PRODUCT MONOGRAPH

^{N} METADOL®

Methadone Hydrochloride Tablets
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

Opioid Analgesic

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THERAPEUTIC CLASSIFICATION

Opioid Analgesic

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 analgesia, subject to certain specified terms and conditions. Physicians seeking an exemption can apply for one directly from the Office of Controlled Substances, Healthy Environments and Consumer Safety Branch, Health Canada, or in some provinces through their College of Physicians and Surgeons. Specific colleges should be consulted for advice on the process to be followed in each province.

Pharmacists may supply methadone to a practitioner holding such an exemption.

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.

The pharmacokinetic parameters of methadone following the administration of a single METADOL 10 mg dose, under fasting conditions, to twenty-four (24) healthy male and female subjects are presented in the table below.

Mean (CV%) Methadone Pharmacokinetic Parameters after Administration of a Single 10 mg dose of Metadol to Healthy Subjects (n=24)

Parameter	Unit	METADOL dose
		1 x 10 mg tablet
C_{max}	(ng/mL)	38.12 (28.3)
T_{max} [a]	(h)	2.50 (1.67 – 5.07)
AUC_{0-72}	(ng.h/mL)	1042.77 (31.0)
AUC_{0-inf}	(ng.h/mL)	1429.78 (45.2)
$T_{1/2}$	(h)	36.71 (32.6)

[a] median (range)

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

Adults:
METADOL (methadone hydrochloride tablets, oral solution and concentrate) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and
- for which alternative options are inadequate.

METADOL is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age):
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, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age):
The safety and efficacy of METADOL has not been studied in the pediatric population. Therefore, the use of METADOL is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

METADOL (methadone hydrochloride) is contraindicated in:

- Patients who are hypersensitive to the active substance (methadone hydrochloride) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the "PHARMACEUTICAL INFORMATION, Composition" section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.

- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery.
- 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.
- Patients naive to opioids.

WARNINGS

SERIOUS WARNINGS AND PRECAUTIONS

METADOL (methadone hydrochloride tablets, oral solution and concentrate) is for oral administration only. This preparation must not be injected. It is recommended that METADOL tablets, oral solution and concentrate, if dispensed, be packaged in child resistant containers and kept out of the reach and sight of children and pets to prevent accidental ingestion.

Methadone hydrochloride, a synthetic opioid, is a controlled substance listed in Schedule I to the Controlled Drugs and Substances Act (CDSA). It is available only through physicians who have received an exemption authorizing them to prescribe methadone from Health Canada. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, METADOL should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

METADOL poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing METADOL, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS). METADOL should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of METADOL. Patients should be monitored for respiratory depression, especially during initiation of METADOL or following a dose increase. METADOL tablets should be swallowed whole; crushing, chewing, or dissolving METADOL tablets can cause rapid release and absorption of a potentially fatal dose of methadone hydrochloride (see WARNINGS).

Accidental Exposure

Accidental consumption of even one dose of METADOL, especially by children, can result in a fatal overdose of methadone hydrochloride (see DOSAGE AND ADMINISTRATION subsection Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of METADOL during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS).

Interaction with Alcohol

The co-ingestion of alcohol with METADOL may result in increased plasma levels and a potentially fatal overdose of methadone hydrochloride (see WARNINGS and DRUG INTERACTIONS).

General

Addiction, Abuse and Misuse:

METADOL is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, METADOL should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as METADOL, should be used with particular care in patients with a history of alcohol and illicit/ prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Cardiovascular

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.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of METADOL and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.

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**). A high degree of "opioid tolerance" does not eliminate the possibility of methadone toxicity.

Neurologic

Interactions with Central Nervous System Depressants (Including Alcohol):

METADOL should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines,

benzodiazepines, centrally-active anti-emetics and other CNS depressants including alcohol. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored (see **DRUG INTERACTIONS**).

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 increase in intracranial pressure. Furthermore, opioids produce side effects that may obscure the clinical course of patients with head injuries. In such patients, METADOL must be used with caution and only if it is deemed essential.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of METADOL for analgesia is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Psychiatric
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.

Respiratory

Respiratory Depression:

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

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.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of METADOL, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with METADOL and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of METADOL are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the METADOL dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Asthma and Other Respiratory Conditions:

METADOL 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 METADOL should be employed only under careful medical supervision at the lowest effective dose.

