PRODUCT MONOGRAPH

^{N} METADOL-D ®

Methadone Hydrochloride Tablets USP
1 mg, 5 mg, 10 mg and 25 mg

Methadone Hydrochloride Oral Solution USP
1 mg/mL

Methadone Hydrochloride Oral Concentrate USP
10 mg/mL

Treatment of Opioid Dependence

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THERAPEUTIC CLASSIFICATION

Treatment of Opioid Dependence

CONDITIONS FOR DISTRIBUTION and USE OF METHADONE

Pursuant to subsection 53(3) of the *Narcotic Control Regulations*, practitioners seeking to use methadone for the treatment of patients, must first obtain a Federal Ministerial exemption pursuant to section 56 of the *Controlled Drugs and Substances Act* (CDSA). Such an exemption will effectively allow the named practitioner to administer, prescribe, provide or sell methadone to patients under their professional care for the treatment of narcotic dependence, subject to certain specified terms and conditions. Exemptions are issued by the Office of Controlled Substances, Healthy Environments and Consumer Safety Branch, Health Canada, directly (see AVAILABILITY OF DOSAGE FORMS), or in some provinces, through the College of Physicians and Surgeons.

Pharmacists may supply methadone to a practitioner holding such an exemption. According to Federal guidelines, pharmacists are to distribute and dispense methadone for oral administration only (tablets, oral concentrate, or oral solution) when used for the treatment of narcotic dependence in detoxification or maintenance programs.

Warning: MAY BE HABIT FORMING

ACTION AND CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in opiate addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the

course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect. The steady-state elimination half-life of methadone is approximately 25 hours. Large inter-individual variability in elimination half-life may necessitate 2 to 9 days for steady-state serum levels.

Acutely, methadone has similar effects to other opioids; however, its pharmacological properties are significantly different from other opioid agonists in that it is extremely long-acting (36 to 48 hours) in humans.

After interruption of chronic dosing, if methadone treatment is to be continued, starting doses should be low and patients should be titrated slowly to effect in order to avoid severe toxicity and respiratory depression.

INDICATIONS AND CLINICAL USE

METADOL-D (Methadone Hydrochloride Tablets, Oral Solution and Concentrate) is indicated for the detoxification treatment of opioid addiction (heroin or other morphine-like drugs) as well as the maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE: If methadone is administered for treatment of heroin dependence for more than 180 days, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy.

CONTRAINDICATIONS

METADOL-D (Methadone Hydrochloride Tablets, Oral Solution and Concentrate) is contraindicated in individuals with known hypersensitivity to the drug. It is also contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

METADOL-D should not be given to patients with diarrhea which is associated with

pseudomembranous colitis caused by cephalosporins, lincomycins (possibly including topical clindamycin), or penicillins, or to patients having diarrhea caused by poisoning, until toxic material has been eliminated from the gastrointestinal tract.

WARNINGS

METADOL-D (Methadone Hydrochloride Tablets, Oral Solution and Concentrate) is for oral administration only. This preparation must not be injected. It is recommended that METADOL-D tablets, oral solution and concentrate, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone Hydrochloride, a synthetic opioid, is a controlled substance (Classification N) under the *Controlled Drugs and Substances Act* (CDSA). It is available only through physicians who have received an exemption from the Minister of Health Canada to prescribe methadone pursuant to section 56 of the CDSA. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE - METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHOLOGICAL DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP UPON REPEATED ADMINISTRATION OF METHADONE AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

Incomplete Cross-Tolerance between Methadone and Other Opioids:
Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is a particular concern for patients tolerant to other μ-opioid agonists when converting to methadone, making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high dose treatment with other opioid agonists. Therefore, it is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (**see DOSAGE AND ADMINISTRATION**, Tables 1 and 2, for appropriate conversion schedules). A high degree of "opioid tolerance" does not eliminate the possibility of methadone toxicity.

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 anaesthetics, phenothiazines, other tranquillizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression,

hypotension, and profound sedation or coma may result. (**see PRECAUTIONS**)

Interactions with Alcohol and Drugs of Abuse
Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone have frequently involved concomitant benzodiazepine abuse.

Anxiety: Since methadone, as used by tolerant subjects as a constant maintenance dosage, is not a tranquillizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of opioid abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of opioid symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increased intracranial pressure. Furthermore, opioids produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions:
Respiratory depression is the chief hazard from methadone hydrochloride. Respiratory depression is a particular potential problem in elderly or debilitated patients as well as those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Methadone hydrochloride should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as; asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative non-opioid analgesics should be considered, and methadone should be employed only under careful medical supervision at the lowest effective dose.

