Doctor Leaflet

Methadone

Concentrated oral solution
*Narcotic prescription required.

Composition

Active ingredient: Methadone HCl 50 mg/ml
To be diluted before administration. The solution should be diluted by the pharmacist to the requested concentration and volume into a new bottle, according to the physician's instructions.

Inactive Ingredients: methylhydroxybenzoate (methyl paraben), propylhydroxybenzoate (propyl paraben), purified water.

Methylhydroxybenzoate and propylhydroxybenzoate may cause allergic reactions (possibly delayed).

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; 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 FOR OPIOID ADDICTION

Addiction, Abuse, and Misuse

Methadone expose 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, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)].*

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Methadone. 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 or following a dose increase *[see Warnings and Precautions (5.3)].*

Accidental Ingestion

Accidental ingestion of even one dose of Methadone, especially by children, can result in a fatal overdose of methadone *[see Warnings and Precautions (5.3)].*

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 *[see Warnings and Precautions (5.4)].*

Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of use of Methadone 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 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 and Precautions (5.5)].*

Cytochrome P450 Interaction

The concomitant use of Methadone 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 can result in an increase in methadone levels *[see Warnings and Precautions (5.6), Drug interactions (7)].*

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 and Precautions (5.7), Drug Interactions (7)].***

- **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 for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

Methadone is indicated for the:

Relief of severe pain.

Detoxification and withdrawal treatment in narcotic addiction.

2 DOSAGE AND ADMINISTRATION

Important General Information

- The peak respiratory depressant effect of methadone occurs later and persists longer than its peak therapeutic 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 agonists.
- With repeated dosing, methadone is retained in the liver and then slowly released, prolonging the duration of potential toxicity.
- Methadone has a narrow therapeutic index, especially when combined with other drugs.

For oral use only.
Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing.
Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another and during dose titration.
While methadone’s duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone’s plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours).
Methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects. Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations.
For these reasons steady-state plasma concentrations and full analgesic effects are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.
The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **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 agonists.**
Treatment of Pain

Optimal methadone initiation and dose titration strategies for the treatment of pain have not been determined. Published equianalgesic conversion ratios between methadone and other opioids are imprecise, providing at best, only population averages that cannot be applied consistently to all patients. It should be noted that many commonly cited equianalgesia tables only present relative analgesic potencies of single opioid doses in non-tolerant patients, thus greatly underestimating methadone's analgesic potency and its potential for adverse effects in repeated-dose settings. Regardless of the dose determination strategy employed, methadone is most safely initiated and titrated using small initial doses and gradual dose adjustments.

As with all opioid drugs, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. The following dosing recommendations should only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient. Prescribers should always follow appropriate pain management principles of careful assessment and ongoing monitoring.

In the selection of an initial dose of methadone, attention should be given to the following:

1. The total daily dose, potency and specific characteristics of the opioid the patient had been taking previously, if any.
2. The relative potency estimate used to calculate an equianalgesic starting methadone dose, in particular, whether it is intended for use in acute or chronic methadone dosing.
3. The patient's degree of opioid tolerance.
4. The age, general condition and medical status of the patient.
5. Concurrent medications, particularly other CNS and respiratory depressants.
6. The type, severity and expected duration of the patient's pain.
7. The acceptable balance between pain control and adverse side effects.

Initiation of Therapy in Opioid Non-Tolerant Patients

When oral methadone is used as the first analgesic in patients who are not already being treated with, and tolerant to, opioids, the usual oral 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 overdosage, taking into account methadone's long elimination half-life.

Conversion from Parenteral Methadone to Oral Methadone

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

Switching Patients to 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.

Conversion ratios in many commonly used equianalgesic dosing tables do not apply in the setting of repeated methadone dosing. Although with single-dose administration the onset and duration of analgesic action, as well as the analgesic potency of methadone and morphine, are similar methadone's potency increases over time with repeated dosing.