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.

Special Population: Use in Pregnancy / Breastfeeding:
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS – NEONATAL OPIOID WITHDRAWAL SYNDROME**).

Use of METADOL for analgesia is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.
Breast-feeding may result in the passage of opioids or other substances into the breast milk. Use of methadone in nursing mothers is contraindicated.

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 (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 agonists drugs:
Patients who are on prolonged methadone therapy may experience withdrawal symptoms when given opioid antagonists or mixed agonist/antagonist drugs. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

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. Since the safety of methadone in this regard has not been established, the use of methadone in patients who have received MAO inhibitors during the previous 14-day period is contraindicated. However, 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 nonmatched 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. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of methadone hydrochloride and/or may precipitate withdrawal symptoms.

Drug-Lifestyle Interaction:
The concomitant use of alcohol should be avoided (see **WARNINGS, Serious Warnings and Precautions Box**).

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.

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
METADOL, 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.

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

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

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

Pregnancy

Teratogenic effects: Pregnancy Category C. There are no controlled studies of methadone use in pregnant women that can be used to establish safety.

Methadone prescribed for analgesia is contraindicated in pregnant women.

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 (see **WARNINGS – Neonatal Opioid Withdrawal Syndrome**).

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.

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 contraindicated for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn.

Nursing mothers: Use of methadone for analgesia is contraindicated in nursing mothers. Methadone is secreted into human milk. 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.

Pediatric Use

The safety and efficacy of METADOL has not been studied in the pediatric population. Therefore, the use of METADOL is not recommended in patients under 18 years of age.

Geriatric Use
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

Initial Administration: The initial METADOL 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, 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 controlled substance listed in Schedule I to the Controlled Drugs and Substances Act (CDSA).** 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, 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 poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone hydrochloride 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 METADOL 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 should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

METADOL tablets should be swallowed whole; crushing, chewing, or dissolving METADOL tablets can cause rapid release and absorption of a potentially fatal dose of methadone hydrochloride (see WARNINGS).

Recommended Dose and Dosage Adjustment

METADOL (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.

For relief of Severe Pain - Dosage should be carefully titrated and adjusted according to the severity of the pain and response of the patient. METADOL should not be used in opioid naive patients. The usual adult oral dose is 2.5 to 10 mg every 4 hours during the first 3 to 5 days,

followed by a fixed dose every 8 to 12 hours depending on the patient's requirements. In geriatric patients the dosage schedule could be given on a once daily basis.

Special Limitations treatment of patients under age 18:
The safety and efficacy of METADOL has not been studied in the pediatric population. Therefore, the use of METADOL is not recommended in patients under 18 years of age.

Dispensing Guideline for Opioid Analgesic

Methadone (Oral Solution and Concentrate) must be dispensed in 100 mL of a vehicle that does not easily lend itself to injection.

METADOL (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 Concentrate (10 mg/mL) and METADOL (1 mg/mL) must be mixed with one of the above solutions (diluents) before dispensing (see PHARMACEUTICAL INFORMATION).

Disposal

METADOL should be kept in a safe place, out of the sight and reach of children before, during and after use. METADOL should not be used in front of children, since they may copy these actions.

Unused or expired METADOL should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is

required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

METADOL should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

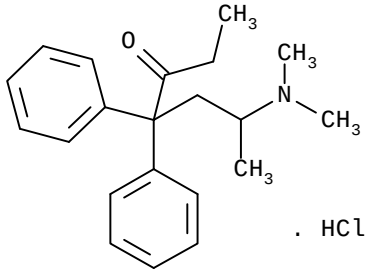
PHARMACEUTICAL INFORMATION

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:

THE TABLET FORMULATION CANNOT BE DISSOLVED IN WATER

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

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

Each **METADOL 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, Meglumine and Microcrystalline Cellulose.

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

This meglumine-based METADOL tablet formulation was studied *in vitro* in different solution media to observe the solubility of its methadone content. The new formulation showed a methadone solubility reduced by 70% to 100% in an aqueous solution. Methadone solubility in alcoholic solutions (ethanol or isopropyl alcohol) or in simulated gastric fluid was not affected by meglumine. However, its solubility in water after evaporation of such an alcoholic solution was reduced by close to 100%.

