METHADONE HYDROCHLORIDE- methadone hydrochloride solution
ATLANTIC BIOLOGICALS CORP.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METHADONE HYDROCHLORIDE ORAL SOLUTION safely and effectively. See full prescribing information for METHADONE HYDROCHLORIDE ORAL SOLUTION.

METHADONE HYDROCHLORIDE oral solution, for oral use CII
Initial U.S. Approval: 1947

WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; LIFE-THREATENING QT PROLONGATION; NEONATAL OPIOID WITHDRAWAL SYNDROME; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and TREATMENT FOR OPIOID ADDICTION

See full prescribing information for complete boxed warning.

- **Ensure accuracy when prescribing, dispensing, and administering Methadone Hydrochloride Oral Solution. Dosing errors due to confusion between mg and mL, and other methadone hydrochloride oral solutions of different concentrations can result in accidental overdose and death. (2.1, 5.1)**
- **Methadone Hydrochloride Oral Solution exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors and conditions. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)**
- **Accidental ingestion of Methadone Hydrochloride Oral Solution, especially in children, can result in fatal overdose of methadone. (5.3)**
- **QT interval prolongation and serious arrhythmia (*torsades de pointes*) have occurred during treatment with methadone. (5.4)**
- **Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of use of Methadone Hydrochloride Oral Solution during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. The balance between the risks of NOWS and the benefits of maternal Methadone Hydrochloride Oral Solution 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. (5.5)**
- **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 (5.6, 7.1)**
- **Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by certified opioid treatment programs as stipulated in 42 CFR 8.12. (1)**

RECENT MAJOR CHANGES

Boxed Warning 3/2017
Warnings and Precautions (5) 3/2017

INDICATIONS AND USAGE

Methadone Hydrochloride Oral Solution is an opioid agonist indicated for the:

- Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

1. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long acting opioids, reserve Methadone Hydrochloride Oral Solution for use in patients for whom alternative treatment options (e.g., non-

opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
2. Methadone Hydrochloride Oral Solution is not indicated as an as-needed (prn) analgesic.
- Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
- Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services. (1)

DOSAGE AND ADMINISTRATION

Management of Pain:

- For opioid naïve patients, initiate methadone hydrochloride treatment with 2.5 mg every 8 to 12 hours. (2.2)
- Titrate slowly with dose increases no more frequent than every 3 to 5 days. (2.3)
- To convert to methadone hydrochloride from another opioid, use available conversion factors to obtain estimated dose. (2.2)
- Initiation of Detoxification and Maintenance Treatment: A single dose of 20 to 30 mg may be sufficient to suppress withdrawal syndrome. (2.5)
- Do not abruptly discontinue methadone in a physically dependent patient. (2.4, 5.15)

DOSAGE FORMS AND STRENGTHS

Oral Solution: Each 5 mL contains 5 mg or 10 mg of Methadone Hydrochloride Oral Solution. (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to methadone (4)

WARNINGS AND PRECAUTIONS

- *Respiratory Depression*: The peak respiratory depressant effect typically occurs later, and persists longer than the peak analgesic effect. (5.3)
- May cause QT interval prolongation and serious arrhythmia. (5.4)
- *Elderly, Cachectic, Debilitated Patients and Those with Chronic Pulmonary Disease*: Monitor closely because of increased risk for life-threatening respiratory depression. (5.7, 5.8)
- *Serotonin Syndrome*: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue Methadone Hydrochloride Oral Solution if serotonin syndrome is suspected. (5.9)
- *Adrenal Insufficiency*: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- *Hypotensive Effect*: Monitor during dose initiation and titration. (5.11)
- *Patients with Head Injury or Increased Intracranial Pressure*: Monitor for sedation and respiratory depression. Avoid use of methadone in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.12)

ADVERSE REACTIONS

Most Common Adverse Reactions are: lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *CYP3A4 Inducers*: Increased risk of more rapid metabolism and decreased effects of methadone. (7.2)
- *CYP3A4 Inhibitors*: Increased risk of reduced metabolism and methadone toxicity. (7.2)
- *Anti-retroviral Agents*: May result in increased clearance and decreased plasma levels of methadone or in certain cases, increased plasma levels and risk of toxicity. (7.2)
- *Potentially Arrhythmogenic Agents*: Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. (7.3)
- *Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics*: Avoid use with methadone because they may reduce analgesic effect of methadone or precipitate withdrawal symptoms. (5.15, 7.4)