Hypotensive Effect: The administration of methadone may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a

depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anaesthetics.

Use in Ambulatory Patients: Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly. Methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy / Breastfeeding:
Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma. The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (**see DOSAGE AND ADMINISTRATION**).

For opioid-dependent pregnant women, methadone maintenance should be provided at the lowest accepted dose which prevents withdrawal symptoms (usually less than 80 mg/day). In later pregnancy, an increase by 10 - 20 mg and/or divided dose may be required.

Treatment should be provided throughout pregnancy to protect the fetus and for a minimum of six months post-partum.

It is the physician's responsibility to ensure that female patients are fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone. Care of such patients should be under the supervision of a physician experienced in the management of such patients.

Special care is required for the infant born to a mother who has been dependent on methadone and/or other opioids. Newborn infants who have been exposed to opioids in uteri within four weeks of delivery are potentially dependent and must be closely observed for withdrawal symptoms for at least two weeks (irritability, seizures, poor feeding, diarrhea and/or a high-pitched cry).

Breast-feeding may result in the passage of opioids or other substances into the breast milk. Use of

methadone in nursing mothers is not recommended, unless in the opinion of the treating physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS

There is significant risk of respiratory depression if the patient is switched abruptly from other opioids to methadone. Conversion to methadone should be undertaken with caution.

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 (>200 mg/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 treatment of opioid addiction.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). 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 increased risk of 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 weighed against the benefit of adequate pain management and the availability of alternative therapies.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone has been considered to outweigh the risk of QT prolongation that has been reported with high doses of methadone.

The use of methadone in patients already known to have prolonged QT interval has not been systemically studied.

In using methadone an individualized benefit to risk assessment should be carried out and should include evaluation of patient presentation and complete medical history. For patients judged to be at risk, careful monitoring of cardiovascular status, including QT prolongation and dysrhythmias and those described previously should be performed.

Special-Risk Patients: Methadone given on a fixed-dose schedule may have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of cardiac conduction abnormalities, respiratory depression, altered mental states and postural hypotension. METADOL-D (Methadone Hydrochloride Tablets, Oral Solution and Concentrate) should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated; those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia.

Acute Abdominal Conditions: The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

DRUG INTERACTIONS:

Opioid antagonist, mixed agonist/antagonist, and partial agonist drugs: Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given opioid antagonists or mixed agonist/antagonist drugs.

Anti-retroviral agents:

Nevirapine: Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Opioid withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Efavirenz: Coadministration of efavirenz in HIV-infected methadone-maintenance patients has resulted in decreased methadone plasma concentrations associated with signs of opioid withdrawal, and necessitating increases in methadone dose.

Ritonavir and Ritonavir/lopinavir: Reduced plasma methadone levels have been observed after administration of ritanovir alone or ritanovir/lopinavir combination. Withdrawal symptoms were however, inconsistently observed. Caution is warranted when administering methadone to patients receiving ritonavir-containing regimens in addition to other drugs known to decrease methadone plasma levels.

Zidovudine: Experimental evidence suggests that methadone increases the area under the concentration-time curve (AUC) of zidovudine with possible toxic effects.

Didanosine and Stavudine: Experimental evidence suggests that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Cytochrome P450 inducers:

The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes.

Rifampin: In patients well-stabilized on methadone, concomitant administration of rifampin resulted in marked reduction in serum methadone levels and concurrent appearance of withdrawal symptoms.

Phenytoin: In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3-4 days) resulted in ~50% reduction in methadone exposure and concurrently withdrawal symptoms occurred. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and the methadone exposure increased and was comparable to pre-phenytoin dose scenario.

St. John's Wort, phenobarbital, carbamazepine: Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 inhibitors: Since the metabolism of methadone is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus patients coadministered with inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), while receiving methadone should be carefully monitored and dosage adjustment made if warranted. Some selective serotonin reuptake inhibitors (SSRI's) (i.e. sertraline, fluvoxamine) upon coadministration may increase methadone plasma levels and result in increased opiate effects or toxicity.

Specifically, repeat dose administration of oral voriconazole (400mg Q12h for 1 day, then 200mg Q12h for 4 days) increased the C_{max} and AUC_ of pharmacologically active R-methadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30-100 mg QD). Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Others:

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.

