PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# $^{N}$METADOL®

Methadone Hydrochloride Tablets

Tablets, 1 mg, 5 mg, 10 mg and 25 mg, Oral

Mfr. Std.

Methadone Hydrochloride Oral Solution

Solution, 1 mg/mL, Oral

USP

Methadone Hydrochloride Oral Concentrate

Concentrate, 10 mg/mL, Oral

USP

Opioid Analgesic

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## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance; Neurologic | 03/2025 |

## TABLE OF CONTENTS

**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

METADOL (methadone hydrochloride tablets, oral solution and concentrate) is indicated in adult patients for:

- the relief of severe pain.

In general, METADOL, as an analgesic, should not be used in opioid naïve patients.

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada. Therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (> 65 years of age):** The safety and efficacy of METADOL in patients 65 years and older have not been established.

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 (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

### 2 CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance methadone hydrochloride or other opioid analgesics, to any ingredient in the formulation, or to any component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or 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 or severe bronchial asthma, chronic obstructive airway, or 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 (central nervous system) depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase inhibitors (MAOIs) (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant or during labour and delivery (see 3 SERIOUS WARNINGS AND PRECAUTIONS and 7.1 Special Populations).
- 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 naïve to opioids.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

**Limitations of Use**
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, METADOL should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see 4 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 7 WARNINGS AND PRECAUTIONS, Addiction, Abuse and Misuse). Appropriate security measures should be taken to safeguard stocks of methadone against diversion. METADOL should be stored securely to avoid theft or misuse.

**Life-threatening Respiratory Depression: OVERDOSE**
Serious, life-threatening, or fatal respiratory depression may occur with use of METADOL. Infants exposed *in-utero* or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of METADOL or following a dose increase.

METADOL must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving METADOL tablets can cause rapid release and absorption of a potentially fatal dose of methadone hydrochloride leading to dangerous adverse events including death (see

7 WARNINGS AND PRECAUTIONS, Addiction, Abuse and Misuse). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects are typically delayed. This characteristic can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

**QT interval prolongation**
Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. 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.

**Accidental Exposure**
Accidental ingestion of even one dose of METADOL especially by children, can result in a fatal overdose of methadone hydrochloride (see 11 STORAGE, STABILITY AND DISPOSAL, 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 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome (NOWS)).

**Interaction with Alcohol**
The co-ingestion of alcohol with METADOL should be avoided as it may result in dangerous additive effects, due to increased plasma levels of methadone hydrochloride, which can result in overdose, serious injury or death (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Use in Drug and Alcohol Addiction and 9.3 Drug-Behavioural Interactions).

**Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants and 9.2 Drug Interactions Overview).

- Reserve concomitant prescribing of METADOL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

**For the management of chronic non-cancer, non-palliative pain, consider the benefits and the risks of higher doses as they are associated with an increased risk of adverse events and overdose. The level of pain should be assessed regularly to evaluate the need for further use of METADOL.**

Patients prescribed methadone should be carefully monitored and provided appropriate supportive psychological and social services.

**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).**

Dosing is to be determined by the physician. Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high inter-patient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.**

METADOL is not indicated for injection or rectal administration.

### 4.2 Recommended Dose and Dosage Adjustment

**Adults (over 18 years):**
Dosage should be carefully titrated and adjusted according to the severity of the pain and response of the patient. 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.

**Patients Not Receiving Opioids at the Time of Initiation of methadone hydrochloride Treatment:**
METADOL should not be used in opioid naive patients.

**Switching Patients from an Alternate Opioid Product:**
When switching from an alternate opioid product to methadone, there is significant risk of respiratory depression if the patient is switched abruptly (see 7 WARNINGS and PRECAUTIONS, Dependence/Tolerance, Incomplete Cross-Tolerance Between Methadone and Other Opioids). Conversion to methadone should be undertaken with caution.

**Dose Titration:**
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response. Dose adjustment

should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

**Use with Non-Opioid Medications:**
If a non-opioid analgesic is being provided, it may be continued. METADOL can be safely used concomitantly with usual doses of other non-opioid analgesics.

**Patients with Hepatic Impairment:**
Dosage adjustments should be based on the patient's clinical response (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

**Patients with Renal Impairment:**
Dosage adjustments should be based on the patient's clinical response (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

**Pediatrics (< 18 years of age):**

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

**Geriatrics (> 65 years of age):**

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. METADOL should be initiated at a low dose and slowly titrated to effect (see 7.1.4 Geriatrics and 10.2 Pharmacodynamics, Special Populations and Conditions, Geriatrics).

**Adjustment or Reduction of Dosage:**

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including METADOL. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal of the drug, these symptoms are usually mild (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Tapering should be individualized and carried out under medical supervision.

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.