Furthermore, the conversion ratio between methadone and other opiates varies dramatically depending on baseline opiate (morphine equivalent) use as shown in the table below. The dose conversion scheme below is derived from various consensus guidelines for converting chronic pain patients to methadone from morphine. Clinicians should consult published conversion guidelines to determine the equivalent morphine dose for patients converting from other opioids.

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

Total Daily Baseline **Oral** Morphine Dose	Estimated Daily **Oral** Methadone Requirement as percent of Total Daily Morphine Dose
< 100 mg	20% to 30%
100 to 300 mg	10% to 20%
300 to 600 mg	8% to 12%
600 mg to 1000 mg	5% to 10%
> 1000 mg	< 5 %

- 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.
- The table **cannot** be used to convert **from** Methadone **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

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. Table 1 has 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 adjusted.

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.

Detoxification and Maintenance Treatment of Opiate Dependence
Induction/Initial Dosing
The initial methadone dose should be administered under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate. Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or money spent per day on illicit drug use.

During the induction phase of methadone maintenance treatment, patients are being withdrawn from opioids and may have opioid withdrawal symptoms. Monitor patients for signs and symptoms of opioid withdrawal including: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilling alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss and consider dose adjustment as indicated.

For Short-term Detoxification
For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2 to 3 days, after which the dose of methadone should be gradually decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients a somewhat slower schedule may be needed.

For Maintenance Treatment
Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

For Medically Supervised Withdrawal after a Period of Maintenance Treatment
There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10 to 14-day intervals should elapse between dose reductions. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

3 DOSAGE FORMS AND STRENGTHS

Concentrated solution for oral use.
Methadone HCl 50 mg/ml.

To be diluted before administration. The solution should be diluted by the pharmacist to the requested concentration and volume into a new bottle, according to the physician's instructions.

Bottles of 200 ml.

4 CONTRAINDICATIONS

Methadone is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)].*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)].*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)].*
- Hypersensitivity (e.g., anaphylaxis) to methadone *[see Adverse Reactions (6)].*
- Hypersensitivity to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

Concentrated oral solution.
Do not dispense the medicine to the patient in this bottle.
The solution should be diluted by the pharmacist to the requested concentration and volume into a new bottle, according to the physician's instructions.
For oral administration only. The preparation must not be injected.

5.1 Addiction, Abuse and Misuse

Methadone solution contains methadone, a Schedule II controlled substance. As an opioid, Methadone expose users to the risks of addiction, abuse, and misuse. As long-acting opioids such as Methadone have pharmacological effects over an extended period of time, there is a greater risk for overdose and death *[see Drug Abuse and Dependence (9)].*

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Methadone. 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, and monitor all patients receiving Methadone 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 abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Methadone, but use in such patients necessitates intensive counseling about the risks and proper use of Methadone along with the intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Warnings and Precautions (5.3)].*

Abuse or misuse of Methadone by snorting or injecting the product will result in the uncontrolled delivery of the methadone and can result in overdose and death *[see Overdosage (10)].*

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. 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.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, healthcare providers are strongly encouraged to do all of the following:

- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed.

- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of methadone, even when used as recommended. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)].* Carbon dioxide (CO2) 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, the risk is greatest during the initiation of therapy or following a dosage increase. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period. Monitor patients closely for respiratory depression, when initiating therapy with Methadone and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of Methadone is essential *[see Dosage and Administration].* Overestimating the Methadone dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of Methadone, especially by children, can result in respiratory depression and death due to an overdose of methadone.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of getting emergency medical help right away in the event of a known or suspected overdose*.*

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration].*

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Methadone.

For Patients Being Treated for Pain

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient.

For Patients Being Treated for Opioid Addiction

Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose.

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with Methadone itself *[see Overdosage (10)].*

Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

Inform patients and caregivers of their options for obtaining naloxone as permitted by the state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and, if naloxone is prescribed, how to treat with naloxone. Emphasize the importance of calling or getting emergency medical help, even if naloxone is administered.

5.4 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, 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 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.