Protease inhibitors:

Agenerase: Coadministration of methadone with Agenerase resulted in a decrease in the C_{max} and AUC of the active methadone enantiomer (R-enantiomer) of 25% and 13% respectively, while the C_{max}, AUC and C_{min} of the inactive methadone enantiomer (S-enantiomer) were decreased by 48%, 40% and 23% respective. When methadone is coadministered with Agenerase, patients should be monitored for methadone underdosing, in particular if low-dose ritonavir is also given. As compared to a non-matched historical control group, coadministration of methadone and Agenerase resulted in a 30%, 27% and 25% decrease in serum Agenerase AUC, C_{max} and C_{min} respectively. No recommendations can be made regarding adjustment of Agenerase dose when Agenerase is coadministered with methadone.

Viracept: When coadministered with Viracept, changes are reported for total plasma methadone; changes for the individual R-enantiomer and S-enantiomer were similar. Dosage of methadone may need to be increased.

Non nucleoside reverse transcriptase inhibitors:

Rescriptor: Dosage of methadone may need to be decreased when coadministered with Rescriptor.

Desipramine: Blood levels of desipramine have increased with concurrent methadone therapy.

Potentially Arrhythmogenic Agents: Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone.

Pharmacodynamic interactions may occur with concomitant use of 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 (hypomagnesemia, hypokalemia). These include diuretics, laxatives, and in rare cases mineralocorticoid hormones.

Interactions with other CNS Depressants: Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma.

Use with Mixed Agonist/Antagonist Opioid Analgesics: Agonist/ antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist, such as Methadone Hydrochloride Injection. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of Methadone Hydrochloride Injection and/or may precipitate withdrawal symptoms.

Anxiety

Methadone, used by tolerant patients at a constant maintenance dosage, is not a tranquilizer. Patients who are maintained on this drug will react to life problems and stresses as do other individuals. Anxiety in a patient on methadone should not be confused with narcotic abstinence and should not prompt treatment by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of symptoms of opioid dependence or pain. Methadone is ineffective for relief of general anxiety.

Acute Pain

Maintenance patients on a stable dose of methadone who experience physical trauma, postoperative pain or other causes of acute pain cannot be expected to derive analgesia from their stable dose of methadone regimens. Such patients should be given analgesics, including opioids, that would be indicated in other patients experiencing similar nociceptive stimulation. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for other, non-tolerant patients.

Risk of Relapse in Patients on Methadone Maintenance Treatment of Opioid Addiction

Abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms (**see**

PRECAUTIONS). Presentation of these symptoms has been associated with an increased risk of susceptible patients to relapse to illicit drug use and should be considered when assessing the risks and benefit of methadone use.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and/or tolerance are not unusual during chronic opioid therapy.

If methadone is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, chronically administered methadone should not be abruptly discontinued.

Special-Risk Patients

Methadone should be given with caution and the initial dose reduced in certain patients, such as the elderly and debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison'=s disease, prostatic hypertrophy, or urethral stricture. The usual precautions appropriate to the use of parenteral opioids should be observed and the possibility of respiratory depression should always be kept in mind.

Information for Patients

Methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery. The patient should be cautioned accordingly.

Methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with methadone, and should be avoided.

If a patient taking methadone experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope), that patient should seek immediate medical

attention.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Data from published reports of carcinogenicity studies indicate that there was a significant increase in pituitary adenomas in female B6C2F1 mice consuming 15 mg/kg/day methadone for two years. This dose was approximately 0.6 times a human daily oral dose of 120 mg/day, on a body surface area basis. However, this finding was not seen in mice consuming 60 mg/kg/day (approximately 2.5 times a human daily oral dose of 120 mg/day). Furthermore, in a two-year study of dietary administration of methadone to Fischer 344 rats, there was no clear evidence for treatment related increase in the incidence of neoplasms, at doses as high as 28 mg/kg/day in males and 88 mg/kg/day in females (approximately 2.3 times and 7.1 times, respectively, a human daily oral dose of 120 mg/day) based on body surface area comparison.

In published reports, methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of Drosophila using feeding and injection procedures. Methadone treatment of male mice increased sex chromosome and autosome univalent chromosomes and translocations in multivalent chromosomes. Methadone tested positive in the *E.coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Pregnancy

Teratogenic effects: Pregnancy Category C. There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by TERIS - the Teratogen Information System - concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as Alimited to fair@), however, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care, improved fetal outcomes, and reduced mortality when compared to pregnant women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who took methadone during pregnancy. These include: the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy. In addition, reported studies generally compare the benefit of methadone to the risk of untreated addiction to illicit drugs; the relevance of these findings to pain patients prescribed methadone during pregnancy is unclear.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to

maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in 3rd trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. The growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioural tests.

