

**METHADONE HYDROCHLORIDE - methadone hydrochloride injection, solution  
Akorn, Inc.**

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**Methadone Hydrochloride Injection, USP CII  
Rx only**

## BOXED WARNING

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; LIFE-THREATENING QT PROLONGATION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and TREATMENT OF OPIOID ADDICTION**

### Addiction, Abuse, and Misuse

Methadone Hydrochloride Injection exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Methadone Hydrochloride Injection, and monitor all patients regularly for the development of these behaviors and conditions (see WARNINGS).

### Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Methadone Hydrochloride Injection. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period. Monitor for respiratory depression, especially during initiation of Methadone Hydrochloride Injection or following a dose increase (see WARNINGS).

### Life-Threatening QT Prolongation

QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred 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. Closely monitor patients with risk factors for development of prolonged QT interval, a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction for changes in cardiac rhythm during initiation and titration of Methadone Hydrochloride Injection (see WARNINGS).

### Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of use of Methadone Hydrochloride Injection during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. The balance between the risks of NOWS and the benefits of maternal Methadone Hydrochloride Injection use may differ based on the risks associated with the mother's underlying condition, pain, or addiction. Advise the patient of the risk of NOWS so that appropriate planning for management of the neonate can occur (see WARNINGS).

### Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The concomitant use of Methadone Hydrochloride Injection with all cytochrome P450 3A4, 2B6, 2C19, 2C9 or 2D6 inhibitors may result in an increase in methadone plasma concentrations, which could cause potentially fatal respiratory depression. In addition, discontinuation of concomitantly used cytochrome P450 3A4 2B6, 2C19, or 2C9 inducers may also result in an increase in methadone plasma concentration. Follow patients closely for respiratory depression and sedation, and consider dosage reduction with any changes of concomitant medications that result in an increase in methadone levels (see WARNINGS, PRECAUTIONS: Drug 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 WARNINGS, PRECAUTIONS: Drug Interactions).

- Reserve concomitant prescribing of Methadone Hydrochloride Injection 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.

**Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction**

For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration (see INDICATIONS AND USAGE).

## DESCRIPTION

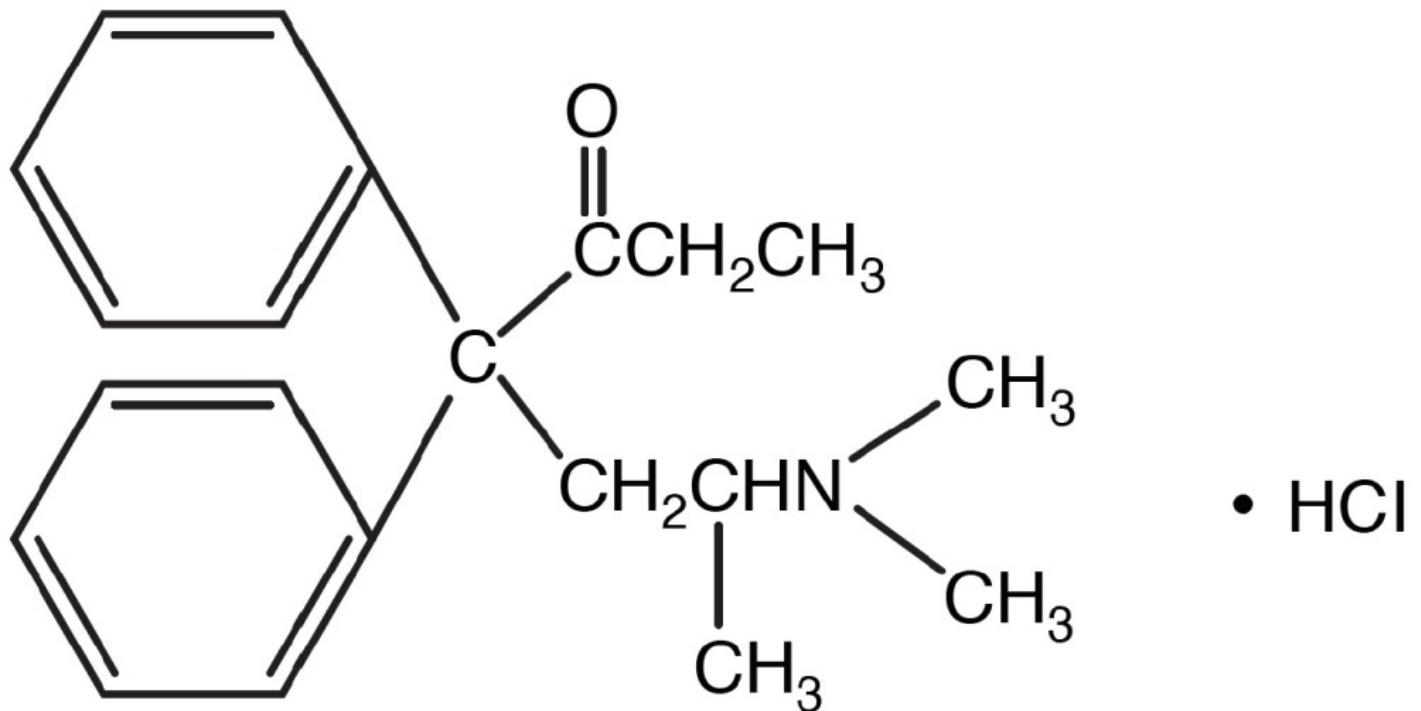
Methadone Hydrochloride Injection, USP, 10 mg/mL is an opioid analgesic.

Each milliliter of Methadone Hydrochloride Injection contains 10 mg (0.029 mmol) of methadone hydrochloride, equivalent to 8.95 mg of methadone free base.

Methadone hydrochloride is a white, crystalline material that is water-soluble.

Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride. Its molecular formula is  $C_{21}H_{27}NO \cdot HCl$  and it has a molecular weight of 345.91. Methadone hydrochloride has a melting point of  $235^{\circ}C$ , and a pKa of 8.25 in water at  $20^{\circ}C$ . Its octanol/water partition coefficient at pH 7.4 is 117. A solution (1:100) in water has a pH between 4.5 and 6.5.

It has the following structural formula:



Methadone Hydrochloride Injection is a sterile injectable solution containing the following inactive ingredients: chlorobutanol, 0.5%, as a preservative, sodium chloride, and water for injection, USP. The pH of the sterile injectable solution may have been adjusted during manufacturing with sodium hydroxide and/or hydrochloric acid.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Methadone hydrochloride is a mu agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also 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.

## **Pharmacodynamics**

### Effects on the Central Nervous System

Methadone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Methadone 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Some NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

### Effects on the 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 is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

### Effects on the Cardiovascular System

Methadone produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

### Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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.

### Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

### Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of methadone for any individual patient may increase over time due to an increase in pain,

the development of a new pain syndrome, and/or the development of analgesic tolerance.

### Concentration–Adverse Reaction Relationships

There is a relationship between increasing methadone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

## **Pharmacokinetics**

### Absorption

Methadone Hydrochloride Injection is intended for parenteral (intravenous, subcutaneous and intramuscular) administration. Methadone pharmacokinetics following subcutaneous and intramuscular administration have not been systematically studied and differences among the various parenteral routes have not been well characterized. As with many drugs, absorption into the systemic circulation may vary with subcutaneous and intramuscular administration.

### Distribution

Methadone is a lipophilic drug and the steady state volume of distribution ranges between 2 L/kg to 6 L/kg. In plasma, methadone is predominantly bound to  $\alpha_1$ -acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

### Elimination

#### *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, CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.

#### *Excretion*

Elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. After single intravenous dose administration the plasma clearance of methadone ranged between 3 L/h to 10 L/h and the terminal half-life ( $t_{1/2}$ ) ranged between 8 to 59 hours. Methadone has been known to persist in the liver and other tissues. Slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

### Specific Populations

#### *Use During Pregnancy*

There are no pharmacokinetic studies of parenteral methadone in pregnancy. The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (see **DOSAGE AND ADMINISTRATION**).

#### *Hepatic Impairment*

Methadone pharmacokinetics have 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 Impairment*

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unchanged methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa = 9.2) compound and the luminal pH of the urinary tract can affect its extraction from plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing methadone or metabolite elimination.

#### *Sex*

The pharmacokinetics of methadone have not been evaluated for sex specificity.

#### *Race*

The pharmacokinetics of methadone have not been evaluated for race specificity.

#### *Age*

##### Geriatric Population:

The pharmacokinetics of methadone have not been evaluated in geriatric population.

##### Pediatric Population:

The pharmacokinetics of methadone have not been evaluated in pediatric population.

### **Drug Interaction Studies**

#### Cytochrome P450 Interactions

Methadone undergoes hepatic N-demethylation by cytochrome P450 (CYP) isoforms, principally CYP3A4, CYP2B6, CYP2C19, CYP2C9 and CYP2D6. Co-administration of methadone with CYP inducers may result in more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to CYP induction activity (see **PRECAUTIONS: Drug Interactions**).

#### Cytochrome P450 Inducers

The following drug interactions were reported following co-administration of methadone with known inducers of cytochrome P450 enzymes:

##### *Rifampin:*

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

##### *Phenytoin:*

In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg twice daily initially for 1 day followed by 300 mg daily for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

##### *St. John's Wort, Phenobarbital, Carbamazepine:*

Administration of methadone with other CYP3A4 inducers may result in withdrawal symptoms.

#### Cytochrome P450 Inhibitors

##### *Voriconazole:*

Voriconazole can inhibit the activity of CYP3A4, CYP2C9, and CYP2C19. Repeat dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for

4 days) increased the peak plasma concentration ( $C_{max}$ ) and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 mg to 100 mg daily). The  $C_{max}$  and AUC of (S)-methadone increased by 65% and 103%, respectively. 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 co-administration. Dose reduction of methadone may be needed (see **PRECAUTIONS: Drug Interactions**).

### Antiretroviral Drugs

Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to CYP induction activity.

*Abacavir, amprenavir, darunavir+ritonavir, efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, lopinavir+ritonavir, saquinavir+ritonavir, tipranvir+ritonavir combination:*

Co-administration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone (see **PRECAUTIONS: Drug Interactions**).

#### *Didanosine and Stavudine:*

Methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered (see **PRECAUTIONS: Drug Interactions**).

#### *Zidovudine:*

Methadone increased the AUC of zidovudine which could result in toxic effects (see **PRECAUTIONS: Drug Interactions**).

### **Pharmacokinetics in Special Populations**

#### *Pregnancy*

There are no pharmacokinetic studies of parenteral methadone in pregnancy. The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (see **DOSAGE AND ADMINISTRATION**).

### **INDICATIONS AND USAGE**

1. For the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate.

#### Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (see **WARNINGS: Addiction, Abuse, and Misuse**) reserve Methadone Hydrochloride Injection for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

2. For use in temporary treatment of opioid dependence in patients unable to take oral medication.

#### Limitations of Use

- Injectable methadone products are not approved for the outpatient treatment of opioid dependence. In this patient population, parenteral methadone is to be used only for patients unable to take oral medication, such as hospitalized patients.

## **Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction**

Code of Federal Regulations, Title 42, Sec 8.

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment: During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.

During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07(b)).

## **CONTRAINDICATIONS**

Methadone Hydrochloride Injection is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity to methadone hydrochloride (e.g. anaphylaxis) or any other ingredient in Methadone Hydrochloride Injection.