5.5 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 Specific Populations (8.1)].*

The balance between the risks of NOWS and the benefits of maternal Methadone 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.

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

Concomitant use of Methadone 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 dosage of Methadone is achieved. Similarly, discontinuation of concomitant CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers in Methadone-treated patients may increase methadone plasma concentrations resulting in fatal respiratory depression. Consider dosage reduction of Methadone 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 *[see Drug Interactions (7)].*

Addition of CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuation of

CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors in patients treated with Methadone may decrease methadone plasma concentrations, reducing efficacy and may lead to opioid withdrawal symptoms in patients physically dependent on methadone. When using Methadone 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 dosage as needed *[see Drug Interactions (7)].*

5.7 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 with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol).

For Patients Being Treated for Pain

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 Drug Interactions (7)].*

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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Warnings and Precautions (5.3)].*

Advise both patients and caregivers about the risks of respiratory depression and sedation when Methadone 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 Drug Interactions (7)].*

For Patients Being Treated for Opioid Addiction

Concomitant use of methadone and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.

As a routine part of orientation to methadone treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, or alcohol.

Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at admission to methadone treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of methadone as a strategy to address benzodiazepine use in methadone-treated patients. However, if a patient is sedated at the time of methadone dosing, ensure that a medically-trained healthcare provider evaluates the cause of sedation, and delays or omits the methadone dose if appropriate.

Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.

For patients in methadone treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's methadone treatment and coordinate care to minimize the risks associated with concomitant use.

If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in methadone treatment for opioid use disorder*[see Warnings and Precautions (5.3)].*

In addition, take measures to confirm that patients are taking the medications prescribed and not diverting or supplementing with illicit drugs. Toxicology screening should test for prescribed and illicit benzodiazepines *[see Drug Interactions (7)].*

5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Methadone in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease

Methadone-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Methadone *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (*5.3*)].*

Monitor such patients closely, particularly when initiating and titrating Methadone and when Methadone is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3, 5.7)].* Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 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- HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), 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 Drug Interactions (7)].* 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 if serotonin syndrome is suspected.

5.10 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.

5.11 Severe Hypotension

Methadone may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an 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) *[see Drug Interactions (7)].* Monitor these patients for signs of hypotension after initiating or titrating the dosage of Methadone. In patients with circulatory shock, Methadone may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Methadone in patients with circulatory shock.

5.12 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_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) Methadone may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Methadone.

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

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

5.13 Risks of Use in Patients with Gastrointestinal Conditions

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

The methadone in Methadone 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.

5.14 Increased Risk of Seizures in Patients with Seizure Disorders

The methadone in Methadone 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 therapy.

5.15 Withdrawal

Do not abruptly discontinue Methadone in a patient physically dependent on opioids. When discontinuing Methadone in a physically dependent patient, gradually taper the dosage. Rapid tapering of methadone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain.

Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances. *[see Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist, including Methadone. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7)].*

5.16 Risks Driving and Operating Machinery

Methadone 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 and

know how they will react to the medication.

5.17 Laboratory Test Interactions

False positive urine drug screens for methadone have been reported for several drugs including diphenhydramine, doxylamine, clomipramine, chlorpromazine, thioridazine, quetiapine, and verapamil.

6 ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- QT Prolongation *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines and other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.9)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*

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 is 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 are advisable.

Other adverse reactions include the following:

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

Cardiovascular: arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, *torsades de pointes,* ventricular fibrillation, ventricular tachycardia

Central Nervous System: agitation, confusion, disorientation, dysphoria, euphoria, insomnia, hallucinations, seizures, visual disturbances, congenital oculomotor disorders (nystagmus, strabismus)

Endocrine: hypogonadism, decreased testosterone

Gastrointestinal: abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic: reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic: hypoglycemia, hypokalemia, hypomagnesemia, weight gain

Renal: antidiuretic effect, urinary retention or hesitancy

Reproductive: amenorrhea, reduced libido and/or potency, reduced ejaculate volume, reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology

Respiratory: pulmonary edema, respiratory depression

Skin and Subcutaneous Tissue: pruritus, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Hypersensitivity: Anaphylaxis has been reported with ingredients contained in Methadone solution.