USE IN SPECIFIC POPULATIONS

- *Pregnancy*: Based on animal data, may cause fetal harm. (8.1)
- *Nursing Mothers*: Methadone has been detected in human milk. Closely monitor infants of nursing women receiving methadone. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; LIFE-THREATENING QT PROLONGATION; NEONATAL OPIOID WITHDRAWAL SYNDROME; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and TREATMENT FOR OPIOID ADDICTION

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering Methadone Hydrochloride Oral Solution. Dosing errors due to confusion between mg and mL, and other methadone hydrochloride oral solutions of different concentrations can result in accidental overdose and death*[see Dosage and Administration (2.1), Warnings and Precautions (5.1)].*

Addiction, Abuse, and Misuse

Methadone Hydrochloride Oral Solution exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Methadone Hydrochloride Oral Solution, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.2)].*

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Methadone Hydrochloride Oral Solution. Monitor for respiratory depression, especially during initiation of Methadone Hydrochloride Oral Solution or following a dose increase *[see Warnings and Precautions (5.3)].*

Accidental Ingestion

Accidental ingestion of even one dose of Methadone Hydrochloride Oral Solution, 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 for changes in cardiac rhythm during initiation and titration of Methadone Hydrochloride Oral Solution *[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 Hydrochloride Oral Solution during pregnancy. NOWS may be life-threatening if not recognized and

treated in the neonate. The balance between the risks of NOWS and the benefits of maternal Methadone Hydrochloride Oral Solution 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)].*

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(5.6), Drug Interactions (7.1)].*

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

Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction

For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration *[see Indications and Usage(1)].*

1 INDICATIONS AND USAGE

Methadone Hydrochloride Oral Solution is indicated for the:

- Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioids, reserve Methadone Hydrochloride Oral Solution for use in patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Methadone Hydrochloride Oral Solution is not indicated as an as-needed (prn) analgesic.
- Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
- Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction

Code ofFederal Regulations, Title 42, Sec 8:Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

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

Regulatory Exceptions To The General Requirement For Certification To Provide Opioid Agonist Treatment:

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis).
- During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07(b)).

2 DOSAGE AND ADMINISTRATION

2.1 Important General Information

- Ensure accuracy when prescribing, dispensing, and administering Methadone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and with other methadone hydrochloride oral solutions of different concentrations, which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.
- Always use a calibrated measuring devise when administering Methadone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately. Health care providers should recommend a dropper that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)].*
- 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.

2.2 Initial Dosing for Management of Pain

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

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

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

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (*5.2*)].* Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases *[see Warnings and Precautions (5.3)].*

Use of Methadone as the First Opioid Analgesic

Initiate with 2.5 mg orally every 8 to 12 hours.

Conversion from Other Oral Opioids to Methadone

Discontinue all other around-the-clock opioid drugs when methadone therapy is initiated. **Deaths have occurred in opioid-tolerant patients during conversion to methadone.**

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is safer to underestimate a patient's 24-hour oral methadone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral methadone requirements which could result in adverse reactions. With repeated dosing, the potency of methadone increases due to systemic accumulation.

Consider the following information in Table 1:

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

Table 1: Conversion Factors to Methadone

Total Daily Baseline <u>**Oral**</u> **Morphine Equivalent Dose**	Estimated Daily <u>**Oral**</u> **Methadone Requirement as Percent of Total Daily Morphine Equivalent 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 %

To Calculate the Estimated Methadone Dose Using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid, convert it to a Morphine Equivalent Dose according to specific conversion factor for that specific opioid, then multiply the Morphine Equivalent Dose by the corresponding percentage in the above table to calculate the approximate oral methadone daily dose. Divide the total daily methadone dose derived from the table above to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).
- For patients on a regimen of more than one opioid, calculate the approximate oral methadone dose for each opioid and sum the totals to obtain the approximate total methadone daily dose. Divide the total daily methadone dose derived from the table above to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component, if necessary, to the appropriate methadone strength(s) available. Always round the dose down, if necessary, to the appropriate methadone strength(s) available.