Patients should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

### 4.3 Reconstitution

**Dispensing Guideline for Opioid Analgesic**
METADOL Oral Solution and Oral Concentrate must be dispensed in 100 mL of a vehicle that does not easily lend itself to injection.

METADOL (Oral Solution and Oral 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.

Note: Both METADOL Oral Concentrate (10 mg/mL) and METADOL Oral solution (1 mg/mL) must be mixed with one of the above solutions (diluents) before dispensing.

**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 (see 11 STORAGE, STABILITY AND DISPOSAL).**

**Pharmacist Compounding Information for Analgesia Preparation Using METADOL Oral Concentrate (10 mg/mL):**

| 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 |

*See **Dispensing Guideline for Opioid Analgesic** sub-section above for recommended diluents, and solution storage.

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

**Analgesia**

**Table 1. 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 10 mg/mL | Diluent | Total quantity of prepared solution per week | METADOL 10 mg/mL | Diluent | Total quantity of prepared solution per week | METADOL 10 mg/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**

**Table 2. 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 10 mg/mL | Diluent | Total quantity of prepared solution per 2 weeks | METADOL 10 mg/mL | Diluent | Total quantity of prepared solution per 2 weeks | METADOL 10 mg/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®
- Allen's® Apple Juice
- Crystal Light® Tangerine-Grapefruit flavoured
- Crystal Light® Lemonade flavoured

### 4.4 Administration

**METADOL tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving METADOL can lead to dangerous adverse events including death (see** 7 WARNINGS AND PRECAUTIONS**).**

For details on reconstitution before administration, refer to 4.3 Reconstitution.

### 4.5 Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

## 5 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.

Other important adverse events reported with methadone overdose include toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, sudden sensorial hearing loss, rhabdomyolysis progressing to renal failure, serotonin syndrome and hypoglycemia.

**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 counteract 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 antagonist 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).**

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 3 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablets<br>1, 5, 10 and 25 mg<br>Methadone hydrochloride | Lactose, magnesium stearate, meglumine and microcrystalline cellulose, FD&C Blue No. 1 (1 and 10 mg), FD&C Yellow No.6 (5 mg), D&C Yellow No.10 aluminium (10 mg). |
| | Solution<br>1 mg/mL<br>Methadone hydrochloride | Citric acid, dextrose, glycerin, methylparaben, polyethylene glycol, sodium benzoate, sodium cyclamate and water |
| | Concentrate<br>10 mg/mL<br>Methadone hydrochloride | Citric acid, dextrose, glycerin, propylene glycol, sodium benzoate, sodium cyclamate and water |

The 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 is available in the following dosage forms: tablets, oral solution and oral concentrate.

METADOL Tablets:

1 mg: Blue, round, flat-faced beveled-edged tablet, scored and debossed “1” on one side and a shield logo on the other side.

5 mg: Peach, round, flat-faced beveled-edged tablets, scored and debossed “5” on one side and a shield logo on the other side.

10 mg: Pale green, round, flat-faced beveled-edged tablets, scored and debossed “10” on one side and a shield logo on the other side.

25 mg: White to off-white, biconvex, caplet shaped tablets, scored and debossed “25” on one side and a shield logo on the other side.

**The tablet formulation cannot be dissolved in water.**

METADOL Oral Solution (1 mg/mL): Clear unflavored and colorless liquid.

METADOL Oral Concentrate (10 mg/mL): Clear unflavored and colorless liquid**.**

**Packaging:**

METADOL Tablets: Available in HDPE bottles of 100.

METADOL Oral Solution: Available in 100 mL and 250 mL amber plastic bottles.

METADOL Oral Concentrate: Available in 100 mL and 250 mL amber glass bottles.

## 7 WARNINGS AND PRECAUTIONS

MAY BE HABIT FORMING.

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

**General**

**Methadone hydrochloride, a synthetic opioid, is a controlled substance listed in Schedule I of the *Controlled Drugs and Substances Act* (CDSA). Appropriate security measures should be taken to safeguard stock of methadone against diversion.**

**Patients should be instructed not to give METADOL (methadone hydrochloride) to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. METADOL should be stored securely to avoid theft or misuse.**

**METADOL should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.**

Patients should be cautioned not to consume alcohol while taking METADOL as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of methadone hydrochloride can occur at particularly high doses. A methadone hydrochloride dose reduction or change in opioid may be required (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Opioid Induced Hyperalgesia).

**Addiction, Abuse and Misuse**

Like all opioids, 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 and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

METADOL is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Like morphine, methadone is a μ-agonist opioid agonist with an abuse liability and is subject to criminal diversion.

**Carcinogenesis and Genotoxicity**

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Genotoxicity sections.

**Cardiovascular**

Methadone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of METADOL.

**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.

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

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

The use of METADOL in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure (see 10.2 Pharmacodynamics).

