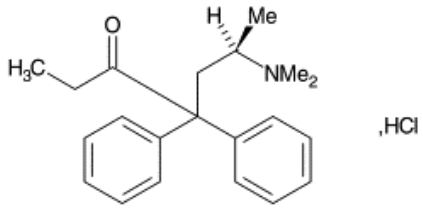
PRODUCT INFORMATION

PHYSEPTONE®

NAME OF THE MEDICINE: Methadone hydrochloride

The chemical name for methadone hydrochloride is 6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride, and the chemical structure is:



and enantiomer

Molecular formula: $C_{21}H_{27}NO,HCl$ Relative molecular mass: 345.9

CAS Number: 61849-14-7

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. Methadone 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.

Each Physeptone tablet also contains the inactive ingredients gelatin, glycerol, lactose, maize starch and magnesium stearate

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.

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.

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 to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methylpyrrolidine, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine together with unchanged methadone. Other metabolites, including methadol and normethadol (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 nonspecifically by the liver and released again mainly unchanged.

Methadone has a half-life of about 15 hours after a single dose in nontolerant subjects. After chronic administration the half-life is about 22 hours. However, 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.

INDICATIONS:

Physeptone is a suitable analgesic in conditions where morphine would make a reasonable alternative, particularly for the relief of pain of visceral origin. It is not recommended for use in ambulant patients.

CONTRAINDICATIONS:

Physeptone, like other opioids, is contraindicated in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions, and obstructive airways disease.

Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of discontinuation of treatment with them.

Obstetric use is not recommended.

Physeptone is contraindicated in individuals who are hypersensitive to methadone.

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

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

Physeptone, as with other opioids, is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilatation or spasm of the colon.

As with all narcotic analgesics, Physeptone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy.

At the recommended dosages, Physeptone 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 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).

Children are very sensitive to the depressant effects of methadone.

In common with all opioids, Physeptone has the potential to produce dependence. 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 opioid analgesics should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see **ADVERSE EFFECTS**).

Physeptone should be used with caution in the presence of the following:

hypothyroidism;
adrenocortical insufficiency;
hypopituitarism;
prostatic hypertrophy;
shock;
diabetes mellitus.

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

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.

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

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**).

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 and lactation: (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 these products should 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 treatment 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 treatment have been reported to have smaller birth weights when compared to infants of non-drug exposed mothers. The infants born to mothers on methadone treatment 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.

From theoretical considerations methadone is likely to be excreted in breast milk. Breast feeding is permissible in mothers receiving methadone 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 μg/mL.

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.

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 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.

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.

ADVERSE EFFECTS :

*****Adverse reactions denoted with an asterisk appear to be more common in ambulatory patients and in those receiving oral therapy.

Respiratory
The major side effect of methadone is respiratory depression.

Gastrointestinal
Reported events include nausea*****, vomiting*****, dry mouth***** and constipation. Nausea and vomiting appear to be more frequent after oral administration than after injection. 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. Methadone is reported to produce less euphoria than morphine.

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**). In rare cases a hypersensitive subject may react with a sudden transient fall in blood pressure; this is short-lived and self-terminating.

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, Physeptone has produced withdrawal symptoms but these are mild. Tolerance and dependence of the morphine type may occur.

Side effects are more common and more severe in ambulant patients.

Subcutaneous administration may cause local irritation.

DOSAGE AND ADMINISTRATION:

Adults: Usual single dose 5-10 mg by mouth, subcutaneous or intramuscular injection.

Owing to its long plasma half-life, caution with repeated dosage should be observed 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 Physeptone 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 the control of pain associated with a chronic condition, it is wise to restrict the dose to the smallest amount which adequately controls the symptoms.

Physeptone has less hypnotic effect than morphine. If it is necessary to give a patient a potent analgesic for a prolonged period, some increase in dose may be necessary.
Children: Not suitable.

OVERDOSAGE:

Symptoms: Toxic doses of methadone cause unconsciousness, pin-point pupils, slow shallow respiration, cyanosis and weak pulse, profound respiratory depression, 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. Often there is a 2-3 hour delay between ingestion and the appearance of symptoms. These symptoms and signs of overdosage parallel those for other opioids.

Treatment: General supportive measures, including ECG monitoring, should be employed as required. Lavage, dialysis and CNS stimulation are contraindicated. The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and the restoration of spontaneous respiration. Intravenous naloxone should be given and repeated at 5-10 minute intervals to attain full benefit. 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.

Acidification of the urine will increase the rate of elimination of the drug via the kidney.

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.

Methadone is not dialysable by either peritoneal or haemodialysis.

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

STORAGE:

Store below 30°C. Keep dry. Protect from light.

PRESENTATION:

Tablets: 10mg Biconvex, white, round tablets branded "WELLCOME U4B" and scored on the upper face, containing methadone hydrochloride 10 mg, in blister packs of 20 tablets.

Injection: 10mg/mL Injection ampoule containing methadone hydrochloride 10 mg/1 mL (preservative free) in packs of 5 ampoules.

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 TGA Approval: 23.04.01
Date of most recent amendment: 18 January 2005
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