Example Conversion from a Single Opioid to Methadone

Step 1: Sum the total daily dose of the opioid (in this case, Morphine Extended Release Tablets 50 mg twice daily)

50 mg Morphine Extended Release Tablets 2 times daily = 100 mg total daily dose of Morphine

Step 2: Calculate the approximate equivalent dose of Methadone Hydrochloride Oral Solution to be given daily (using 15% from Table 1)

100 mg total daily dose of Morphine x 15% (10% to 20% per Table 1) = 15 mg Methadone Hydrochloride Oral Solution daily

Step 3: Calculate the approximate equivalent dose of Methadone Hydrochloride Oral Solution to be given every 12 hours. Round down, if necessary, to the appropriate dosing strength.

15 mg daily / 2 doses every 12 hours = 7.5 mg Methadone Hydrochloride Oral Solution every 12 hours

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to methadone from other opioids.

Methadone Hydrochloride Oral Solution is not interchangeable with parenteral methadone hydrochloride (e.g., 10 mg parenteral methadone to 10 mg oral methadone).

2.3 Titration and Maintenance of Therapy for Pain

Individually titrate methadone to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving methadone to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Because of individual variability in the pharmacokinetic profile (i.e., terminal half-life ($T_{1/2}$) from 8 to 59 hours in different studies *[see Clinical Pharmacology (12.3)]*), titrate methadone slowly, with dose increases no more frequent than every 3 to 5 days. However, because of this high variability, some patients may require substantially longer periods between dose increases (up to 12 days). Monitor patients closely for the development of potentially life-threatening adverse reactions (e.g., CNS and respiratory depression).

Patients who experience breakthrough pain may require a dose increase of

methadone, or may need rescue medication with an appropriate dose of an immediate-release medication. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the methadone dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced and/or the dosing interval adjusted (i.e., every 8 hours or every 12 hours). Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of Methadone for Pain

When a patient no longer requires therapy with methadone for pain, use a gradual downward titration, of the dose every two to four days, to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue methadone.

2.5 Induction/Initial Dosing for Detoxification and Maintenance Treatment of Opioid Addiction

For detoxification and maintenance of opioid dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including the limitations on unsupervised administration.

Administer the initial methadone dose under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. An initial 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.

To make same-day dosing adjustments, have the patient wait 2 to 4 hours for further evaluation, when peak levels have been reached. Provide an additional 5 to 10 mg of methadone 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. Adjust the dose 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). When adjusting the dose, keep in mind that methadone levels will accumulate over the first several days of dosing; deaths have occurred in early treatment due to the cumulative effects. Instruct patients that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Use lower initial doses for patients whose tolerance is expected to be low at treatment entry. Any patient who has not taken opioids for more than 5 days may no longer be tolerant. Do not determine initial doses based on previous treatment episodes or dollars spent per day on illicit drug use.

Short-term Detoxification: For patients preferring a brief period of medically supervised withdrawal, titrate the patient to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. After 2 to 3 days of stabilization, gradually decrease the dose of methadone. Decrease the dose of methadone on a daily basis or at 2-day intervals, keeping the amount of methadone sufficient to keep withdrawal symptoms at a tolerable level. Hospitalized patients may tolerate a daily reduction of 20% of the total daily dose. Ambulatory patients may need a slower schedule.

2.6 Titration and Maintenance Treatment of Opioid Dependence Detoxification

Titrate patients in maintenance treatment to a dose that prevents opioid withdrawal symptoms for 24 hours, reduces drug hunger or craving, and blocks or attenuates the euphoric effects of self-administered opioids, ensuring that the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

2.7 Medically Supervised Withdrawal After a Period of Maintenance

Treatment for Opioid Addiction

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. Dose reductions should generally be less than 10% of the established tolerance or maintenance dose, and 10 to 14-day intervals should elapse between dose reductions. Apprise patients of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

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

Abrupt opioid discontinuation can lead to development of opioid withdrawal syndrome *[see Drug Abuse and Dependence (9.3)]*. Opioid withdrawal symptoms have been associated with an increased risk of relapse to illicit drug use in susceptible patients.