**Dependence/Tolerance**

As with other opioids, tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of METADOL.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, 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.

Abuse or intentional misuse of methadone may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in

patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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 (see 4.2 Recommended Dose and Dosage, Adjustment or Reduction of Dosage). Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see 8 ADVERSE REACTIONS).

**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 7 WARNINGS AND PRECAUTIONS, Respiratory and 4 DOSAGE AND ADMINISTRATION). A high degree of "opioid tolerance" does not eliminate the possibility of methadone toxicity.

**Use in Drug and Alcohol Addiction:** METADOL is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to METADOL unless used under extreme caution and awareness.

**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 2 CONTRAINDICATIONS).

**Driving and Operating Machinery**

METADOL may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of methadone hydrochloride with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

**Endocrine and Metabolism**

**Adrenal Insufficiency**: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

**Gastrointestinal**

Methadone hydrochloride and other morphine-like opioids have been shown to decrease bowel motility. The administration of methadone hydrochloride or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see 2 CONTRAINDICATIONS).

**Hepatic/Biliary/Pancreatic**

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.

**Neurologic**

**Head Injury:** The respiratory depressant effects of methadone hydrochloride, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of head injury, other intracranial lesions or a pre=existing increase in intracranial pressure. Also, methadone hydrochloride may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, methadone hydrochloride must be used with extreme caution and only if it is deemed essential (see 2 CONTRAINDICATIONS).

**Interactions with CNS Depressants (including benzodiazepines and alcohol):** METADOL should be used with caution and in a reduced dosage during concomitant administration of other opioids analgesics, general anesthetics, phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, gabapentinoids, baclofen, centrally-active anti-emetics and other CNS depressants including

alcohol. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see 9.2 Drug Interactions Overview). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when METADOL is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see 9 DRUG INTERACTIONS).

METADOL should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS, 8 ADVERSE REACTIONS, Sedation and 9 DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

**Opioid Induced Hyperalgesia:** Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intraoperative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e., non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

**Serotonin Toxicity / Serotonin Syndrome:** Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with methadone,

including METADOL, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Drugs).

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and ocular clonus or inducible clonus.

If concomitant treatment with METADOL and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Serotonergic Drugs). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

**Renal**

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

**Reproductive Health: Female and Male Potential**

- **Fertility**

  Long term use of opioids may be associated with symptoms such as infertility (see 8.5 Post-Market Adverse Reactions, Androgen deficiency).

- **Function**

  Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido or erectile dysfunction (see 8.5 Post-Market Adverse Reactions, Androgen deficiency).

**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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Methadone hydrochloride should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see 2 CONTRAINDICATIONS).

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.

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.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of METADOL are essential (see 4 DOSAGE AND ADMINISTRATION). Overestimating the METADOL dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups and 4 DOSAGE AND ADMINISTRATION).

**Sleep Apnea**: Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage; 7 WARNINGS AND PRECAUTIONS; Dependence/Tolerance).

**Use in Patients with Chronic Pulmonary Disease:** METADOL should be administered with extreme caution to patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve (such as asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma), hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with METADOL, as in these patients, even usual therapeutic doses of METADOL may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. These patients should be monitored and use of alternative non-opioid analgesics should be considered, if possible, and METADOL should be employed only under careful medical supervision at the lowest effective dose. The use of METADOL is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2 CONTRAINDICATIONS).

### 7.1 Special Populations

**Special Risk Groups:** Methadone hydrochloride 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 oral 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, myxedema, toxic psychosis, 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. 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.

### 7.1.1 Pregnant Women

No controlled studies of methadone use in pregnant women have been conducted. METADOL crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of opioids during pregnancy can result in respiratory difficulties and withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome).

Studies show methadone exposure to be associated with an increased risk of very pre-term birth (< 32 weeks of gestation), being small for gestational age (< 10th percentile), admission to the neonatal unit, and diagnosis of a major congenital anomaly.

Several studies have suggested that infants prenatally exposed to methadone present decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. Moreover it has been suggested that prenatally exposed infants are at a higher risk of presenting neurodevelopmental and neuropsychological impairments, as well as visual (see 7.1.1 Pregnant Women, Neonate Growth and Development).

Additional information on the potential risks of methadone with pre-natal opioid exposure may be derived from animal data (see 16 NON-CLINICAL TOXICOLOGY, Teratogenicity).

**Neonate Growth and Development:** Exposure to opioids *in utero* can result in the development of the life-threatening, Neonatal Opioid Withdrawal Syndrome (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, 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.

Prenatal opioid exposure, including to methadone, is suggested to have an effect on the visual system and on brain development.