## **WARNINGS**

### **Addiction, Abuse and Misuse**

Methadone Hydrochloride Injection contains methadone, a Schedule II controlled substance. As an opioid, Methadone Hydrochloride Injection exposes users to the risks of addiction, abuse, and misuse.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Methadone Hydrochloride Injection. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Methadone Hydrochloride Injection, and monitor all patients receiving Methadone Hydrochloride Injection for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of Methadone Hydrochloride Injection for the proper management of pain in any given patient. Patients at increased



risk may be prescribed opioids such as Methadone Hydrochloride Injection, but use in such patients necessitates intensive counseling about the risks and proper use of Methadone Hydrochloride Injection along with the intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Methadone Hydrochloride Injection. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

### **Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory depression and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO<sub>2</sub>) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Methadone Hydrochloride Injection, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of Methadone Hydrochloride Injection.

To reduce the risk of respiratory depression, proper dosing and titration of Methadone Hydrochloride Injection are essential. Overestimating the Methadone Hydrochloride Injection dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

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

Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, in the short-term use setting. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

### **Life-Threatening QT Prolongation**

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. In most patients on the lower doses typically used for maintenance, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients. The effects of methadone on the QT interval have been confirmed in *in vivo* laboratory studies, and methadone has been shown to inhibit cardiac potassium channels in *in vitro* studies.

Closely monitor patients with risk factors for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia and hypomagnesemia), a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone.

Evaluate patients developing QT prolongation while on methadone treatment for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs that might cause electrolyte abnormalities, and drugs that might act as inhibitors of methadone metabolism.

Only initiate methadone hydrochloride tablets therapy for pain in patients for whom the anticipated benefit outweighs the risk of QT prolongation and development of dysrhythmias that have been reported with high doses of methadone.

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

### **Neonatal Opioid Withdrawal Syndrome**

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Advise the patient of the risk of NOWS so that appropriate planning for management of the neonate can occur. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly (see **PRECAUTIONS: Pregnancy**).

The balance between the risks of NOWS and the benefits of maternal Methadone Hydrochloride Injection use may differ based on the risks associated with the mother's underlying condition, pain or addiction, and the risks of the alternative treatments.

- For management of pain, prescribers should discuss all available treatment options with females of reproductive potential, including non-opioid and non-pharmacologic options.
- Untreated opioid addiction often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. NOWS can result from in utero exposure to opioids regardless of the source. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

### **Risks of Concomitant Use of Cytochrome P450 3A4, 2B6, 2C19, 2C9, or 2D6 Inhibitors or Discontinuation P450 3A4, 2B6, 2C19, or 2C9 Inducers**

Concomitant use of Methadone Hydrochloride Injection with CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors, may increase plasma concentrations of methadone, prolong opioid adverse reactions, and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Methadone Hydrochloride Injection is achieved. Similarly, discontinuation of concomitant CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers in Methadone Hydrochloride Injection-treated patients may increase methadone plasma concentrations resulting in fatal respiratory depression. Consider dosage reduction of Methadone Hydrochloride Injection when using concomitant CYP3A4, CYP2B6, CYP2C19, CYP2C9 or CYP2D6 inhibitors or discontinuing CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers in methadone-treated patients, and follow patients closely at frequent intervals for signs and symptoms of respiratory depression and sedation.

Addition of CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuation of a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors in patients treated with Methadone Hydrochloride Injection may decrease methadone plasma concentrations, reducing efficacy and may lead to opioid withdrawal symptoms in patients physically dependent on methadone. When using Methadone Hydrochloride Injection with CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuing

CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors, follow patients for signs or symptoms of opioid withdrawal and consider increasing the Methadone Hydrochloride Injection dosage as needed.

### **Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Methadone Hydrochloride Injection with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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 **PRECAUTIONS: Drug Interactions**).

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 Methadone Hydrochloride Injection 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 **PRECAUTIONS: Drug Interactions, Information for Patients**).

### **Serotonin Syndrome with Concomitant Use of Serotonergic Drugs**

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of methadone with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see **PRECAUTIONS: Drug Interactions**). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Methadone Hydrochloride Injection if serotonin syndrome is suspected.

### **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.

### **Severe Hypotension**

Methadone Hydrochloride Injection may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Methadone Hydrochloride Injection. In patients with circulatory shock, Methadone Hydrochloride Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Methadone Hydrochloride Injection in patients with circulatory shock.

### **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Methadone Hydrochloride Injection may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Methadone Hydrochloride Injection.

Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of Methadone Hydrochloride Injection in patients with impaired consciousness or coma.

### **Risks of Use in Patients with Gastrointestinal Conditions**

Methadone Hydrochloride Injection is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The methadone in Methadone Hydrochloride Injection may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

### **Increased Risk of Seizures in Patients with Seizure Disorders**

The methadone in Methadone Hydrochloride Injection may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Methadone Hydrochloride Injection therapy.

### **Withdrawal**

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist, including Methadone Hydrochloride Injection. In these patients, mixed agonists/antagonist and partial agonist

analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms (see **PRECAUTIONS: Drug Interactions**).

When discontinuing Methadone Hydrochloride Injection, gradually taper the dosage (see **DOSAGE AND ADMINISTRATION**). Do not abruptly discontinue Methadone Hydrochloride Injection (see **DRUG ABUSE AND DEPENDENCE**).

### **Risks Driving and Operating Machinery**

Methadone Hydrochloride Injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Methadone Hydrochloride Injection and know how they will react to the medication (see **PRECAUTIONS: Information for Patients**).

## **PRECAUTIONS**

### **General**

Methadone given on a fixed-dose schedule may have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of cardiac conduction abnormalities, respiratory depression, altered mental states and postural hypotension. Methadone Hydrochloride Injection should be used with caution in elderly and debilitated patients; 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.