2.9 Considerations for Management of Acute Pain During Methadone Maintenance Treatment

Patients in methadone maintenance treatment for opioid dependence who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. When opioids are required for management of acute pain in methadone maintenance patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients due to the opioid tolerance induced by methadone.

2.10 Dosage Adjustment During Pregnancy

Methadone clearance may be increased during pregnancy. During pregnancy, a woman's methadone dose may need to be increased or the dosing interval decreased. Methadone should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)].*

3 DOSAGE FORMS AND STRENGTHS

Each 5 mL of clear or nearly clear orange colored Methadone Hydrochloride Oral Solution USP contains methadone hydrochloride USP 5 mg or 10 mg. The concentration of the 5 mg per 5 mL solution is 1 mg/mL and the concentration of the 10 mg per 5 mL solution is 2 mg/mL.

4 CONTRAINDICATIONS

Methadone Hydrochloride Oral Solution is contraindicated in patients with:

- Significant respiratory depression.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
- Known or suspected paralytic ileus.
- Hypersensitivity (e.g., anaphylaxis) to methadone *[see Adverse Reactions (6)].*

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. Avoid dosing errors that may result from confusion between mg and mL and confusion with methadone hydrochloride oral solution of different concentrations, when prescribing, dispensing, and administering Methadone Hydrochloride Oral Solution. Ensure that the dose is communicated clearly and dispensed accurately. A household teaspoon or tablespoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device. Health care providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage.

5.2 Addiction, Abuse and Misuse

Methadone Hydrochloride Oral Solution contains methadone, a Schedule II controlled substance. As an opioid, methadone exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)].* As long-acting opioids such as methadone have pharmacological effects over an extended period of time, the risk of addiction in any individual is unknown. It can occur in patients appropriately prescribed methadone and in those who obtain the drug illicitly. 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 or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of methadone for the proper management of pain in any given patient. Patients at increased risk may be prescribed long-acting opioids such as methadone, but use in such patients necessitates intensive counseling about the risks and proper use of methadone along with intensive monitoring for signs of addiction, abuse, or misuse. Abuse or misuse of methadone by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the methadone and can result in overdose and death *[see Overdosage (10)].*

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed methadone and in those who obtain the drug illicitly. 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 or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of methadone for the proper management of pain in any given patient. Patients at increased risk may be prescribed long-acting opioids such as methadone, but use in such patients necessitates intensive counseling about the risks and proper use of methadone along with intensive monitoring for signs of addiction, abuse, or misuse.

Opioid agonists such as methadone 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 *[see Patient Counseling Information (17)].* Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of long-acting opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)].* Carbon dioxide (CO_2) 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 dose increase. **The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak analgesic effect, especially during the initial dosing period.** Closely monitor patients for respiratory depression when initiating therapy with methadone and following dose increases.

Increases

To reduce the risk of respiratory depression, proper dosing and titration of methadone are essential *[see Dosage and Administration (2.2, 2.3)]*. Overestimating the methadone dose 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 overdose of methadone.

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

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

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

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 be aware of the risk of NOWS *[see Use in Specific Populations (8.1)]*. Methadone Hydrochloride Oral Solution use may differ based on the risks associated with the

Monitor

Monitor and manage accordingly.

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 from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see 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.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Methadone Hydrochloride Oral Solution 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), Patient Counseling Information (17)].*

5.7 Use in Elderly, Cachectic, and Debilitated Patients

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

5.8 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with methadone, as in these patients, even usual therapeutic doses of methadone may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (*5.3*)].* Consider the use of alternative non-opioid analgesics in these patients if possible.

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 Hydrochloride Oral Solution with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, $5HT_3$ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7.5)].* This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Methadone Hydrochloride Oral Solution 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 1 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 Hypotensive Effect

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 (7.1)].* Monitor these patients for signs of hypotension after initiating or titrating the dose of methadone.

5.12 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking methadone who may be susceptible to the intracranial

effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with methadone. Methadone may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. 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 Use in Patients with Gastrointestinal Conditions

Methadone is contraindicated in patients with paralytic ileus. Avoid the use of methadone in patients with other gastrointestinal obstruction.

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

5.14 Use in Patients with Convulsive or Seizure Disorders

Methadone may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during methadone therapy.