Lower performance on tests of cognitive function and neurodevelopmental abnormalities have been found in some, although not all, studies and children have been shown to demonstrate mild, but persistent deficits in performance on psychometric and behavioral tests. It is unclear whether these differences in performance are caused by the direct effects of in-utero exposure to methadone or indirectly by genetic and environmental risk factors, or are a consequence of pre-term birth.

**Ophthalmic Abnormalities:** Infants prenatally exposed to methadone are at risk of a range of visual problems, the underlying causes of which are not clear. Ophthalmic abnormalities included reduced acuity, nystagmus, delayed visual maturation, strabismus, refractive errors, and cerebral visual impairment. Those infants with NOWS severe enough to receive pharmaceutical treatment may be at particular risk of developing nystagmus. Delayed visual development has also been reported. Exposure to opioid including methadone, during pregnancy may result in permanently reduced vision and nystagmus.

**Labour and Delivery:** Since methadone has a long duration of action, can cross the placental barrier and is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma, METADOL is contraindicated for obstetric analgesia, during labour 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. Naloxone, a drug that counters the effects of opiates, should be readily available if METADOL is used in this population.

### 7.1.2 Breast-feeding

Since methadone has a long duration of action, can cross the placental barrier and is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma, METADOL is contraindicated for obstetric analgesia in nursing mothers. Cases of death have been reported in association with methadone in children less than one year of age exposed through breast milk.

Women being treated with methadone, 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.

### 7.1.3 Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 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 and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 10.2 Pharmacodynamics, Special Populations and Conditions, Geriatrics).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

Adverse effects of METADOL are similar to those of other opioid analgesics, and represent an

extension of pharmacological effects of the drug class.

**The major hazards of methadone are respiratory and central nervous system depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock and cardiac arrest and death have occurred.**

The most frequently observed adverse effects of METADOL include light-headedness, 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.

**Sedation:** Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

**Nausea and Vomiting:** Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

**Constipation:** Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Other adverse reactions that have been reported in patients 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

**Metabolic and Nutritional:** Hypokalemia, hypomagnesemia, weight gain

**Nervous:** Agitation, confusion, seizures, disorientation, dysphoria, euphoria, insomnia

**Ocular:** Visual disturbances

**Respiratory:** Pulmonary edema

**Special senses:** Visual disturbances

**Urogenital:** Antidiuretic effect, amenorrhea, urinary retention or hesitancy, reduced libido and/or potency

**Abnormal Hematologic and Clinical Chemistry Findings:** Reversible thrombocytopenia has been described in patients with chronic hepatitis.

### 8.5 Post-Market Adverse Reactions

**Androgen deficiency:** Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

**Metabolic and Nutritional:** Hypoglycemia

**Nervous system Disorders:** Serotonin toxicity/Serotonin syndrome

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

- Risks from concomitant use of opioids and benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol))
    - Reserve concomitant prescribing of METADOL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate

- Consider dose reduction of CNS depressants in situations of concomitant prescribing
- Follow patients for signs and symptoms of respiratory depression and sedation

- MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. METADOL is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days.

### 9.2 Drug Interactions Overview

**Interactions with CNS Depressants (including benzodiazepines and alcohol):**

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids; sedatives; gabapentinoids such as pregabalin, baclofen; hypnotics; antidepressants; anxiolytics; tranquilizers; muscle relaxants; general anesthetics; antipsychotics; phenothiazines; neuroleptics; antihistamines; antiemetics; and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Driving and Operating Machinery). METADOL should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

**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 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.

**Cytochrome P450 inducers:**

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

Rifampin/Rifampicin: 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.

Phenobarbital, carbamazepine: Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms (see also 9.6 Drug-Herb Interactions).

**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.

**Monoamine Oxidase Inhibitors (MAOIs):**

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.

**Opioid antagonist, mixed agonist/antagonist, and partial agonists drugs:**

Agonist/ antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) when administered concomitantly with a pure opioid agonist, such as methadone hydrochloride may reduce the analgesic effect of methadone hydrochloride and/or may precipitate withdrawal symptoms, the latter being a particular risk to patients on prolonged methadone therapy.

**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.

**Serotonergic Drugs:** Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon co-administration with METADOL and result in increased opioid effects and/or toxicity.

Coadministration of METADOL with serotonergic drugs, such as a Selective Serotonin Re-uptake Inhibitor, a Serotonin Norepinephrine Re-uptake Inhibitor or other serotonergic drug,

may increase the risk of serotonin syndrome, a potentially life-threatening condition (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin toxicity / Serotonin syndrome). If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue METADOL if serotonin syndrome is suspected.

