will not be reversed by naloxone.

In opioid dependent patients the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of an opioid antagonist in such a person should be avoided if possible. If it must be used to treat serious respiratory depression in the physically dependent person the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

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 or haemodialysis.

Contact the Poisons Information Centre (telephone 131126) for advice on overdose management.

PRESENTATION & STORAGE CONDITIONS

Oral liquid containing methadone hydrochloride 5 mg/mL.

Pack sizes: 200 mL, 1 litre

Store below 25°C. Protect from light.

POISON SCHEDULE OF THE MEDICINE: S8- Controlled Drug

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

Date of Approval TGA: 7 August 2006.
Safety Related Notification: 22 February 2007

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