5.15 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, 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 (7.4)].*

When discontinuing methadone, gradually taper the dose *[see Dosage and Administration (2.4)].* Do not abruptly discontinue methadone.

5.16 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (*5.2*)]*
- 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 Other CNS Depressants *[see Warnings and Precautions (*5.6*)]*
- Serotonin Syndrome *[see Warnings and Precautions (*5.9*)]*
- Adrenal Insufficiency *[see Warnings and Precautions (*5.10*)]*
- Hypotensive Effect *[see Warnings and Precautions (*5.11*)]*

- Gastrointestinal Effects *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*

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

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

Other adverse reactions include the following, and are listed by organ system:

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

Endocrine: hypogonadism

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

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

Metabolic: hypokalemia, hypomagnesemia, weight gain

Renal: 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. Advise patients how to recognize such a reaction and when to seek medical attention.

Maintenance on a Stabilized Dose: During prolonged administration of methadone, as in a methadone maintenance treatment program, constipation and sweating often persist and hypogonadism, decreased serum testosterone and reproductive effects are thought to be related to chronic opioid use.

Methadone for the Detoxification and Maintenance Treatment of Opioid Dependence: During the induction phase of methadone maintenance treatment, patients are being withdrawn from illicit opioids and may have opioid withdrawal symptoms. Monitor patients for signs and symptoms 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.

7 DRUG INTERACTIONS

7.1 Benzodiazepines and other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.6)]*.

7.2 Drugs Affecting Cytochrome P450 Isoenzymes

Methadone undergoes hepatic N-demethylation by cytochrome P450 (CYP) isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6 *[see Clinical Pharmacology (12.3)]*.

Because CYP3A4 isoenzyme plays a major role in the metabolism of methadone, drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone which could lead to an increase in methadone plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced

with concomitant use of CYP 2C9 and 3A4 inhibitors. If co-administration with methadone is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

CYP3A4 Inducers: May increase the metabolism of methadone and, therefore, may cause increased clearance of the drug which could lead to a decrease in methadone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to methadone. If co-administration with methadone is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

After stopping a CYP3A4 inducer, as the effects of the inducer decline, methadone plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. If co-administration or discontinuation of a CYP3A4 inducer with methadone is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Effects of Antiretroviral Agents With CYP3A4 Inhibitory Activity: Concomitant administration 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 tipranvir+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 *[see Drug Interactions (7.1)]*.

Effects of Antiretroviral Agents Without CYP3A4 Inhibitory Activity: Evidence has accumulated 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. Experimental evidence has demonstrated that methadone increased the AUC of zidovudine, which could result in toxic effects.

Didanosine: Dose interactions have not substantially altered.

Stavudine: Dose interactions have not substantially altered.

Zidovudine: Dose interactions have not substantially altered.

7.3 Potentially Arrhythmogenic Agents

Monitor patients closely for cardiac conduction changes when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Similarly, monitor patients closely when prescribing methadone concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval, including diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

7.4 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of methadone or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving methadone.

7.5 Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT_3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine

oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Methadone Hydrochloride Oral Solution if serotonin syndrome is suspected.

7.6 Antidepressants

Therapeutic Doses of Monoamine Oxidase (MAO) Inhibitors

Therapeutic doses of MAO inhibitors have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small, incremental doses of methadone are administered over the course of several hours while the patient's blood pressure and vital signs are carefully observed.

Tricyclic Antidepressants

Tricyclic antidepressants may potentiate the effects of methadone. Monitor patients for signs of sedation and respiratory depression when concurrent methadone administration.

7.7 Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioids may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when methadone is used concurrently with anticholinergic drugs.

7.8 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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.

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see BOXED WARNING, Warnings and Precautions (*5.5*)]*.

Teratogenic Effects

Pregnancy Category C: There are no adequate and well controlled studies in pregnant women. Methadone should be used during pregnancy only if the potential

benefit justifies the potential risk to the fetus.

Methadone has been shown to be teratogenic in the hamster at doses 2 times the human daily oral dose (120 mg/day on a mg/m^2 basis) and in mice at doses equivalent to the human daily oral dose (120 mg/day on a mg/m^2 basis). Increased neonatal mortality and significant differences in behavioral tests have been reported in the offspring of male rodents that were treated with methadone prior to mating when compared to control animals. Methadone has been detected in human amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in neonatal urine at lower concentrations than corresponding maternal urine.