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study found that in hamster fetuses, subcutaneous methadone doses of 31 mg/kg or greater (estimated exposure was approximately 2 times a human daily oral dose of 120 mg/day on a mg/m^2 basis, or equivalent to a human daily intravenous dose of 120 mg/day) on day 8 of gestation produced exencephaly and neurological effects. Some of the reported effects were observed at doses that were maternally toxic. In another study, a single subcutaneous dose of 22-24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m^2 basis; or half a human daily intravenous dose of 120 mg/day) on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m^2 basis; or 1.5 and 3 times a human daily intravenous dose of 120 mg/day) during days 6-15 and 6-18, respectively.

Nonteratogenetic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth but may be delayed for two to four weeks. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid dose or maternal dose. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether the risk of sudden infant death syndrome (SIDS) is increased in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1-2 hours after a maintenance dose of methadone in late pregnancy compared to controls. Published animal studies suggest that perinatal exposure to opioids including methadone may alter neuronal development and behaviour in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociception responses and sensitivity to other drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including the cholinergic, dopaminergic noradrenergic and serotonergic systems.

Clinical Pharmacology for Pregnancy: Pregnant women have significantly lower trough plasma concentrations, increased plasma methadone clearance and shorter half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with methadone. [**See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION**].

Labor and Delivery: As with all opioids, administration of methadone to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone because they may precipitate acute withdrawal.

Nursing mothers: Methadone is secreted into human milk. There is no information on use of parenteral methadone in breast feeding, or on the safety of the high doses of methadone typically used in chronic pain treatment. The safety of breastfeeding while taking oral methadone is also controversial. At maternal oral doses of 10-80 mg/day, methadone concentrations from 50 to 570μg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentration at steady state. Peak methadone levels in milk occur approximately 4-5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4μg/kg/day, which is approximately 2/3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Women on high dose methadone maintenance, who are already *breast feeding, should be counselled to wean breast-feeding gradually in order to prevent neonatal abstinence syndrome*. Methadone-treated mothers considering nursing an opioid-naïve infant

should be counselled of the presence of methadone in breast milk.

Because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use
Clinical studies of Methadone Hydrochloride Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment
The use of methadone has not been extensively evaluated in patients with renal insufficiency.

Hepatic Impairment
The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender
The use of methadone has not been evaluated for gender specificity.

ADVERSE REACTIONS

Heroin Withdrawal: During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea , sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, "sleepy yen", weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking

movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration: The initial methadone dose should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce adverse effects.

THE MAJOR HAZARDS OF METHADONE ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, SYSTEMIC HYPOTENSION. RESPIRATORY ARREST, SHOCK, CARDIAC ARREST AND DEATH HAVE OCCURRED.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses of methadone are advisable.

Other adverse reactions that have been reported in patients (including opioid addicts taking methadone for detoxification or maintenance) receiving methadone include the following:

Body as a Whole: asthenia (weakness), edema, headache
Cardiovascular: Arrhythmias, bigeminal rhythms, bradycardia, extrasystoles, tachycardia, Torsade de Pointes, ventricular fibrillation, ventricular tachycardia. ECG abnormalities, prolonged QT interval, T-wave inversion, cardiomyopathy, flushing, heart failure, hypotension, palpitations, phlebitis, syncope.
Digestive: Abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis
Haematologic and Lymphatic: Reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis.
Metabolic and Nutritional: Hypokalemia, hypomagnesemia, weight gain
Nervous: Agitation, confusion, seizures, disorientation, dysphoria, euphoria, insomnia
Respiratory: Pulmonary edema
Skin and appendages:
Intramuscular and Subcutaneous: Local tissues reactions (pain, erythema, swelling), particularly with continuous subcutaneous infusion
Intravenous: Pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria
Special senses: Visual disturbances
Urogenital: Antidiuretic effect, amenorrhea, urinary retention or hesitancy, reduced libido and/or potency

Maintenance on a Stabilized Dose: During prolonged administration of methadone, as in a methadone maintenance treatment program, there is a gradual, yet progressive disappearance of

side effects over a period of several weeks. However, constipation and sweating persist.