METADOL 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 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 should be stored at 15° - 30°C. Bottles should be kept tightly closed. Protect METADOL tablets from light. Protect METADOL Oral Concentrate and Oral Solution from light and freezing.

AVAILABILITY OF DOSAGE FORMS

METADOL 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 beveled-edged tablet, scored and debossed "1" on one side and Paladin shield logo on the other side. Available in HDPE bottles of 100.

5 mg: Peach, round, flat-faced beveled-edged tablets, scored and debossed "5" on one side and Paladin shield-logo on the other side. Available in HDPE bottles of 100.

10 mg: Pale green, round, flat-faced beveled-edged tablets, scored and debossed "10" on one side and Paladin shield logo on the other side. Available in HDPE bottles of 100.

25 mg: White to off-white, biconvex, caplet shaped tablets, scored and debossed "25" on one side and Paladin shield logo on the other side. Available in HDPE bottles of 100.

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

METADOL 10 mg/mL Oral Concentrate:
Each 1 mL of clear unflavored and colorless liquid contains 10 mg of methadone hydrochloride USP. METADOL is available in 100 mL and 250 mL amber glass 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 Analgesia Preparation Using METADOL Oral Concentrate:

To prepare a 100 mL stock solution of various strengths of methadone, use METADOL concentrate 10 mg/mL and one of the following diluents:

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

Dilution Chart to prepare 100 mL of Solution		
Concentration of Solution	METADOL (concentrate)	Diluent
1 mg/mL	10 mL	90 mL
2 mg/mL	20 mL	80 mL
2.5 mg/mL	25 mL	75 mL
5 mg/mL	50 mL	50 mL
7.5 mg/mL	75 mL	25 mL
10 mg/mL	100 mL	0 mL

Note: Solution must be stored under refrigeration, for no longer than 1 week (apple juice) and for no longer than 2 weeks containing any of the other diluents indicated above.

Calculation tables are provided hereafter indicating the individual total quantity of METADOL concentrate and diluent required for the prescribed duration of the treatment of severe pain:

ANALGESIA

CALCULATION TABLE OF DIFFERENT DILUTIONS FOR THE QUANTITY REQUIRED FOR 1 WEEK TREATMENT

Prescribed Unit Dose	Quantity for 1 daily dose regimen (Once Daily)			Quantity for 2 times daily dose regimen			Quantity for 3 times daily dose regimen		
	METADOL 10mg/mL	Diluent	Total quantity of prepared solution per week	METADOL 10mg/mL	Diluent	Total quantity of prepared solution per week	METADOL 10mg/mL	Diluent	Total quantity of prepared solution per week
1 mg	0.7 mL	6.3 mL	7 mL	1.4 mL	12.6 mL	14 mL	2.1 mL	18.9 mL	21 mL
2.5 mg	1.75 mL	15.75 mL	17.5 mL	3.5 mL	31.5 mL	35 mL	5.25 mL	47.25 mL	52.5 mL
5 mg	3.5 mL	31.5 mL	35 mL	7 mL	63 mL	70 mL	10.5 mL	94.5 mL	105 mL
7.5 mg	5.25 mL	47.25 mL	52.5 mL	10.5 mL	94.5 mL	105 mL	15.75 mL	141.75 mL	157.5 mL
10 mg	7 mL	63 mL	70 mL	14 mL	126 mL	140 mL	21 mL	189 mL	210 mL

Each 1 mL of these dilutions contains 1 mg of methadone

e.g. 5 mg b.i.d. => 5 mL (prepared solution) b.i.d.

METADOL has been found compatible with 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