Dosage Adjustment During Pregnancy: The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during 2nd and 3rd trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone to achieve therapeutic effect *[see Dosage and Administration (2.10)]*.

Effects on the Neonate

Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Monitor newborn for withdrawal signs and symptoms including: poor feeding, irritability, excessive crying, tremors, rigidity, hyper-active reflexes, increased respiratory rate, diarrhea, sneezing, yawning, vomiting, fever, and seizures. The intensity of the neonatal withdrawal syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal *[see Warnings and Precautions (5.5)]*.

Human Data: Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs; the relevance of these findings to pain patients prescribed methadone during pregnancy is unclear. Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly 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 appears to occur after the first trimester of pregnancy.

A review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as “limited to fair”). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). A retrospective case series of 101 pregnant, opioid-dependent women who underwent inpatient opioid detoxification with methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in the 3rd trimester. Recent studies suggest an increased risk of premature delivery in opioid-dependent women exposed to methadone during pregnancy, although the presence of confounding factors makes it difficult to determine a causal relationship. Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced

birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. Children prenatally exposed to methadone have been reported to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests. In addition, several studies suggest that children born to opioid-dependent women exposed to methadone during pregnancy may have an increased risk of visual development anomalies; however, a causal relationship has not been established.

There are conflicting reports on whether Sudden Infant Death Syndrome occurs with an increased incidence in infants born to women treated with methadone during pregnancy. Abnormal fetal non-stress tests have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Animal Data: Methadone did not produce teratogenic effects in rat or rabbit models. Methadone produced teratogenic effects following large doses, in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately 2 times a human daily oral dose of 120 mg/day on a mg/m^2 basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and “various other lesions.” The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m^2 basis) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m^2 basis) administered during days 6 to 15 and 6 to 18, respectively.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone prior to mating. In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs.

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

Additional data have been published indicating that methadone treatment of male

rats (once a day for three consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naïve female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. Methadone is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

8.3 Nursing Mothers

Methadone is secreted into human milk. At maternal oral doses of 10 to 80 mg/day, 5 to 570 ng/L in milk have been 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. 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. Cases of sedation and respiratory depression in infants exposed to methadone through breast milk have been reported. Caution should be exercised when methadone is administered to a nursing woman.

Advise women who are being treated with methadone and who are breastfeeding or express a desire to breastfeed of the presence of methadone in human milk. Instruct breastfeeding mothers how to identify respiratory depression and sedation in their babies and when it may be necessary to contact their healthcare provider or seek immediate medical care. Breastfed infants of mothers using methadone should be weaned gradually to prevent development of withdrawal symptoms in the infant.

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. In general, start elderly patients at the low end of the dosing range, taking into account the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients. Closely monitor elderly patients for signs of respiratory and central nervous system depression.

8.6 Renal Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Since 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.

8.7 Hepatic Impairment

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

8.8 Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions(6)].*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methadone is a mu-agonist opioid with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. Methadone can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (*5.2*)].*

9.2 Abuse

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.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the counter drug to get “high”, or the use of steroids for performance enhancement and muscle building.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: 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 addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of lost prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with pain.

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

Methadone, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly

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. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV. Proper assessment and selection of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

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 results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. Methadone should be withdrawn gradually from the patient's regimen *[see Dosage and Administration (2.4)].* If methadone is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

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

10 OVERDOSAGE

Clinical Presentation

Acute overdosage of methadone is manifested by respiratory depression, somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment 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.

The opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to methadone overdose. Such agents should be administered cautiously to patients who are known, or suspected to be, physically dependent on methadone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The duration of reversal would be expected to be less than the duration of