Selection of patients for treatment with methadone should be governed by the same principles that apply to the use of other parenteral opioids (see **INDICATIONS AND USAGE**). Physicians should individualize treatment in every case (see **DOSAGE AND ADMINISTRATION**), taking into account the high degree of interpatient variability in response to and metabolism of methadone.

### **Information for Patients**

#### Addiction, Abuse, and Misuse

Inform patients that the use of Methadone Hydrochloride Injection, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death (see **WARNINGS**). Instruct patients not to share Methadone Hydrochloride Injection with others and to take steps to protect Methadone Hydrochloride Injection from theft or misuse.

#### Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting Methadone Hydrochloride Injection or when the dosage is increased, and that it can occur even at recommended dosages (see **WARNINGS**). Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

#### Symptoms of Arrhythmia

Instruct patients to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, near syncope, or syncope) when taking methadone (see **WARNINGS**).

#### Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if Methadone Hydrochloride Injection are used with benzodiazepines or other CNS depressants, including alcohol,

and not to use these concomitantly unless supervised by a health care provider (see **WARNINGS, PRECAUTIONS: Drug Interactions**).

#### Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications (see **WARNINGS, PRECAUTIONS: Drug Interactions**).

#### MAOI Interaction

Inform patients to avoid taking Methadone Hydrochloride Injection while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking Methadone Hydrochloride Injection (see **PRECAUTIONS: Drug Interactions**).

#### Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms (see **WARNINGS**).

#### Hypotension

Inform patients that Methadone Hydrochloride Injection may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) (see **WARNINGS**).

#### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained Methadone Hydrochloride Injection. Advise patients how to recognize such a reaction and when to seek medical attention (see **CONTRAINDICATIONS, ADVERSE REACTIONS**).

#### Pregnancy

##### *Neonatal Opioid Withdrawal Syndrome*

Advise women that if they are pregnant while being treated with Methadone Hydrochloride Injection, the baby may have signs of withdrawal at birth and that withdrawal is treatable (see **BOXED WARNING, WARNINGS: Neonatal Opioid Withdrawal Syndrome, PRECAUTIONS: Pregnancy**).

##### *Embryo-Fetal Toxicity*

Inform female patients of reproductive potential that Methadone Hydrochloride Injection can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy (see **PRECAUTIONS: Pregnancy**).

#### Lactation

Instruct nursing mothers using Methadone Hydrochloride Injection to watch for signs of methadone toxicity in their infants, which include increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's healthcare provider immediately if they notice these signs. If they cannot reach the healthcare provider right away, instruct them to take the baby to the emergency room or call 911 (or local emergency services) (see **PRECAUTIONS: Lactation**).

#### Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible (see **PRECAUTIONS: Females and Males of Reproductive Potential**).

#### Driving or Operating Heavy Machinery

Inform patients that Methadone Hydrochloride Injection may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication (see **WARNINGS**).

#### Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention (see **CLINICAL PHARMACOLOGY: Pharmacodynamics, ADVERSE REACTIONS**).

### Drug Interactions

<b>Inhibitors of CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6</b>	
<i>Clinical Impact:</i>	<p>Methadone undergoes hepatic N-demethylation by several cytochrome P450 (CYP) isoforms, including CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6. The concomitant use of Methadone Hydrochloride Injection and CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors can increase the plasma concentration of methadone, resulting in increased or prolonged opioid effects, and may result in a fatal overdose, particularly when an inhibitor is added after a stable dose of Methadone Hydrochloride Injection is achieved. These effects may be more pronounced with concomitant use of drugs that inhibit more than one of the CYP enzymes listed above.</p> <p>After stopping a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor, as the effects of the inhibitor decline, the methadone plasma concentration can decrease (see <b>CLINICAL PHARMACOLOGY</b>), resulting in decreased opioid efficacy or withdrawal symptoms in patients physically dependent on methadone.</p>
<i>Intervention:</i>	<p>If concomitant use is necessary, consider dosage reduction of Methadone Hydrochloride Injection until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor is discontinued, follow patients for signs of opioid withdrawal and consider increasing the Methadone Hydrochloride Injection dosage until stable drug effects are achieved.</p>
<i>Examples:</i>	<p>Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), fluconazole, fluvoxamine, some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine)</p>
<b>Inducers of CYP3A4, CYP2B6, CYP2C19, or CYP2C9</b>	
<i>Clinical Impact:</i>	<p>The concomitant use of Methadone Hydrochloride Injection and CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers can decrease the plasma concentration of methadone (see <b>CLINICAL PHARMACOLOGY</b>), resulting in decreased efficacy or onset of withdrawal symptoms in patients physically dependent on methadone. These effects could be more pronounced with concomitant use of drugs that can induce multiple CYP enzymes.</p> <p>After stopping a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer, as the effects of the inducer decline, the methadone plasma concentration can increase (see <b>CLINICAL PHARMACOLOGY</b>), which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, sedation, or death.</p>

<i>Intervention:</i>	If concomitant use is necessary, consider increasing the Methadone Hydrochloride Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer is discontinued, consider Methadone Hydrochloride Injection dosage reduction and monitor for signs of respiratory depression and sedation.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin, St. John's Wort, Phenobarbital
<b>Benzodiazepines and other Central Nervous System (CNS) Depressants</b>	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	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 <b>WARNINGS, PRECAUTIONS</b> ).
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
<b>Potentially Arrhythmogenic Agents</b>	
<i>Clinical Impact:</i>	Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents or drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia).
<i>Intervention:</i>	Monitor patients closely for cardiac conduction changes.
<i>Examples:</i>	<u>Drugs known to have potential to prolong QT interval:</u> Class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. <u>Drugs capable of inducing electrolyte disturbances:</u> Diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.
<b>Serotonergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome (see <b>WARNINGS, PRECAUTIONS</b> ).
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Methadone Hydrochloride Injection if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT <sub>3</sub> receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
<b>Monoamine Oxidase Inhibitors (MAOIs)</b>	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome (see <b>PRECAUTIONS</b> ) or opioid toxicity (e.g., respiratory depression, coma) (see <b>PRECAUTIONS</b> ).
<i>Intervention:</i>	The use of Methadone Hydrochloride Injection is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<b>Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics</b>	
<i>Clinical Impact:</i>	May reduce the analgesic effect of Methadone Hydrochloride Injection and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine



<b>Muscle Relaxants</b>	
<i>Clinical Impact:</i>	Methadone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Methadone Hydrochloride Injection and/or the muscle relaxant as necessary.
<b>Diuretics</b>	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
<b>Anticholinergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when Methadone Hydrochloride Injection is used concomitantly with anticholinergic drugs.

### Anti-Retroviral Agents

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

*Efavirenz:* Co-administration of efavirenz in HIV-infected methadone-maintenance patients has resulted in decreased methadone plasma concentrations of methadone 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 ritonavir alone or ritonavir/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.

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

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

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 (HDD). However, this finding was not seen in mice consuming 60 mg/kg/day (approximately 2.5 times

the HDD). 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, the HDD).

### Mutagenesis

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.

### Impairment of Fertility

Published animal studies show that methadone treatment of males can alter reproductive function. Methadone produces decreased sexual activity (mating) of male rats at 10 mg/kg/day (corresponding to 0.3 times the human daily oral dose of 120 mg/day based on body surface area). Methadone also produces a significant regression of sex accessory organs and testes of male mice and rats at 0.2 and 0.8 times the HDD, respectively. Decreased serum levels of testosterone were observed in male rats that were treated with methadone (1.3 mg/kg/day to 3.3 mg/kg/day for 14 days, corresponding to 0.1 to 0.3 times the HDD) or 10 mg/kg/day to 15 mg/kg/day for 10 days (0.8 to 1.2 times the HDD).

### **Pregnancy**

#### Risk Summary

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy (see **WARNINGS**). There are no adequate and well controlled studies in pregnant women.

Pregnant women in methadone maintenance programs may have reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes and risk of continued or relapsing illicit opioid use. These risks should be considered in women treated with Methadone Hydrochloride Injection for maintenance treatment of opioid addiction.

For women treated with Methadone Hydrochloride Injection for pain severe enough to require an opioid analgesic, Methadone Hydrochloride Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) in the hamster at doses 2 times the human daily oral dose of 120 mg/day on a mg/m<sup>2</sup> basis (HDD) and in mice at doses equivalent to the HDD. Administration of methadone to pregnant animals during organogenesis and through lactation resulted decreased litter size, increased pup mortality, decreased pup body weights, developmental delays, and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD. Administration of methadone to male rodents prior to mating with untreated females resulted in increased neonatal mortality and significant differences in behavioral tests in the offspring at exposures comparable to and less than the HDD (see **Data**).

Based on animal data, advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## Clinical Considerations

### *Disease-associated Maternal and Embryo-fetal risk*

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

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

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

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

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

### *Fetal/Neonatal Adverse Reactions*

Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with Methadone Hydrochloride Injection.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly (see **BOXED WARNING, WARNINGS: Neonatal Opioid Withdrawal Syndrome**).

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

Abnormal fetal non-stress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 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 behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociception responses and sensitivity to other drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including the cholinergic, dopaminergic, noradrenergic and serotonergic systems.

### Clinical Pharmacology for Pregnancy

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

### Labor and Delivery

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

### Data

#### *Animal Data*

Formal reproductive and developmental toxicology studies for methadone have not been conducted. Exposure margins for the following published study reports are based on a human daily dose (HDD) of 120 mg methadone using a body surface area comparison.

In a published study in pregnant hamsters, a single subcutaneous dose of methadone ranging from 31 mg/kg (2 times the HDD) to 185 mg/kg on Gestation Day 8 resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting neural tube defects including exencephaly, cranioschisis, and “various other lesions.” The majority of the doses tested also resulted in maternal death. In a study in pregnant mice, a single subcutaneous dose of 22 mg/kg to 24 mg/kg methadone (approximately equivalent to the HDD) administered on Gestation Day 9 produced exencephaly in 11% of the embryos. In another study in pregnant mice, subcutaneous doses up to 28 mg/kg/day methadone (equivalent to the HDD) administered from Gestation Day 6 to 15 resulted in no malformations, but there were increased postimplantation loss and decreased live fetuses at 10 mg/kg/day or greater (0.4 times the HDD) and decreased ossification and fetal body weight at 20 mg/kg/day or greater (0.8 times the HDD). In a second study of pregnant mice dosed with subcutaneous doses up to 28 mg/kg/day methadone from Gestation Day 6 to 15, there was decreased pup viability, delayed onset of development of negative phototaxis and eye opening, increased righting reflexes at 5 mg/kg/day or greater (0.2 times the HDD), and decreased number of live pups at birth and decreased pup weight gain at 20 mg/kg/day or greater (0.8 times the HDD). No effects were reported in a study of pregnant rats and rabbits at oral doses up to 40 mg/kg (3 and 6 times, respectively, the HDD) administered from Gestation Days 6 to 15 and 6 to 18, respectively.

When pregnant rats were treated with intraperitoneal doses of 2.5 mg/kg, 5 mg/kg, or 7.5 mg/kg methadone from one week prior to mating, through gestation until the end of lactation period, 5 mg/kg or greater (0.4 times the HDD) methadone resulted in decreases in litter size and live pups born and 7.5 mg/kg (0.6 times the HDD) resulted in decreased birth weights. Furthermore, decreased pup viability and pup body weight gain at 2.5 mg/kg or greater (0.2 times the HDD) were noted during the preweaning period.