### 9.3 Drug-Behavioural Interactions

The concomitant use of alcohol should be avoided (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

### 9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 4 – Established or Potential Drug-Drug Interactions**

| Proper/Common Name | Source of Evidence | Effect | Clinical Comment |
|---|---|---|---|
| Monoamine oxidase inhibitors | C | ↑ Methadone | May also increase the risk of serotonin syndrome, a potentially life-threatening condition. |
| Selective serotonin re-uptake inhibitors | C | ↑ Methadone | May increase methadone plasma levels upon co-administration with METADOL and result in increased opioid effects and/or toxicity. |
| SSRIs, SNRIs, TCAs, MAOIs (including linezolide and methylene blue), triptans, other serotonergic drugs (e.g., lithium) and serotonin-precursors such as L-tryptophan | C, T | ↑ Methadone | May also increase the risk of serotonin syndrome, a potentially life-threatening condition. |
| Potentially arrhythmogenic agents | T, C | ↑ Methadone | Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with METADOL.<br><br>Pharmacodynamic interactions may occur with concomitant use of METADOL and potentially arrhythmogenic agents such as Class |

| | | | |
|---|---|---|---|
| | | | I and III anti-arrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.<br><br>Caution should also be exercised when prescribing METADOL concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones. |
| Abacavir, efavirenz, nelfinavir, nevirapine, ritonavir | CT, C | ↓ Methadone | Co-administration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Patients taking methadone who begin treatment with these anti-retroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. |
| Lopinavir + ritonavir combination | T | ↓ Methadone | Co-administration may result in increased clearance or decreased plasma levels of methadone. |
| Amprenavir | CT | ↓ Methadone | Methadone blood concentrations are decreased by the administration of abacavir plus amprenavir. |
| Histamine H2 antagonists such as cimetidine | T | ↑ Methadone | Can reduce the protein binding of methadone resulting in increased opioid action. |
| Delavirdine | T | ↑ Methadone | Dosage of methadone may need to be decreased when co-administered with delavirdine. |
| Rifampin / Rifampicin | C | ↓ Methadone | Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary. |
| Ciprofloxacin | C | ↑ Methadone | Plasma levels of methadone may increase with concurrent |

| | | | |
|---|---|---|---|
| | | | administration of ciprofloxacin due to inhibition of CYP1A2 and CYP3A4. Concomitant use may lead to sedation, confusion and respiratory depression. |
| Erythromycin | T, C | ↑ Methadone | Theoretically erythromycin may increase methadone levels due to decreased methadone metabolism. |
| Fluconazole | CT, C | ↑ Methadone | May raise methadone levels, due to decreased methadone metabolism. |
| Ketoconazole | T | ↑ Methadone | May raise methadone levels, due to decreased methadone metabolism. |
| Vorizonazole | CT, C | ↑ Methadone | May raise methadone levels due to decreased methadone metabolism. |
| Phenytoin, Carbamazepine | C | ↓ Methadone | Induces methadone metabolism with resulting risk of reduced analgesic effect and/or precipitating withdrawal symptoms. Adjustment of the dose of methadone should be considered. |
| Phenobarbital | T | ↓ Methadone | Induces methadone metabolism with resulting risk of reduced analgesic effect and/or precipitating withdrawal symptoms. |
| Primidone | T | ↓ Methadone | Induces methadone metabolism with resulting risk of reduced analgesic effect and/or precipitating withdrawal symptoms. |
| Domperidone and metoclopramide | T | ↑ Methadone | May increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity. |
| Methadone | T | ↓ Ciprofloxacin | Reduced serum concentrations of ciprofloxacin may occur. |
| Methadone | C | ↓ Didanosine<br>↓ Stavudine | Experimental evidence demonstrated that methadone decreased the area under the concentration-time curve (AUC) and peak levels for didanosine and |

| | | | |
|---|---|---|---|
| | | | stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered. |
| Methadone | CT | ↑ Zidovudine | Experimental evidence demonstrated that methadone increased the AUC of zidovudine which could result in toxic effects. |
| Methadone | C | ↑ Desipramine | Plasma levels of desipramine have increased with concurrent methadone administration. |
| Methadone | T | ↓ Domperidone and Metoclopramide | Methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity. |
| Methadone | T | ↓ Mexiletine | Methadone delays the absorption of mexiletine. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

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

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Methadone is an opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the *l*-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The *d*-isomer lacks significant respiratory depressant activity but does have antitussive effects. Methadone also has some agonist actions at the κ and σ opioid receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the oculomotor nerve, and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a pA2 value similar to its antagonism of morphine. Like many basic drugs, methadone enters mast cells and releases histamine by a nonimmunological mechanism.

Similar to morphine, both isomers are 5-HT(3) receptor antagonists, although *l*-methadone producing greater inhibition than d-methadone. Methadone causes a dependence syndrome of the morphine type. Cross-tolerance between morphine and methadone has been demonstrated, as steady-state plasma methadone concentrations required for effectiveness (C50%) were higher in abstinent rats previously dosed with morphine, as compared to controls.