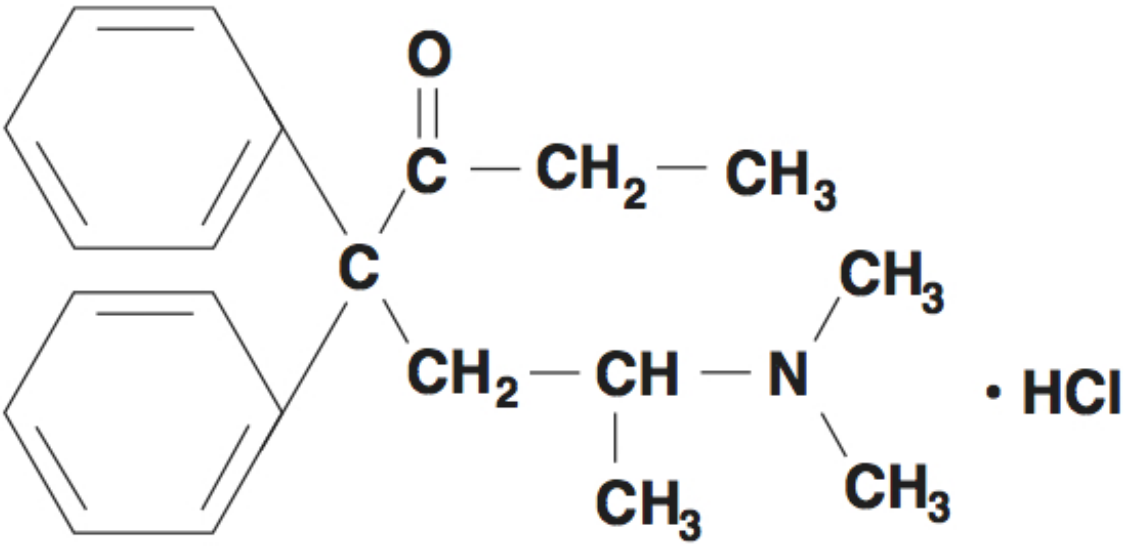
action of methadone, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal produced 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 hydrochloride USP is a white powder that is water-soluble. Its molecular formula is C21H27NO• HCl and it has a molecular weight of 345.91. Methadone hydrochloride has a melting point of 235°C, and a pKa of 8.25 in water at 20°C. Its octanol/water partition coefficient at pH 7.4 is 117. A solution (1:100) in water has a pH between 4.5 and 6.5.

It has the following structural formula:



Each 5 mL of oral solution contains 5 mg or 10 mg of methadone hydrochloride USP and the following inactive ingredients: alcohol (8%), benzoic acid, citric acid, FD&C Red #40, FD&C Yellow #6, flavoring (lemon), glycerin, sorbitol, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

qualitatively similar to that of morphine, differs in that the onset is slower, the duration is also 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. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

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 is primarily distributed.

Metabolism. Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine. Methadone appears to be a substrate for P-glycoprotein but its pharmacokinetics do not appear to be significantly altered in the case of P-glycoprotein polymorphism or inhibition.

Elimination. Elimination of methadone is mediated by extensive liver metabolism, 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 activity.

Drug Interactions. Methadone undergoes hepatic N-demethylation by cytochrome P450 (CYP) isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration 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 (7.2)].* Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Cytochrome P450 Inducers: The following drug interactions were reported following coadministration 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 precipitation of withdrawal symptoms.

Phenytoin: The 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: Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone.

Voriconazole: Repeated 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 coadministration. Dose reduction of methadone may be needed *[see Drug Interactions (7.2)]*.

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

Abacavir, amprenavir, darunavir+ritonavir, efavirenz, nelfinavir, nevirapine, ritonavir, telaprevir, lopinavir+ritonavir, saquinavir+ritonavir, tipranvir+ritonavir combination: Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone *[see Drug Interactions (7.2)]*.

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 (7.2)].*

Zidovudine: Methadone increased the AUC of zidovudine which could result in toxic effects *[see Drug Interactions (7.2)].*

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 (mg/m^2). 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 a human daily oral dose of 120 mg/day, based on body surface area comparison. 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 a human daily oral dose of 120 mg/day, based on body surface area comparison. 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.

Published animal studies show that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats.