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.

Androgen Deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)].*

7 DRUG INTERACTIONS

Inhibitors of CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6	
Clinical Impact:	Methadone undergoes hepatic N-demethylation by several cytochrome P450 (CYP) isoforms, including CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6. The concomitant use of Methadone 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 is achieved. These effects may be more pronounced with concomitant use of drugs that inhibit more than one of the CYP enzymes listed above. After stopping a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor, as the effects of the inhibitor decline, the methadone plasma concentration can decrease *[see Clinical Pharmacology (12.3)],* resulting in decreased opioid efficacy or withdrawal symptoms in patients physically dependent on methadone.
Intervention:	If concomitant use is necessary, consider dosage reduction of Methadone until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor is

	discontinued, follow patients for signs of opioid withdrawal and consider increasing the Methadone dosage until stable drug effects are achieved.
Examples:	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)
Inducers of CYP3A4, CYP2B6, CYP2C19, or CYP2C9	
Clinical Impact:	The concomitant use of Methadone and CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers can decrease the plasma concentration of methadone *[see Clinical Pharmacology (12.3)],* 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. After stopping a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer, as the effects of the inducer decline, the methadone plasma concentration can increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, sedation, or death.
Intervention:	If concomitant use is necessary, consider increasing the Methadone 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 dosage reduction and monitor for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin, St. John's Wort, Phenobarbital
Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Intervention:	For Patients Being Treated for Pain 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 Warnings and Precautions (5.7)].* If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Warnings and Precautions (5.1, 5.3, 5.7)].* For Patients Being Treated for Opioid Addiction Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in treatment for opioid use disorder*[see Warnings and Precautions (5.1, 5.3, 5.7)].*
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Potentially Arrhythmogenic Agents	
Clinical Impact:	Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents or drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia).
Intervention:	Monitor patients closely for cardiac conduction changes.
Examples:	Drugs known to have potential to prolong QT interval: Class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. Drugs capable of inducing electrolyte disturbances: Diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.9)].*
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Methadone if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5- HT3 receptor antagonists,

	drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.9)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	The use of Methadone is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Methadone and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact:	Methadone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Methadone and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Warnings and Precautions (5.3, 5.7)]*
Examples:	Cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Methadone is used concomitantly with anticholinergic drugs.

Paradoxical Effects of Antiretroviral Agents on Methadone

Concurrent use of certain antiretroviral agents with CYP3A4 inhibitory activity, alone and in combination, such as abacavir, amprenavir, darunavir+ritonavir, efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, lopinavir+ritonavir, saquinavir+ritonavir, and

tipranavir+ritonavir, has resulted in increased clearance or decreased plasma levels of methadone. This may result in reduced efficacy of Methadone and could precipitate a withdrawal syndrome. Monitor methadone-maintained patients receiving any of these anti-retroviral therapies closely for evidence of withdrawal effects and adjust the methadone dose accordingly.

Effects of Methadone on Antiretroviral Agents

Didanosine and Stavudine: Experimental evidence demonstrated that methadone decreased the area under the concentration-time curve (AUC) and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine: Experimental evidence demonstrated that methadone increased the AUC of zidovudine, which could result in toxic effects.

Effects of Methadone on Antidepressants:

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The majority of available data from clinical trials, observational studies, case series, and case reports on methadone use in pregnancy do not indicate an increased risk of major malformations specifically due to methadone.

Pregnant women involved in methadone maintenance programs have been reported to have improved prenatal care leading to reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors, including maternal use of illicit drugs, nutrition, infection and psychosocial circumstances, complicate the interpretation of investigations of the children of women who take methadone during pregnancy. Information is limited regarding dose and duration of methadone use during pregnancy, and most maternal exposure in these studies appears to occur after the first trimester of pregnancy *(see Data).*

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.6)].*

In published animal reproduction studies, methadone 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^2 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.