Some data indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to product neurotoxic effects in animals.

### 10.2 Pharmacodynamics

Prolongation of the QT interval associated with methadone can lead to potentially fatal ventricular arrhythmias and is caused by block of the rapid component of the cardiac delayed rectifier K(+) current (I(Kr)), which is encoded by hERG related gene. In vitro effects of methadone have been compared to heroin in human embryonic kidney cells expressing hERG currents, with methadone exhibiting 100-fold higher potency (IC50 4.8 µM) at inhibiting hERG than heroin (IC50 427 µM) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Cardiac Conduction Effects).

**Central Nervous System:** Methadone hydrochloride produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in $CO_2$ tension and to electrical stimulation.

Methadone hydrochloride depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Methadone hydrochloride causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

**Gastrointestinal Tract and Other Smooth Muscle:** Methadone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

**Cardiovascular System:** Methadone hydrochloride may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

**Endocrine System:** Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

**Immune System:** *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

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.

### 10.3 Pharmacokinetics

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.

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.

**Table 5 – Mean (CV%) Methadone pharmacokinetic parameters after administration of a single 10 mg dose of METADOL to healthy subject (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)

### Absorption

Methadone is one of the more lipid soluble opioids, and is well absorbed from the gastrointestinal tract. Following oral administration, the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

### Distribution

Methadone undergoes fairly extensive first pass metabolism. It is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in lung, liver and kidneys being much higher than in the blood. Methadone is unusual in the opioid class, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to a1-acid glycoprotein (85% to 90%). Marked variations in plasma levels occur in dependent persons on a stable dose of oral methadone, without any relation to symptoms. Methadone is secreted in saliva, sweat, breast milk, amniotic fluid and umbilical cord plasma. The concentration in cord blood is about half the maternal levels.

### Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are

responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

**Elimination**

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life (T½) was highly variable and ranged between 8 and 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

**Special Populations and Conditions**

- **Pediatrics (< 18 years of age):** The pharmacokinetics of METADOL have not been evaluated in the pediatric population. Individuals under 18 years of age should not take METADOL.

- **Geriatrics (> 65 years of age):** The Pharmacokinetics of METADOL have not been evaluated in the geriatric population. 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.
- **Hepatic Insufficiency:** 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.
- **Renal Insufficiency:** The use of methadone has not been extensively evaluated in patients with renal insufficiency.

## 11 STORAGE, STABILITY AND DISPOSAL

Dispense in tight containers, protect from light. Store at room temperature (15°C to 30°C). Oral solution and oral concentrate should be protected from freezing.

**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.

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

## 12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

**PART II: SCIENTIFIC INFORMATION**

## 13 PHARMACEUTICAL INFORMATION

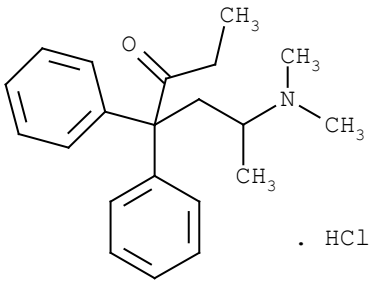
### Drug Substance

Proper name: Methadone Hydrochloride

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

Molecular formula and molecular mass: $C_{21}H_{27}NO$ HCl; 345.91 g/mol

Structural formula:




Physicochemical properties:

**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 coefficient:** 2.1 [log P octanol/water at pH 7.4]
**Melting point:** 233°C - 236°C

## 14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

## 15 MICROBIOLOGY

No data available.

## 16 NON-CLINICAL TOXICOLOGY

### General 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 extreme 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.

**Carcinogenicity:**

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.

**Genotoxicity:**

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.

**Reproductive and Developmental Toxicology:**

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

**Teratogenicity:**

Methadone does not appear to be teratogenic or embryotoxic 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.

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.

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.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**$^{N}$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 a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your healthcare professional.
- Life-threatening breathing problems can happen while taking METADOL, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- METADOL may cause heartbeat problems that can be life-threatening in rare cases. Symptoms may include fainting, heart palpitations (feeling a rapid, pounding or irregular heartbeat), dizziness or lightheadedness. If you think you might have heartbeat or heart rhythm problems, get immediate medical help.
- 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.
- If you took METADOL while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
    - has changes in their breathing (such as weak, difficult or fast breathing)
    - is unusually difficult to comfort
    - has tremors (shakiness)
    - has increased stools, sneezing, yawning, vomiting, or fever

  Seek immediate medical help for your baby.
- Taking METADOL with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

**What is METADOL used for?**

METADOL is used in adults for the long-term management of pain, when:

- The pain is severe enough to require daily, around-the-clock painkillers
- The healthcare professional 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?**

Medicinal ingredient: methadone hydrochloride

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
  5 mg: FD&C Yellow No. 6
  10 mg: FD&C Yellow No. 10 Aluminum, FD&C Blue No. 1
- METADOL oral solution contains citric acid, dextrose, glycerin, methylparaben, polyethylene glycol, sodium benzoate, sodium cyclamate and water.
- METADOL oral concentrate contains citric acid, dextrose, glycerin, propylene glycol, sodium benzoate, sodium cyclamate and water.