ANALGESIA
CALCULATION TABLE OF DIFFERENT DILUTIONS
FOR THE QUANTITY REQUIRED FOR 2 WEEKS TREATMENT

Prescribed Unit Dose	Quantity for 1 daily dose regimen (Once Daily)			Quantity for 2 times daily dose regimen			Quantity for 3 times daily dose regimen		
	METADOL 10mg/mL	Diluent	Total quantity of prepared solution per 2 weeks	METADOL 10mg/mL	Diluent	Total quantity of prepared solution per 2 weeks	METADOL 10mg/mL	Diluent	Total quantity of prepared solution per 2 weeks
1 mg	1.4 mL	12.6 mL	14 mL	2.8 mL	25.2 mL	28 mL	4.2 mL	37.8 mL	42 mL
2.5 mg	3.5 mL	31.5 mL	35 mL	7 mL	63 mL	70 mL	10.5 mL	94.5 mL	105 mL
5 mg	7 mL	63 mL	70 mL	14 mL	126 mL	140 mL	21 mL	189 mL	210 mL
7.5 mg	10.5 mL	94.5 mL	105 mL	21 mL	189 mL	210 mL	31.5 mL	283.5 mL	315 mL
10 mg	14 mL	126 mL	140 mL	28 mL	252 mL	280 mL	42 mL	378 mL	420 mL

Each 1 mL of these dilutions contains 1 mg of methadone

e.g. 5 mg b.i.d. => 5 mL (prepared solution) b.i.d.

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

Grape flavoured Kool-Aid®
Orange flavoured Tang®
Crystal Light® Tangerine-Grapefruit flavoured
Crystal Light® Lemonade flavoured

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 were 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.

Carcinogenicity and Genotoxicity

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.

Reproduction Toxicity

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.

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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION
^{N}METADOL®

Methadone Hydrochloride Tablets
Methadone Hydrochloride Oral Solution
Methadone Hydrochloride Oral Concentrate

Read this carefully before you start taking **METADOL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **METADOL**.

Serious Warnings and Precautions

- **Even if you take METADOL as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death.**
- **Life-threatening breathing problems can happen while taking METADOL, especially if not taken as directed.**
- **Never give anyone your METADOL. They could die from taking it. If a person has not been prescribed METADOL, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **Babies born to mothers who have taken METADOL (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

What is METADOL used for?

METADOL is used for the long-term management of pain, when:
- the pain is severe enough to require daily, around-the-clock painkillers
- the doctor determines that other treatment options are not able to effectively treat your pain

METADOL is NOT used ("as needed") to treat pain that you only have once in a while.

How does METADOL work?

METADOL is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in METADOL tablets?

Medicinal ingredients: methadone hydrochloride USP
Non-medicinal ingredients: METADOL tablets contain: lactose, magnesium stearate, meglumine and microcrystalline cellulose.

The following tablet strengths also contain:
1 mg: FD&C Blue No.1 Lake
5 mg: FD&C Yellow No. 6 Lake
10 mg: D&C Yellow No. 10 Aluminium Lake, FD&C Blue No.1 Lake

What are the ingredients in METADOL Oral Solution?

Medicinal ingredients: methadone hydrochloride USP
Non-medicinal ingredients: citric acid, dextrose, glycerin, methylparaben, polyethylene glycol, sodium benzoate, sodium cyclamate and water.

What are the ingredients in METADOL Concentrate Solution?

Medicinal ingredients: methadone hydrochloride USP
Non-medicinal ingredients: citric acid, dextrose, glycerin, propylene glycol, sodium benzoate, sodium cyclamate and water

METADOL comes in the following dosage forms:

METADOL tablets of 1 mg, 5mg, 10 mg, and 25 mg: Bottles of 100 tablets.
METADOL Oral Solution 1mg/mL: 100 mL and 250 mL bottles.
METADOL Oral Concentrate 10mg/mL: 100 mL and 250 mL bottles.

Do not use METADOL if:

- your doctor did not prescribe it for you
- you are allergic to methadone hydrochloride or other opioid analgesics or to any of the other ingredients of METADOL **(see What are the ingredients in METADOL?)**
- have never used an opioid analgesic before
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have a severe diarrhea caused by antibiotics
- you have a head injury or other risks for seizures
- you suffer from alcoholism
- you have taken a certain type of antidepressant (MAO inhibitors) within the last 14 days.
- you are pregnant or plan to become pregnant, breastfeeding, or in labour
- you are under 18 years of age

Do not use METADOL tablets if:

- You have rare inherited diseases which affect how your body uses the sugar lactose (because lactose is an ingredient in METADOL).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take METADOL. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver disease
- have low blood pressure
- are going to have, or recently had, a planned surgery
- have past or current depression
- suffer from chronic or severe constipation
- have, or had in the past abdominal pain, thyroid gland problems, prostate problems, unusual narrowing of the urethra, adrenal gland problems such as Addison's disease, seizure, convulsions, hallucinations, or severe mental problems.