Dosage Adjustment During Pregnancy: Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with Methadone. Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery *[see Dosage and Administration and Clinical Pharmacology (12.3)].* Withdrawal signs and symptoms should be closely monitored and the dose adjusted as necessary.

Fetal/Neonatal Adverse Reactions: Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with Methadone.

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 Warnings and Precautions (5.6)].*

Labor or Delivery: Opioid-dependent women on methadone maintenance therapy may require additional analgesia during labor.

Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data: The majority of available data from clinical trials, observational studies, case series, and case reports on methadone use in pregnancy do not indicate an increased risk of major malformations specifically due to methadone. Findings regarding specific major malformations, decreased fetal growth, premature birth and Sudden Infant Death Syndrome have been inconsistent. Children prenatally exposed to methadone have been reported to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests and visual abnormalities.

In a multicenter, double-blind, randomized, controlled trial [Maternal Opioid Treatment: Human Experimental Research (MOTHER)] designed primarily to assess neonatal opioid withdrawal effects, opioid-dependent pregnant women were randomized to buprenorphine (n=86) or methadone (n=89) treatment, with enrollment at an average gestational age of 18.7 weeks in both groups. A total of 28 of the 86 women in the buprenorphine group (33%) and 16 of the 89 women in the methadone group (18%) discontinued treatment before the end of pregnancy.

Among women who remained in treatment until delivery, there was no difference between methadone-treated and buprenorphine-treated groups in the number of neonates requiring NOWS treatment or in the peak severity of NOWS. Buprenorphine- exposed neonates

required less morphine (mean total dose, 1.1 mg vs. 10.4 mg), had shorter hospital stays (10.0 days vs. 17.5 days), and shorter duration of treatment for NOWS (4.1 days vs. 9.9 days) compared to the methadone-exposed group. There were no differences between groups in other primary outcomes (neonatal head circumference), or secondary outcomes (weight and length at birth, preterm birth, gestational age at delivery, and 1-minute and 5-minute Apgar scores), or in the rates of maternal or neonatal adverse events. The outcomes among mothers who discontinued treatment before delivery and may have relapsed to illicit opioid use are not known. Because of the imbalance in discontinuation rates between the methadone and buprenorphine groups, the study findings are difficult to interpret.

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 JBT/Jd mice, a single subcutaneous dose of 22 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 post-implantation 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, 5, 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 demonstrate 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-naive 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-naive 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-naive 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.

8.2 Lactation

Risk Summary

Based on two small clinical studies, methadone was present in low levels in human milk, but the exposed infants in these studies did not show adverse reactions. 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. There have been rare case reports of sedation and respiratory depression in infants exposed to methadone through breast milk (*see Data*). Monitor infants exposed to Methadone through breastmilk for excess sedation and respiratory depression. 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.

Data

In a study of ten breastfeeding women maintained on oral methadone doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk were reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose.

In a study of twelve breastfeeding women maintained on oral methadone doses of 20 to 80 mg/day, methadone concentrations from 39 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.

8.3 Females and Males of Reproductive Potential

Infertility

The effect of Methadone on fertility is unknown. 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 (6), Clinical Pharmacology (12.2), Nonclinical Pharmacology (13.1)].* 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.

In published animal studies, methadone produces a significant regression of sex accessory organs and testes of male mice and rats and administration of methadone to pregnant rats reduced fetal blood testosterone and androstenedione in male offspring *[see Nonclinical Toxicology (13)].*

8.4 Pediatric Use

The safety, effectiveness, and pharmacokinetics of methadone in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between 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 slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)].*

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.

8.6 Hepatic Impairment

Methadone pharmacokinetics have 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.

8.7 Renal Impairment

Methadone pharmacokinetics have 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.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methadone contain methadone, a Schedule-II controlled substance.