DRUG ABUSE AND DEPENDENCE

Methadone is a μ-agonist opioid with an abuse liability similar to that of morphine and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Abuse

Drug addiction is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug addiction is treatable, utilizing a multi-disciplinary approach, but relapse is common.

Drug seeking behaviour is very common to addicts and drug abusers. Drug seeking tactics include emergency calls or visits near the end of the office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). Doctor shopping (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addictions.

Physical Dependence and Tolerance

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposed, often in combination with other psychoactive substances. Methadone Hydrochloride Injection, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of Methadone Hydrochloride Injection poses a risk of overdose and death. This risk is increased with concurrent abuse of Methadone Hydrochloride Injection with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Infants born to mothers physically dependant on opioids may also be physically dependent and

may exhibit respiratory difficulties and withdrawal symptoms (**See PRECAUTIONS; Pregnancy and Labor and Delivery**)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and 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 non-tolerant person, especially a child, takes a large dose of methadone, effective narcotic antagonists are available to counter-act the potentially lethal respiratory depression. THE PHYSICIAN MUST REMEMBER, HOWEVER, THAT METHADONE IS A LONG-ACTING DEPRESSANT (THIRTY-SIX TO FORTY-EIGHT 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 may need to be treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependant on opioids, the administration of the usual dose of an opioid antagonist may 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. If antagonists must be used to treat serious respiratory depression in the physically dependant patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used 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.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON OPIOIDS, THE ADMINISTRATION OF THE USUAL DOSE OF 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 PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST (10 - 20% OF THE USUAL RECOMMENDED INITIAL DOSE OF THE ANTAGONIST).

DOSAGE AND ADMINISTRATION

METADOL-D (Methadone Hydrochloride Tablets, Oral Solution and Concentrate) can only be prescribed by physicians who have received an exemption pursuant to section 56 of the CDSA from the Minister of Health Canada to prescribe methadone (**see AVAILABILITY OF DOSAGE FORMS**). Patients prescribed methadone should be carefully monitored and provided appropriate supportive psychological and social services.

After interruption of chronic dosing, if methadone treatment is to be continued, starting doses should be low and patients should be titrated slowly to effect in order to avoid severe toxicity and respiratory depression.

Detoxification: Detoxification using methadone is the administration of gradually decreasing doses over a period not exceeding 180 days. Oral, 15 to 40 mg once a day or as needed to control observed withdrawal symptoms; dosage to be reduced at one- or two-day intervals according to patient response.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg per day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for two to three days, and then the amount of methadone normally will be gradually

decreased. The rate at which methadone is decreased will be determined separately with each patient. The dose of methadone can be decreased on a daily basis or at two-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20 percent of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 180 days, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment--In maintenance treat respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the opioid tolerance of the new patient. If such a patient has been a heavy user of heroin up to the day of admission, he/she may be given 20 mg 4 to 8 hours later or 40 mg in a single oral dose. If the patient enters treatment with little or no opioid tolerance (e.g., if he/she has recently been released from jail or other confinement), the initial dosage may be one-half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional 10 mg doses may be administered as needed. Subsequently, the dosage should be adjusted individually, as tolerated and required, up to a level of 80 mg daily. The majority of patients can be treated at a dose lower than 80 mg/day.

Maximum Daily Dose: Up to 120 mg per day.

***Special Considerations for a Pregnant Patient*:** Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels should be kept as low as possible if continued methadone treatment is deemed necessary. It is the physician's responsibility to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone. (see the **WARNINGS** section)

Special Limitations treatment of patients under age 18: The safety, effectiveness and dosage regimen of methadone for use in the treatment of adolescents have not been established.

Treatment of Opioid Dependence:

The Therapeutic Products Programme Guideline: Dispensing Methadone for the Treatment of Opioid Dependence (H42-2/62-1994) states:
"Methadone must be dispensed in 100 mL of a vehicle that does not easily lend itself to injection."

METADOL-D (Oral Solution and Concentrate) has been found compatible with 100 mL of the

following diluents prepared, where applicable, according to the manufacturer's instructions:

- Grape flavoured Kool-Aid®
- Orange flavoured Tang®
- Allen's® Apple Juice
- Crystal Light® Tangerine-Grapefruit flavoured
- Crystal Light® Lemonade flavoured

®Tang, Kool-Aid and Crystal Light are registered TMs of Kraft Foods, Inc., Northfield, Illinois.

®Allen's is a registered TM of Cadbury Beverages B.V., Amsterdam, Netherlands.

