Summary of Product Characteristics (SmPC)

Name of the medicinal product
Methadone Hydrochloride Oral Concentrate BP 5 mg/ml

Qualitative and Quantitative Composition
Each ml contains:
Methadone Hydrochloride BP ..... 5 mg
Flavored Base ..... q.s.
For the full list of excipients, see section 6.1

Pharmaceutical form
Oral Concentrate
A Clear, Orange colored liquid.

Clinical particulars

Therapeutic indications

For use in the treatment of opioid drug addiction (as a narcotic abstinence syndrome suppressant).

Posology and method of administration

As per directed by physician.
Methadone is to be taken only by mouth. To prevent upset stomach, it should be taken with food or milk.
It usually is taken every 3-4 hours as necessary for severe pain or every 6-8 hours for chronic pain. If it is to be taken as part of a treatment program, the doctor will prescribe the required dosing schedule.
Dosage to be taken as prescribed. The dosage should not be increased, taken more frequently or for a longer period of time without doctor's approval.
Also, if used for a long period of time at high doses, Methadone should not be stopped suddenly without first consulting the doctor. When used for extended periods, METHADONE HCL may not work as well and may require different dosing.

Contraindications

Hypersensitivity to methadone.
Patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

Special warnings and precautions for use

Use During 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 foetus.
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.

Renal Impairment

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

Interaction with other medicinal products and other forms of interaction

Interaction with Pentazocine

Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.

Interaction with Rifampin

The concurrent administration of rifampin may possibly reduce the blood concentration of methadone. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Interaction with Monoamine Oxidase (MAO) Inhibitors

Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small

incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Interaction with Other Central-Nervous-System Depressants

Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Pregnancy and Breast feeding

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Effects on ability to drive and use machines

Effect on ability to drive automobiles and controlled mechanical equipment.

Undesirable effects

Nervous system

Central nervous system effects are common, and include sleepiness or insomnia, respiratory depression, dizziness, and visual disturbances. Other neurologic side effects are rare, but include tardive dyskinesia and choreic movements.

Cardiovascular

Cardiovascular effects include hypotension, bradycardia, and edema. Rare cases of cardiac arrest have been reported.

Gastrointestinal

Gastrointestinal effects common to long-term methadone use are constipation and appetite abnormalities.

Methadone may cause contraction of the sphincter of Oddi, which may increase intrabiliary pressure and worsen, rather than relieve, biliary colic.

Other

Increased sweating is common after chronic methadone use.

Laboratory changes associated with methadone include mild lymphocytosis and increased serum protein, albumin, and globulin.

Hypersensitivity

Hypersensitivity to methadone is rare, but may include rash, pruritus, and edema.

Psychiatric

Psychological dependence may develop. One study has suggested that detoxification from methadone maintenance therapy may result in the development of an organic mood syndrome in many patients.

Endocrine

Methadone may stimulate thyroxine binding globulin (TBG), resulting in increased TBG, total T3 and T4, but unaltered free T3 and T4. Hyperprolactinemia has been associated with methadone therapy.

Genitourinary

Urinary retention and decreased libido have been reported.

Respiratory

Patients on methadone may have a blunted response to hypercarbia.

Renal

A case of rhabdomyolysis and subsequent acute renal failure following ingestion of large doses of methadone has been reported.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Overdose

Symptoms

Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), 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

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a nontolerant person, especially a child, takes a large dose of methadone, effective narcotic antagonists are available to counteract the potentially lethal respiratory depression. The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas the antagonists act for much shorter periods (one to three hours). The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to over dosage of methadone, the use of other respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered naloxone is the drug of choice to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.
Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in opioid dependence ATC code: N07BC02 Methadone is an opioid analgesic in the same manner of morphine and like morphine is 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 the response of structurally and sterically specific opiate receptor sites in the brain, spinal cord and nervous system. Methadone is an opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the κ and σ opiate receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the automotor nerve and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a pA2 value similar to its antagonism of Morphine. Like many basic drugs, Methadone enters mast cells and releases histamine by a non-immunological mechanism. It causes a dependence syndrome of the Morphine type.

Pharmacokinetic properties

Absorption: methadone is rapidly absorbed following oral administration, but undergoes considerable first-pass metabolism. The bioavailability is above 80 %. Steady state concentrations are reached within 5-7 days. Distribution: distribution volume: 5 L/kg. Protein binding: up to 90 %, but with great individual differences. Methadone binds mainly to alpha1-glycoprotein acid, but also to albumin and other plasma and tissue proteins. Plasma: the full blood ratio is around 1:3. It is distributed to tissue with higher concentrations in the liver, lungs and kidneys than in the blood. Metabolism: catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are also involved, but to a smaller extent. Metabolism is mainly Ndemethylisation, which produces the most important metabolites: 2- ethylidine, 1,5-dimethyl-3,3 - diphenylpyrrolidine (EDDP) and 2-ethyl5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), which are both inactive. Hydroxylation to methanol succeeded by Ndemethylisation to normethadol also occurs to some extent. Other metabolic

reactions also occur, and at least eight other metabolites are known. Elimination: elimination half-life: single dose: 10-25 hours. Repeated doses: 13-55hours. Plasma clearance is around 2 ml/min/kg. About 20-60 % of the dose is eliminated in urine over 96 hours (about 33 % in unmodified form, about 43 % as EDDP and about 5-10 % as EMDP). The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment compared to normal overdoses. Elimination of unmodified methadone in urine is pHdependent and increases with increasing acidity of the urine. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses. About 75 % of overall elimination is unconjugated. Special populations There are no significant differences in the pharmacokinetics between men and women. The clearance of methadone is decreased only to some extent in elderly (>65 years). Because of increased exposure, caution is advised in the treatment of patients with renal and hepatic impairment

Preclinical safety data

Methadone at high doses caused birth abnormalities in marmots, hamsters and mice, in which most reports were of exencephaly and defects in the central nervous system. Rachischisis in the cervical region was found occasionally in mice. Nonclosure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. A reduced number of young was found in rats and increased mortality, growth retardation, neurological behavioural effects and reduced brain weight were found in the pups. Reduced ossification of the digits, sternum and skull was found in mice and a smaller number of fetuses per litter. No carcinogenicity studies have been carried out.

Pharmaceuticals particulars

List of excipients

Propylene glycol, Sucrose, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate , Poloxamer 407, Citric Acid Anhydrous , Lemon Flavor , Sunset yellow FCF, Sodium hydroxide & Purified water.

Incompatibilities

None known

Shelf life

36 months

Special precautions for storage

Store in a dry place at a temperature not exceeding 30°C.

Nature and contents of container

1 litre HDPE Jar

Special precautions for disposal and other handling

Not applicable

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Date of revision of text
Not applicable

Dosimetry

Not applicable

Instructions for preparation of Radiopharmaceuticals

Not Applicable