9.2 Abuse

Methadone contain methadone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. Methadone can be abused and are subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)].*

All patients treated with opioids for pain management require careful monitoring for signs of abuse and addiction, since 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 a 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 in 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 a 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 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 healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. 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. Healthcare 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, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record- keeping of prescribing information, including quantity, frequency, and renewal requests, as required.

Proper assessment and selection 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.

Risks Specific to Abuse of Methadone

Abuse of Methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone and alcohol or other substances. Methadone is for oral use

only and must not be injected. With intravenous abuse some inactive ingredients can result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid 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 is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting 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.

Do not abruptly discontinue Methadone in a patient physically dependent on opioids. Rapid tapering of Methadone in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing Methadone, gradually taper the dosage using a patient-specific plan that considers the following: the dose of Methadone the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Warnings (5.15)].*

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)].*

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.5)].*

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with methadone 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 *[see Clinical Pharmacology (12.2)].* In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Methadone overdosage is associated with rhabdomyolysis. Seek medical attention, especially if abuse/misuse results in prolonged immobilization. Acute toxic leukoencephalopathy has been reported after methadone overdose, often weeks after apparent recovery from the initial intoxication. Hearing loss has been reported after methadone overdose, in some cases permanent.

Treatment of Overdose

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

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

Because the duration of reversal would be expected to be less than the duration of action of methadone in Methadone, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to opioid antagonists is suboptimal or not sustained, administer additional antagonist as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the 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 begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-hepatanone hydrochloride.
Methadone solution is available for oral administration containing 50 mg/ml methadone hydrochloride. Methadone contains the following inactive ingredients: methylhydroxybenzoate (methyl paraben), propylhydroxybenzoate (propyl paraben), purified water.
Methylhydroxybenzoate and propylhydroxybenzoate may cause allergic reactions (possibly delayed).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methadone hydrochloride is a mu-agonist; a synthetic opioid with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone is for analgesia and for detoxification or maintenance in opioid addiction. The methadone withdrawal 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.

12.2 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 *[see Adverse Reactions (6)].* 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 *[see Adverse Reactions (6)].*

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 *[see Dosage and Administration].*

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 *[see Dosage and Administration].*

12.3 Pharmacokinetics

Absorption

Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1,255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution

Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to α1-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 the urine. Methadone appears to be a substrate for P-glycoprotein but its pharmacokinetics do not appear to be significantly altered in case of P- glycoprotein polymorphism or inhibition.

Excretion: The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life ($T_{1/2}$) was highly variable and ranged between 8 to 59 hours in different studies. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Also, since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

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 Drug Interactions (7)].*

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 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 Drug Interactions (7)].*

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, Tipranavir+Ritonavir Combination:
Co-administration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone *[see Drug Interactions (7)].*
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 Drug Interactions (7)].*
Zidovudine:Methadone increased the AUC of zidovudine which could result in toxic effects *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed

15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (HDD). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times the HDD. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times the HDD. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis

There are several published reports on the potential genetic toxicity of methadone. Methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E. coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays. In contrast, 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.

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. Methadone treatment of pregnant rats from Gestation Day 14 to 19 reduced fetal blood testosterone and androstenedione in males. Decreased serum levels of testosterone were observed in male rats that were treated with methadone (1.3 to 3.3 mg/kg/day for 14 days, corresponding to 0.1 to 0.3 times the HDD) or 10 to 15 mg/kg/day for 10 days (0.8 to 1.2 times the HDD).

16 HOW SUPPLIED/STORAGE AND HANDLING

Concentrated solution for oral use.

To be diluted before administration. The solution should be diluted by the pharmacist to the requested concentration and volume into a new bottle, according to the physician's instructions.

Clear, colorless solution.

Brown glass bottles of 200 ml, with child resistance cap.

Store below 25°C. Protect from light.

Once the bottle is opened, it should be stored below 25°C and the solution can be used within 6 months, but no later than the expiration date printed on the package.Store Methadone solution securely and dispose of properly.

17 REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.
Registration number: 105 67 29097

Revised in September 2021 according to MOHs guidelines.