Diluted solutions should be refrigerated (2°C to 8°C) and stored for a period not exceeding 7 days in Allen's®Apple Juice, and 14 days in all other diluents mentioned above.

Note: For both METADOL-D Concentrate (10 mg/mL) and METADOL-D Solution (1 mg/mL) must be mixed with one of the above solutions (diluents) before dispensing (**see PHARMACEUTICAL INFORMATION**).

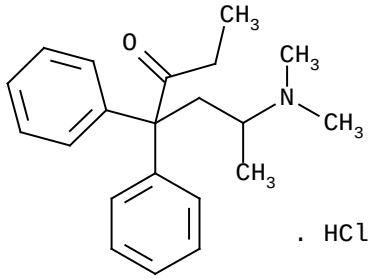
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Methadone Hydrochloride

Chemical Name: 6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride

Structural Formula:



Molecular Formula: $C_{21}H_{27}NO.HCl$

Molecular Weight: 345.91

Description: White odourless crystalline powder with a bitter taste.

Solubility: Soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerin.

pKa and pH: A 1% solution in water has a pH of 4.5 - 5.6; pKa (20°C) 8.23;
pH of the Oral Concentrate: 1.0 - 6.0,
pH of the dilute oral solution: 1.0 - 4.0.

Partition co-efficient: 2.1 [log P octanol/water @ pH 7.4]

Melting point: 233°C - 236°C

Composition:

Each **METADOL-D 1 mg tablet** contains 1 mg Methadone Hydrochloride USP.
The non-medicinal ingredients are (alphabetically): FD&C Blue No.1 Lake, Lactose, Magnesium Stearate and Microcrystalline Cellulose.

Each **METADOL-D 5 mg tablet** contains 5 mg Methadone Hydrochloride USP.
The non-medicinal ingredients are (alphabetically): FD&C Yellow No. 6 Lake, Lactose, Magnesium Stearate and Microcrystalline Cellulose.

Each **METADOL-D 10 mg tablet** contains 10 mg Methadone Hydrochloride USP.
The non-medicinal ingredients are (alphabetically): D&C Yellow No. 10 Aluminium Lake, FD&C Blue No.1 Lake, Lactose, Magnesium Stearate and Microcrystalline Cellulose.

Each **METADOL-D 25 mg tablet** contains 25 mg Methadone Hydrochloride USP.
The non-medicinal ingredients are (alphabetically): Lactose, Magnesium Stearate and Microcrystalline Cellulose.

METADOL-D Oral Solution 1 mg/mL contains: Methadone Hydrochloride USP (1 mg/mL).
The non-medicinal ingredients are (alphabetically): Citric Acid (added to adjust the pH), Dextrose, Glycerin, Methylparaben, Polyethylene Glycol, Sodium Benzoate, Sodium Cyclamate and Water.

METADOL-D Oral Concentrate 10 mg/mL contains: Methadone Hydrochloride USP (10 mg/mL). The non-medicinal ingredients are (alphabetically): Citric Acid (added to adjust the pH), Dextrose, Glycerin, Propylene Glycol, Sodium Benzoate, Sodium Cyclamate and Water.

Note: Methadone (Concentrate and Solution) must be dispensed in 100 mL of a vehicle that does not easily lend itself to injection (**see DOSAGE AND ADMINISTRATION**).

Stability and Storage Recommendations:
METADOL-D should be stored at 15° - 30°C. Keep tightly closed. Protect METADOL-D Tablets from light. Protect METADOL-D Oral Concentrate and Oral Solution from light and freezing.

AVAILABILITY OF DOSAGE FORMS

METADOL-D Tablets are available for oral use in potencies of 1, 5, 10 and 25 mg of Methadone Hydrochloride USP.

1 mg:	Blue, round, flat-faced bevelled edge tablets, scored and imprinted 1 on one side and "P" logo on the other side. Available in HDPE bottles of 100 and blister packs of 4 x 25.
5 mg:	Peach, round, flat face, bevelled edge tablets, scored and imprinted 5 on one side and "P" logo on the other side. Available in HDPE bottles of 100 and blister packs of 4 x 25.

10 mg: Pale green, round, flat face, bevelled edge tablets, scored and imprinted 10 on one side and "P" logo on the other side. Available in HDPE bottles of 100 and blister packs of 4 x 25.

25 mg: White to off-white, biconvex, caplet shaped tablets, scored and imprinted 25 on one side and "P" logo on the other side. Available in HDPE bottles of 100 and blister packs of 4 x 25.