**METADOL comes in the following dosage forms:**

METADOL tablets: 1 mg, 5 mg, 10 mg and 25 mg
METADOL Oral Solution: 1 mg/mL
METADOL Oral Concentrate: 10 mg/mL

**Do not use METADOL if:**

- your healthcare professional did not prescribe it for you
- you are allergic to methadone hydrochloride, other opioids or any of the other ingredients in METADOL
- you have never taken an opioid before
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing or cor pulmonale (a heart problem related to lung issues)
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines

- you have a condition where the bowel does not work properly (ileus) or have severe pain in your abdomen
- you have severe diarrhea caused by antibiotics or food poisoning
- you have a head injury or other risks for seizure
- you suffer from alcoholism or alcohol withdrawal
- you are going to have a surgery or operation, or have had a surgery within the last 24 hours
- you are taking, or have taken within the past 14 days, a certain type of antidepressant called Monoamine Oxidase Inhibitor (MAOIs)
- you are pregnant or planning to become pregnant, or you are in labour or delivery
- you are breastfeeding

**Do not use METADOL tablets if:**

- you have rare inherited diseases which affect how your body uses sugar lactose. METADOL tablets contain lactose.

**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 drugs or prescription drug or alcohol abuse
- you are taking any other medications
- are drinking or planning to drink alcohol, or take medications that contain alcohol
- have, or are at risk for, heart disease or heart rhythm problems. Ask your healthcare professional if you are not sure
- have low blood pressure
- have kidney or liver problems
- have problems with your thyroid, adrenal or prostate gland
- have epilepsy or a history of seizures (convulsions)
- are over 65 years of age
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea)
- have, or have a history or, problems with your mood (such as depression or anxiety), or other mental health problems
- have difficulty urinating
- suffer from chronic or severe constipation
- suffer from migraines
- are lactose intolerant

**Other warnings you should know about:**

**Opioid dependence and addiction:** Like any opioid, METADOL may cause mental and physical dependence; it also has the potential to cause addiction. There are important differences between physical dependence and addiction. If you use opioids for a long time, you may develop tolerance. This means that you may need higher doses of METADOL to feel the same level of

pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer METADOL with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

**Pregnancy, nursing, labour and delivery:** Do not use METADOL while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. METADOL can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking METADOL, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your health care professional will monitor and guide you on how to slowly stop taking METADOL. This may help avoid serious harm to your unborn baby.

**Driving and using machines:** Before you do tasks which may require special attention, you should wait until you know how you react to METADOL. METADOL can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

**Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your healthcare professional may do tests, give you another medication, and slowly take you off METADOL.

**Serotonin toxicity (also known as serotonin syndrome):** METADOL can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take METADOL with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

**Sexual Function/Reproduction:** Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

**Sleep Apnea**: Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

**Worsening Pain:** Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking METADOL.

**Testing and check-ups:** Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping)
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing)
- low blood pressure
- problems with your heart rhythm.

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

**Serious Drug Interactions**

Serious drug interactions with METADOL include:

- benzodiazepines used to help you sleep or that help reduce anxiety.
- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
  - alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking METADOL. It can lead to drowsiness, unusually slow or weak breathing, serious side effects, or a fatal overdose.
  - other opioids and mixed opioid agonists/antagonists used to relieve pain (e.g., pentazocine, nalbuphine, butorphanol, and buprenorphine);
  - anesthetics used during surgery;
  - hypnotics used to help with sleeping;
  - antidepressants used for depression and mood disorders (e.g., tricyclic antidepressants; serotonin norepinephrine re-uptake inhibitors (SNRIs); and selective serotonin re-uptake inhibitors (SSRIs) such as sertraline and St. John's Wort);
  - anxiolytics, tranquilizers, and phenothiazines used to treat mental or emotional disorders;
  - muscle relaxants used to treat muscle spasms and back pain (e.g., baclofen);
  - antipsychotics and neuroleptics used to treat mental health disorders;
  - antihistamines used to treat allergies;
  - antiemetics used to prevent nausea or vomiting;
  - sedatives which may enhance the drowsiness;
  - pregabalin, used to treat nerve pain;
  - gabapentin, used to prevent and control seizures in the treatment of epilepsy
  - beta blockers used to lower blood pressure;
- monoamine oxidase inhibitors (MAOIs) used to treat depression. Do not take METADOL with MAOIs or if you have taken MAOI's in the last 14 days.