Additional animal data demonstrates evidence for neurochemical changes in the brains of offspring from

methadone-treated pregnant rats, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems at doses below the HDD. Other animal studies have reported that prenatal and/or postnatal exposure to opioids including methadone alters neuronal development and behavior in the offspring including alterations in learning ability, motor activity, thermal regulation, nociceptive responses, and sensitivity to drugs at doses below the HDD. Treatment of pregnant rats subcutaneously with 5 mg/kg methadone from Gestation Day 14 to 19 (0.4 times the HDD) reduced fetal blood testosterone and androstenedione in males.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone at doses comparable to and less than the HDD for 1 to 12 days before and/or during mating (with more pronounced effects in the first 4 days). In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Examination of uterine contents of methadone-naïve female mice bred to methadone-treated male mice (once a day for three consecutive days) indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states at 1 mg/kg/day or greater (0.04 times the HDD). Chromosome analysis revealed a dose-dependent increase in the frequency of chromosomal abnormalities at 1 mg/kg/day or greater.

Studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of “paternal” methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

## **Lactation**

### Risk Summary

Based on two studies in 22 breastfeeding women maintained on methadone treatment, methadone was present in low levels in human milk, and did not show adverse reactions in breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for methadone and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

### Clinical Considerations

Advise breastfeeding women taking methadone to monitor the infant for increased drowsiness and breathing difficulties.

### Data

In a study of ten breastfeeding women maintained on oral methadone doses of 10 mg/day to 80 mg/day, methadone concentrations from 50 mcg/L to 570 mcg/L in milk were reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state.

In a study of twelve breastfeeding women maintained on oral methadone doses of 20 mg/day to 80 mg/day, methadone concentrations from 39 mcg/L to 232 mcg/L in milk were reported. Based on an

average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day which is approximately 2% to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone.

There have been rare cases of sedation and respiratory depression in infants exposed to methadone through breast milk.

## **Females and Males of Reproductive Potential**

### Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (see **ADVERSE REACTIONS**).

Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported.

### **Pediatric Use**

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

### **Geriatric Use**

Clinical studies of Methadone Hydrochloride Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Elderly patients (aged 65 years or older) may have increased sensitivity to methadone. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Methadone Hydrochloride Injection slowly in geriatric patients and monitor closely for signs of respiratory depression (see **WARNINGS, PRECAUTIONS**).

Methadone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

### **Hepatic Impairment**

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways; therefore patients with liver impairment may be at risk of increased systemic exposure to methadone after multiple dosing. Start these patients on lower doses and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression.

### **Renal Impairment**

The use of methadone has not been extensively evaluated in patients with renal insufficiency. Since unmetabolized methadone and its metabolites are excreted in urine to a variable degree, start these patients on lower doses and with longer dosing intervals and titrate slowly while carefully monitoring

for signs of respiratory and central nervous system depression.

## **ADVERSE REACTIONS**

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse (see **WARNINGS**)
- Life Threatening Respiratory Depression (see **WARNINGS**)
- QT Prolongation (see **WARNINGS**)
- Neonatal Opioid Withdrawal Syndrome (see **WARNINGS**)
- Interactions with CNS Depressants (see **WARNINGS**)
- Serotonin Syndrome (see **WARNINGS**)
- Adrenal Insufficiency (see **WARNINGS**)
- Severe Hypotension (see **WARNINGS**)
- Gastrointestinal Adverse Reactions (see **WARNINGS**)
- Seizures (see **WARNINGS**)
- Withdrawal (see **WARNINGS**)

The following adverse reactions associated with the use of methadone were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses of methadone are advisable. Other adverse reactions that have been reported in patients (including opioid addicts taking methadone for detoxification or maintenance) receiving methadone include the following:

Body as a Whole: asthenia (weakness), edema, headache

Cardiovascular: Arrhythmias, bigeminal rhythms, bradycardia, extrasystoles, tachycardia, Torsade de Pointes, ventricular fibrillation, ventricular tachycardia. ECG abnormalities, prolonged QT interval, T-wave inversion, cardiomyopathy, flushing, heart failure, hypotension, palpitations, phlebitis, syncope

Digestive: Abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic and Lymphatic: Reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis.

Metabolic and Nutritional: Hypokalemia, hypomagnesemia, weight gain

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

Respiratory: Pulmonary edema

Skin and Appendages: Intramuscular and Subcutaneous: Local tissue reactions (pain, erythema, swelling), particularly with continuous subcutaneous infusion

Intravenous: Pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses: Visual disturbances

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

Serotonin Syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Methadone Hydrochloride Injection.

Androgen Deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.

## **DRUG ABUSE AND DEPENDENCE**

### **CONTROLLED SUBSTANCE**

Methadone Hydrochloride Injection contains methadone, a Schedule II controlled substance.

#### **Abuse**

Methadone Hydrochloride Injection contains methadone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. Methadone Hydrochloride Injection can be abused and is subject to misuse, addiction, and criminal diversion.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional, non-therapeutic use of prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal.

“Drug seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of the office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating health care providers. “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addictions. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Methadone Hydrochloride Injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity and frequency, as required by state and federal law, is strongly advised.

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

#### **Dependence**



Both tolerance and physical dependence can develop during chronic therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Methadone Hydrochloride Injection should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION**). If Methadone Hydrochloride Injection is abruptly discontinued in a physically-dependent patient, an abstinence withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy (see **BOXED WARNING, WARNINGS: Neonatal Opioid Withdrawal Syndrome, PRECAUTIONS: Pregnancy**).