METADOL-D 1 mg/mL Oral Solution:
Each 1 mL of clear unflavored and colorless liquid contains 1 mg of Methadone Hydrochloride USP. METADOL-D is available in 100 mL and 250 mL amber plastic bottles.

METADOL-D 10 mg/mL Oral Concentrate:
Each 1 mL of clear unflavored and colorless liquid contains 10 mg of Methadone Hydrochloride USP. METADOL-D is available in 100 mL and 250 mL amber glass bottles, as well as in 1 L amber plastic bottles.

Physicians who wish to receive an exemption pursuant to section 56 of the CDSA, from the Minister of Health Canada, must contact:

The Office of Controlled Substances
Healthy Environments and Consumer Safety Branch
A/L 3503B
Ottawa, Ontario
K1A 1B9

Pharmacist Compounding Information for Treatment of Opioid Dependence Preparation Using METADOL-D Oral Concentrate:

Dilution Chart to prepare 100 mL of Solution		
Daily Dose	METADOL-D (concentrate)	Diluent
20 mg	2 mL	qs at 100 mL
40 mg	4 mL	qs at 100 mL
60 mg	6 mL	qs at 100 mL
80 mg	8 mL	qs at 100 mL
100 mg	10 mL	qs at 100 mL

METADOL-D has been found compatible with 100 mL of the following diluents prepared, where applicable, according to the manufacturer's instructions:

- Grape flavoured Kool-Aid®
- Orange flavoured Tang®
- Allen's® Apple Juice
- Crystal Light® Tangerine-Grapefruit flavoured
- Crystal Light® Lemonade flavoured

®Tang, Kool-Aid and Crystal Light are registered TMs of Kraft Foods, Inc., Northfield, Illinois.

®Allen's is a registered TM of Cadbury Beverages B.V., Amsterdam, Netherlands.

Diluted solutions should be refrigerated (2°C to 8°C) and stored for a period not exceeding 7 days in Allen's®Apple Juice, and 14 days in all other diluents mentioned above.

INFORMATION FOR THE PATIENT

^{N}METADOL-D®

(Methadone Hydrochloride)

What is ^{N}METADOL-D?

METADOL-D is a tablet or solution of methadone to be taken orally.

What is ^{N}METADOL-D used for?

Methadone is also used to control withdrawal symptoms in patients being treated for narcotic drug dependence.

WHEN YOU SHOULD NOT TAKE THIS MEDICINE:

Do not take this medicine if you have ever had an allergic reaction to methadone or to other types of narcotic pain medicine such as codeine.

HOW TO TAKE AND STORE THIS MEDICINE:

- Your doctor will tell you how much to take and how often. It is very important to take this medicine as your doctor has prescribed. Follow the directions exactly as indicated on the label.
- The product can be taken as given to you by the pharmacist or as directed by the pharmacist.
- If taking the solution measure the dose carefully using a measuring spoon or medicine cup.
- Keep all medicine out of the reach of children.
- Store in a refrigerator. Do not freeze.

IF YOU MISS A DOSE:

- Take the missed dose as soon as possible.
- If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose.
- Do not take two doses at the same time.

IF YOU MISS MORE THAN ONE DOSE

Patients should contact their doctor immediately.

OTHER MEDICATIONS AND FOODS TO AVOID:

- Ask your doctor or pharmacist before taking any other medicine, including over-the-counter products as they may affect your response to methadone.
- Avoid drinking alcohol.
- Make sure your doctor knows if you are taking any other kind of medicine that could make you drowsy, such as sedatives, cold or allergy medicine, sleeping pills, muscle relaxants, or strong pain killers.

WARNING:

- Check with you doctor before taking methadone if you have asthma, seizures, low blood pressure, liver or kidney disease.
- If you are pregnant or breastfeeding, talk to your doctor before taking this medicine.
- This medicine can be habit-forming. Do not take more than what your doctor has prescribed.
- If you have taken this medicine for several weeks, ask your doctor before stopping, you may need to take smaller and smaller doses before stopping completely.
- This medicine may cause dizziness or confusion. Be careful if driving a car or using machinery.

SIDE EFFECTS:

Call your doctor right away if you have any of these side effects :

- Fast or slow heartbeat.
- Trouble breathing.
- Hives, skin rash, or itching.
- Severe confusion, hallucinations.

If you have these less serious side effects, tell your doctor.