Other warnings you should know about:

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to METADOL. Drowsiness, dizziness, or lightheadedness, can especially occur after the first dose and when the dose is increased.

Abuse, Addiction and Physical Dependence: There is a risk of abuse or addiction with all opioids. Some patients, particularly those who have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking opioids, such as METADOL. Patients who have taken METADOL for a period of time may develop physical dependence, and should not abruptly stop taking it. See "**Discontinuation**:" section of this leaflet.

While there are important differences between physical dependence and addiction, each is a reason for close medical supervision and honest questions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with METADOL:

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking METADOL. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose

- other sedative drugs which may enhance the drowsiness caused by METADOL
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take METADOL with MAO inhibitors or if you have taken MAOi's in the last 14 days before treatment with METADOL.
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- drugs used for the treatment of epilepsy (e.g. phenytoin, carbamazepine);
- antihistamines (for allergies) or cold medicines
- anti-emetics (for prevention of vomiting)
- diuretics
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- anti-retroviral, anti-fungal and antibiotic drugs
- drugs that use a system called CYP3A4 in the body (e.g. erythromycin, sertraline)
- any non-prescription, (over the counter) medication including laxatives
- any herbal remedies including the herbal remedy St. John's Wort (primarily used for the treatment of depressive moods).

How to take METADOL tablets:

Swallow whole. Do not break, chew, dissolve or crush.

Usual Adult Starting Dose:

Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly.
Do not use METADOL for injection or rectal administration.
The usual adult oral dose is 2.5 mg to 10 mg every 4 hours during the first 3 to 5 days, followed a fixed dose every 8 to 12 hours depending on your requirements.

Your prescribed dose of METADOL **Oral Solution** and **Oral Concentrate** will be dispensed to you in either grape Kool-Aid®, orange Tang®, Allen's® apple juice, tangerine-grapefruit or lemonade Crystal Light®. Any remaining solution should be refrigerated (2°C to 8°C) for not more than 14 days or 7 days if diluted in Allen's® Apple Juice.

In patients 65 years old and older, METADOL could be given once a day.

Your dose of METADOL will be clearly labeled on the medication bottle. Be sure to follow the directions on the label exactly; this is very important. Do not increase or decrease your dose without consulting your doctor. If your dosage is changed by your doctor, be sure to write it down at the time your doctor calls or sees you, and follow the new directions exactly. Review your pain regularly with your doctor to determine if you still need **METADOL**. Be sure to use **METADOL** only for the condition for which it was prescribed.

Discontinuation:

After you stop **METADOL,** you should take the unused medication to your pharmacist for disposal.

Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms such as body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, tremors or shivering, stomach cramps, vomiting, tachycardia, trouble with sleeping, unusual increase in sweating, weakness and yawning.

You should not stop taking **METADOL** all at once if you have been taking it for more than a few days.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If you think you have taken too much METADOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in succession, talk to your doctor before restarting your medication.

Refilling Prescriptions for METADOL:

A new written prescription is required from your doctor each time you need more METADOL. Therefore, it is important that you contact your doctor before your current supply runs out.

Do not seek additional prescriptions for this medicine from any other doctor – unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase or any other complaint develop as a result of taking METADOL, tell your doctor immediately.

What are possible side effects from using METADOL?

These are not all the possible side effects you may feel when taking METADOL. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness, insomnia
- Dizziness, fainting
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating, facial flushing
- Constipation

Talk with your doctor or pharmacist about ways to prevent constipation when you start using METADOL.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin, seizures.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting, light-headedness.	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

METADOL should be stored at room temperature (15°- 30°C) and protected from light. Protect METADOL Oral Concentrate and METADOL Oral Solution from light and freezing. Keep bottles tightly closed.
Keep unused or expired METADOL in a secure place to prevent theft, misuse or accidental exposure.
Keep out of sight and reach of children and pets. Accidental ingestion by a child is dangerous and may result in death. If a child accidently takes METADOL, get emergency help right away.

Disposal:

METADOL should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about METADOL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website; the manufacturer's website http://www.paladinlabs.com, or by calling 1-888-867-7426.

This leaflet was prepared by Paladin Labs Inc.

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