## **OVERDOSAGE**

### **Clinical Presentation**

Acute overdose with Methadone Hydrochloride Injection can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

### **Treatment of Overdose**

In the case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to methadone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to methadone overdose.

The physician must remember that methadone is a long-acting depressant (36 to 48 hours), whereas the antagonists act for much shorter periods (one to three hours). Because the duration of opioid reversal is expected to be less than the duration of action of methadone in Methadone Hydrochloride Injection, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent

patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

## **DOSAGE AND ADMINISTRATION**

### **Important General Information**

Consider the following important factors that differentiate methadone from other opioids:

- The peak respiratory depressant effect of methadone occurs later and persists longer than its peak pharmacologic effect.
- A high degree of opioid tolerance does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other opioid agonists.
- There is high interpatient variability in absorption, metabolism, and relative analgesic potency. Population-based conversion ratios between methadone and other opioids are not accurate when applied to individuals.
- With repeated dosing, methadone is retained in the liver and then slowly released, prolonging the duration of potential toxicity.
- Steady-state plasma concentrations are not attained until 3 to 5 days after initiation of dosing.
- Methadone has a narrow therapeutic index, especially when combined with other drugs.

### **Methadone Hydrochloride Injection for Management of Pain**

Methadone Hydrochloride Injection should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Consider the following important factors that differentiate methadone from other opioid analgesics:

- There is high interpatient variability in absorption, metabolism, and relative analgesic potency. Population-based equianalgesic conversion ratios between methadone and other opioids are not accurate when applied to individuals.
- The duration of analgesic action of methadone is 4 to 8 hours (based on single-dose studies) but the plasma elimination half-life is 8 to 59 hours.
- With repeated dosing, the potency of methadone increases due to systemic accumulation.
- Steady-state plasma concentrations, and full analgesic effects, are not attained until at least 3 to 5 days on a dose, and may take longer in some patients.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (see **WARNINGS**).

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Methadone Hydrochloride Injection and adjust the dosage accordingly (see **WARNINGS**).

Methadone Hydrochloride Injection may be administered intravenously, subcutaneously or intramuscularly. The absorption of subcutaneous and intramuscular methadone has not been well characterized and appears to be unpredictable. Local tissue reactions may occur.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### Initiation of Therapy in Opioid Non-Tolerant Patients

When parenteral methadone is used as the first analgesic in patients who are not already being treated with, and tolerant to, opioids, the usual intravenous methadone starting dose is 2.5 mg to 10 mg every 8 to 12 hours, slowly titrated to effect. More frequent administration may be required during methadone initiation in order to maintain adequate analgesia, and extreme caution is necessary to avoid overdose, taking into account methadone's long elimination half-life.

### Conversion from Oral Methadone to Parenteral Methadone

Conversion from oral methadone to parenteral methadone should initially use a 2:1 dose ratio (e.g., 10 mg oral methadone to 5 mg parenteral methadone).

### Switching Patients to Parenteral Methadone from Other Chronic Opioids

Switching a patient from another chronically administered opioid to methadone requires caution due to the uncertainty of dose conversion ratios and incomplete cross-tolerance. Deaths have occurred in opioid tolerant patients during conversion to methadone.

The potency of methadone relative to other opioid analgesics is nonlinear and increases with increasing dose. Table 1 provides an estimated conversion factor for use when converting patients from another opioid to methadone. Because of the high inter-patient variability in absorption, metabolism, and relative potency, it is critical to avoid overestimating the methadone dose which can lead to fatal respiratory depression. It is safer to underestimate a patient's 24-hour methadone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour methadone dosage and manage an adverse reaction due to an overdose. The dose conversion scheme below is derived from various consensus guidelines for converting chronic pain patients to methadone from morphine. The guidelines used to construct this table, however, were all designed for converting patients from oral morphine to oral methadone. The third column assumes a 2:1 ratio for converting from oral to intravenous methadone. Clinicians should consult published conversion guidelines to determine the equivalent morphine dose for patients converting from other opioids.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** another oral opioid analgesic **to** methadone hydrochloride tablets.
- The table **cannot** be used to convert **from** methadone hydrochloride tablets **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

**Table 1. Oral Morphine to Intravenous Methadone Conversion for Chronic Administration**

<b>Total Daily Baseline Oral Morphine Dose</b>	<b>Estimated Daily Oral Methadone Requirement as Percent of Total Daily Morphine Dose</b>	<b>Estimated Daily Intravenous Methadone as Percent of Total Daily Oral Morphine Dose*</b>
< 100 mg	20% to 30%	10% to 15%
100 to 300 mg	10% to 20%	5% to 10%
300 to 600 mg	8% to 12%	4% to 6%
600 mg to 1,000 mg	5% to 10%	3% to 5%
> 1,000 mg	< 5%	< 3%

\* The total daily methadone dose derived from the table above may then be divided to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).

**Table 2. Parenteral Morphine to Intravenous Methadone Conversion for Chronic Administration (Derived from Table 1, Assuming a 3:1 Oral:Parenteral Morphine Ratio)**

<b>Total Daily Baseline Parenteral Morphine Dose</b>	<b>Estimated Daily Parenteral Methadone Requirement as Percent of Total Daily Morphine Dose*</b>
10 mg to 30 mg	40% to 66%
30 mg to 50 mg	27% to 66%
50 mg to 100 mg	22% to 50%
100 mg to 200 mg	15% to 34%
200 mg to 500 mg	10% to 20%

\* The total daily methadone dose derived from the table above may then be divided to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).