- Drowsiness, dizziness, or weakness
- Headache
- Dry mouth, nausea or vomiting
- Constipation
- Excessive sweating, facial flushing (redness)

IF YOUR PAIN INCREASES OR IF YOU HAVE OTHER SIDE EFFECTS THAT YOU THINK ARE CAUSED BY THIS MEDICINE, CONSULT WITH YOUR DOCTOR.

PRESCRIPTION RUNNING OUT:

When you need more METADOL-D a new written prescription is required from your doctor. It is very important that you do not miss any doses of your medication, contact your doctor to ensure that there is enough time to renew your prescription.

PHARMACOLOGY

Many of the actions of methadone, in various animal species, are characteristic of those seen with other opioid agonists which exert their activity primarily at the mu receptor. The analgesic effect and other morphine-like properties of methadone are exhibited chiefly by the l-form.

The effect of methadone in common laboratory animal paradigms is qualitatively the same as that of morphine, e.g., the Straub reaction in mice, purposeless excitement in cats, and effects on behaviour and reflex activity in decorticate, decerebrate and spinal dogs and cats. Methadone has an effect similar to that of morphine on circulation and respiration and on smooth muscle. In rats or dogs chronically injected, tolerance to the analgesic effect of methadone develops at nearly the same rate as for morphine. However, dogs rendered only moderately tolerant to methadone are even more tolerant to other opioids than they are to methadone itself.

The heightened activity and increased lability found for methadone in the rat may be related to the persistence of pharmacologically active concentrations of the drug. Exposure to the prenatal period produces a significant delay in postnatal brain growth associated with a reduction in brain DNA content measured at 21 days of age. Studies of plasma drug concentrations indicate a plasma half-life in the rat of only a few hours, but studies using titrated methadone indicate that following prenatal administration, methadone accumulates and persists in neonatal brain and liver for long periods and may alter the maturation of the cholinergic-adrenergic or catecholamine systems.

Gravid rats administered a 5, 10, or 15 mg/kg regimen of methadone on the last two weeks of gestation showed blood levels of methadone which were dose-related, corresponding to the levels found in human subjects receiving daily maintenance doses of approximately 30, 60 and 100 mg, respectively.

Methadone, like morphine, blocks ovulation in the rat but only at doses approaching toxicity.

TOXICOLOGY

In animals methadone is three to ten times more toxic than morphine, according to the species, and two to three times more toxic than meperidine.

In comparative acute toxicity studies in rats, methadone on a weight-for weight basis is about 10 times more toxic than morphine orally, about 6 times more toxic subcutaneously, and about 25

times more toxic intravenously. The l-isomer of methadone, which accounts for nearly all the analgesic activity of the racemic mixture, is little if any more toxic than dl-methadone.

The following Table summarizes the acute toxicity data for dl-methadone obtained in rats and mice:

	LD_{50} values (mg/kg)	
Route	**Mouse**	**Rat**
s.c.	27	48
i.p.	31	33
i.v.	18	-

A single dog injected subcutaneously with 50 mg/kg of dl-methadone suffered violent convulsions, and died 4 hours after injection.

Rats administered a daily dose of 4 mg/kg methadone hydrochloride subcutaneously for ten weeks showed retarded growth. At autopsy, the only gross change noted was a slight increase in liver weight to body weight ratio. Considerable local subcutaneous irritation was observed at the injection sites.

Young adult mongrel female dogs (n=8) injected twice daily on weekdays, and once daily on weekends, with a dose of 2 mg/kg of methadone for up to 16 weeks, exhibited the following **e**xtreme side effects: general depression, narcosis, and sedation. Tolerance to these effects was shown to develop much more slowly with methadone than with morphine. Other long-term effects were bradycardia to which no tolerance developed, vomiting, and reduction in voltages of P and R waves on the electrocardiogram. Signs observed after withdrawal of methadone included increase in resting respiratory rate, tachycardia, loss of appetite, and pronounced muscular tremors, with twitching and rigidity.

Methadone has been found to be teratogenic in the hamster. However, reproduction studies in rats and rabbits revealed no evidence of teratogenicity or embryotoxicity.

Administration of a 5, 10, 15 or 20 mg/kg regimen of methadone to gravid rats on the last two weeks of gestation showed a dose-related increase in resorptions and stillbirths, but no teratogenicity. The two intermediate dose levels produced body weights that were reduced at birth but similar to controls by weaning.

Behavioral teratology studies have suggested that dose levels producing a relatively high maternal and offspring mortality may yield survivors that are more resistant to the toxic effects of the drug and thus not show effects seen among the lower dose-level groups.

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