**The following may also interact with METADOL:**

- anticonvulsants used to treat seizures (e.g., phenytoin, carbamazepine, phenobarbital)
- anticoagulants used to thin the blood and prevent blood clots (e.g., warfarin and other coumarins)
- antiretrovirals used to treat viral infections (e.g., nevirapine, efavirenz, ritonavir, lopinavir, zidovudine, didanosine, stavudine)
- antifungals used to treat fungal infections (e.g., ketoconazole, voriconazole)
- antibiotics used to treat bacterial infections (e.g., erythromycin, rifampin)
- medicines used to treat migraines (e.g., triptans)
- antiarrhythmics used to treat an abnormal heart rhythm
- calcium channel blockers used to lower blood pressure

- medicines used to regulate salt and water balances in the body (e.g., diuretics, mineralocorticoid hormones, laxatives)

**How to take METADOL:**

- Take METADOL exactly as your healthcare professional tells you to. Do NOT increase, decrease, or stop taking your dose without talking to your healthcare
- METADOL must be taken orally, by mouth. Do NOT take METADOL any other way.
- **Swallow METADOL tablets whole.** Do not break, chew, dissolve or crush.
- 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®.
- Do not use METADOL for injection or rectal administration.

**Usual dose:**

Your dose is tailored/personalized just for you. Your healthcare professional will prescribe you the lowest dose that works to control your pain. During treatment, your healthcare professional may adjust your dose based on the severity of your pain and your response to the treatment. Follow their instructions closely.

Review your pain regularly with your healthcare professional to determine if you still need METADOL. Be sure to take METADOL only for the condition for which it was prescribed.

If your pain increases or you develop any side effects as a result of taking METADOL, tell your healthcare professional immediately.

**Stopping your Medication:**

If you have been taking METADOL for more than a few days, you should not stop taking it all of a sudden.

Your healthcare professional will monitor and guide you on how to slowly stop taking METADOL. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble with sleeping
- an unusual increase in sweating

- heart palpitations
- an unexplained fever
- weakness
- vomiting
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking METADOL.

**Refilling your prescription for METADOL:**
A new written prescription is required from your healthcare professional each time you need more METADOL. Therefore, it is important that you contact your healthcare professional before your current supply runs out.

Only obtain prescriptions for this medicine from the healthcare professional in charge of your treatment. Do not seek prescriptions from other healthcare professionals unless you switch to another healthcare professional for your pain management.

**Overdose:**

If you think you, or a person you are caring for, have taken too much METADOL, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Signs of overdose with METADOL may include:

- unusually slow or weak breathing
- dizziness;
- confusion;
- extreme drowsiness;
- muscle weakness;
- cold and clammy skin;
- slow heart rate;
- shrinking or widening of pupils.

**Missed dose:**

It is important that you do not miss any doses. However, if you miss a 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 a row, talk to your healthcare professional before restarting your medication.

**What are possible side effects from using METADOL?**

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

Side effects with METADOL may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Lightheadedness
- Nausea, vomiting, poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating, facial flushing
- Constipation. Talk with your healthcare professional about ways to prevent constipation when you start using METADOL.
- Low sex drive, impotence (erectile dysfunction), infertility

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Frequency/Side Effect/Symptom** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **RARE** | | | |
| **Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing | | | ✓ |
| **Bowel Blockage** (impaction)**:** abdominal pain, severe constipation, nausea | | | ✓ |
| **Heart problems**: heart palpitations, fast, slow or irregular heartbeat, chest pain, chest tightness | | ✓ | |
| **Hypotension** (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up) | ✓ | | |
| **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak | | | ✓ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Frequency/Side Effect/Symptom** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin, seizures | | | |
| **Respiratory Depression:** slow, shallow or weak breathing | | | ✓ |
| **Serotonin toxicity (also known as Serotonin syndrome):** a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles | | | ✓ |
| **Withdrawal:** nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating | | ✓ | |
| **UNKNOWN FREQUENCY** | | | |
| **Disorder of the adrenal gland:** nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, or low blow pressure | | ✓ | |
| **Sleep apnea:** stop breathing for short periods of time during your normal nightly sleep | | ✓ | |

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

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- Store at room temperature (15°- 30°C) in tight container, protected from light. Protect METADOL Oral Concentrate and METADOL Oral Solution from freezing.
- Refrigerate (2°C to 8°C) METADOL Oral Solution and Oral Concentrate diluted with Allen's® Apple Juice for not more than 7 days, or 14 days if diluted with any other juice.
- Keep unused or expired METADOL in a secure place to prevent theft, misuse or accidental exposure. It should be kept under lock, out of sight and reach of children and pets.
- Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes METADOL, get emergency help right away.
- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://knighttx.com), by emailing medinfo@knighttx.com or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

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