*Note:* Equianalgesic methadone dosing varies not only between patients, but also within the same patient, depending on baseline morphine (or other opioid) dose. Tables 1 and 2 have been included in order to illustrate this concept and to provide a safe starting point for opioid conversion. Methadone dosing should not be based solely on these tables. Methadone conversion and dose titration methods should always be individualized to account for the patient’s prior opioid exposure, general medical condition, concomitant medication, and anticipated breakthrough medication use. The endpoint of titration is achievement of adequate pain relief, balanced against tolerability of opioid side effects. If a patient develops intolerable opioid related side effects, the methadone dose, or dosing interval, may need to be decreased.

## **Methadone Hydrochloride Injection for Treatment of Opioid Dependence**

### Detoxification and Maintenance Treatment of Opioid Dependence

For detoxification and maintenance of opiate dependence, methadone should be administered in accordance with the treatment standards cited in 42CFR Section 8.12, including limitations on unsupervised administration. Injectable methadone products are not approved for the outpatient treatment of opioid dependence. Parenteral methadone should be used only for patients who are unable to take oral medication, such as during hospitalization. The patient’s oral methadone dose should be converted to an equivalent parenteral dose using the considerations above.

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

Abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms (see **PRECAUTIONS**). Presentation of these symptoms has been associated with an increased risk of susceptible patients to relapse to illicit drug use and should be considered when assessing the risks and benefit of methadone use.

### Considerations for Management of Acute Pain During Methadone Maintenance Treatment

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

## Dosage Adjustment During Pregnancy

Methadone clearance may be increased during pregnancy. Several small studies have demonstrated significantly lower trough methadone plasma concentrations and shorter methadone half-lives in women during their pregnancy compared to after their delivery. During pregnancy a woman's methadone dose may need to be increased, or their dosing interval decreased. Methadone should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

## **HOW SUPPLIED**

Methadone Hydrochloride Injection USP, 200 mg/20 mL (10 mg/mL) is available in:

NDC 17478-380-20                      20 mL Multi-dose Vials: One vial per carton

**Storage:** Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

**Protect from light. Store in carton until contents have been used.**

Manufactured by: **Akorn, Inc.**

Lake Forest, IL 60045

MH00N Rev. 04/19

Principal Display Panel Text for Container Label:

NDC 17478-380-20

Methadone HCl

Injection, USP CII

200 mg/20 mL


(10 mg/mL)

For Parenteral Use

20 mL Multi-dose Vial

Rx only

The image shows a rectangular label with rounded corners and a red border. On the left side, it lists the NDC number (17478-380-20), the product name (Methadone HCl Injection, USP), and the concentration (200 mg/20 mL, 10 mg/mL) in a green box. Below this, it specifies 'For Parenteral Use', '20 mL Multi-dose Vial', and 'Rx only'. A stylized 'II' logo is positioned to the right of the product name. The right side of the label contains detailed information: 'Each mL contains:' followed by 'Active: Methadone Hydrochloride, 10 mg.' and 'Preservative: Chlorobutanol (chloroform derivative) 0.5%.' It also includes 'Storage' instructions, 'Usual Dosage' information, and a warning to 'Protect from light' and 'Store in carton until contents have been used.' At the bottom right, it lists the manufacturer 'Mfd. by: Akorn, Inc., Lake Forest, IL 60045' and the revision date 'MHAAL Rev. 09/15'. A barcode is located on the right side of the label, with the number '(01)00317478380207' printed vertically next to it. At the bottom right corner, the words 'LOT' and 'EXP.' are printed vertically.

NDC 17478-380-20  
**Methadone HCl Injection, USP**   
200 mg/20 mL  
(10 mg/mL)  
For Parenteral Use  
20 mL Multi-dose Vial  
Rx only

Each mL contains:  
**Active:** Methadone Hydrochloride, 10 mg.  
**Preservative:** Chlorobutanol (chloroform derivative) 0.5%.  
**Storage:** Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].  
**Usual Dosage:** See package insert for dosage information.  
**Protect from light.**  
**Store in carton until contents have been used.**

Mfd. by: Akorn, Inc.  
Lake Forest, IL 60045

MHAAL Rev. 09/15

(01)00317478380207

LOT  
EXP.

Principal Display Panel Text for Carton Label:

NDC 17478-380-20

Methadone

Hydrochloride

Injection, USP CII

200 mg/20 mL

(10 mg/mL)

For Parenteral Use

One 20 mL Multi-dose Vial

Rx only Akorn logo



## METHADONE HYDROCHLORIDE

methadone hydrochloride injection, solution

### Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:17478-380

<b>Route of Administration</b>	INTRAMUSCULAR, INTRAVENOUS, SUBCUTANEOUS	<b>DEA Schedule</b>	CII	
<b>Active Ingredient/Active Moiety</b>				
	<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>	
	METHADONE HYDROCHLORIDE (UNII: 229809935B) (METHADONE - UNII:UC6VBE7V1Z)	METHADONE HYDROCHLORIDE	10 mg in 1 mL	
<b>Inactive Ingredients</b>				
	<b>Ingredient Name</b>	<b>Strength</b>		
	SODIUM CHLORIDE (UNII: 451W47IQ8X)			
	SODIUM HYDROXIDE (UNII: 55X04QC32I)			
	HYDROCHLORIC ACID (UNII: QTT17582CB)			
	WATER (UNII: 059QF0KO0R)			
	CHLOROBUTANOL (UNII: HM4YQM8WRC)			
<b>Packaging</b>				
<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:17478-380-20	20 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product	10/30/2017	
<b>Marketing Information</b>				
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>	
ANDA	ANDA208306	10/30/2017		

**Labeler** - Akorn, Inc. (117696770)

**Registrant** - Akorn Operating Company LLC (117693100)

<b>Establishment</b>			
<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Akorn, Inc.		117696790	LABEL(17478-380) , PACK(17478-380)

<b>Establishment</b>			
<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Akorn, Inc.		117696832	ANALYSIS(17478-380) , STERILIZE(17478-380) , MANUFACTURE(17478-380)