16 HOW SUPPLIED/STORAGE AND HANDLING

Product: 17856-3555

NDC: 17856-3555-2 1 mL in a SYRINGE

NDC: 17856-3555-5 5 mL in a CUP, UNIT-DOSE

NDC: 17856-3555-1 2 mL in a CUP

Product: 17856-3556

NDC: 17856-3556-5 10 mL in a CUP

NDC: 17856-3556-6 5 mL in a CUP, UNIT-DOSE

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Medication Errors

Instruct patients how to measure and take the correct dose of Methadone Hydrochloride Oral Solution and to always use a calibrated measuring device when administering Methadone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately *[see Warnings and Precautions (5.1)].*

Advise patients that Methadone Hydrochloride Oral Solution, is available in two concentrations: 5 mg/5 mL and 10 mg/5 mL. Inform patients about which concentration they have been prescribed and provide detailed instruction on how to measure and take the correct dose of Methadone Hydrochloride Oral Solution, and to always use the enclosed measuring device when administering Methadone Hydrochloride Oral Solution, to ensure that the dose is measured and administered accurately.

If the prescribed concentration is changed, instruct patients on how to correctly measure the new dose to avoid errors which could result in accidental overdose and death.

Addiction, Abuse, and Misuse

Inform patients that the use of methadone, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.2)].* Instruct patients not to share methadone with others and to take steps to protect methadone from theft or misuse.

Life-threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting methadone or when the dose is increased, and that it can occur even at recommended doses *[see Warnings and*

*Precautions (*5.3*)].* Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (*5.3*)].* Instruct patients to take steps to store methadone securely and to dispose of unused methadone by flushing the tablets down the toilet.

Symptoms of Arrhythmia

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

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if Methadone Hydrochloride Oral Solution is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (*5.6*), Drug Interactions (7.1)].*

Serotonin Syndrome

Inform patients that Methadone Hydrochloride Oral Solution could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (*5.9*), Drug Interactions (7.5)].*

Adrenal Insufficiency

Inform patients that Methadone Hydrochloride Oral Solution could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (*5.10*)].*

Important Administration Instructions

Instruct patients how to properly take methadone, including the following:

- Advise patients to always use a calibrated oral syringe/dosing cup when administering Methadone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately *[see Warnings and Precautions (5.1)]*
- Advise patients never to use household teaspoons or tablespoons to measure Methadone Hydrochloride Oral Solution
- Use methadone exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Do not discontinue methadone without first discussing the need for a tapering regimen with the prescriber

Hypotension

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

Driving or Operating Heavy Machinery

Inform patients that methadone may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in methadone. Advise patients how to recognize such a reaction and when to seek medical attention.

Neonatal Opioid Withdrawal Syndrome

Advise women that if they are pregnant while being treated with Methadone Hydrochloride Oral Solution, the baby may have signs of withdrawal at birth and that withdrawal is treatable *[see Warnings and Precautions (*5.5*), Specific Populations (8.1)].*

Breastfeeding

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

Disposal of Unused Methadone

Advise patients to flush the unused methadone down the toilet when methadone is [illegible] **p.**

Medication Guide

Methadone Hydrochloride (meth' a done hye" droe klor' ide)
Oral Solution USP, CII
Rx only

Methadone Hydrochloride Oral Solution is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse than can lead to death.
- Not for use to treat pain that is not around-the-clock
- Also used to manage drug addiction.

Important information about Methadone Hydrochloride Oral Solution:

- **Get emergency help right away if you take too much Methadone Hydrochloride Oral Solution (overdose).** When you first start taking methadone, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking Methadone Hydrochloride Oral Solution with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing

problems, coma, and death.
- Never give anyone your methadone. They could die from taking it. Store methadone away from children and in a safe place to prevent stealing or abuse. Selling or giving away methadone is against the law.

Do not take Methadone Hydrochloride Oral Solution if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking Methadone Hydrochloride Oral Solution, tell your healthcare provider if you have a history of:

- head injury, seizures • pancreas or gallbladder problems
- liver, kidney, thyroid problems • abuse of street or prescription drugs, alcohol
- problems urinating addiction or mental health problems
- heart rhythm problems (Long QT syndrome)

Tell your healthcare provider if you are:

- **pregnant or plan to become pregnant.** If you take Methadone Hydrochloride Oral Solution while pregnant, your baby may have symptoms of opioid withdrawal or respiratory depression at birth. Talk to your doctor if you are pregnant or plan to become pregnant.
- **breastfeeding.** Methadone Hydrochloride Oral Solution passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking methadone with certain other medicines may cause serious side effects.

When taking Methadone Hydrochloride Oral Solution:

- Do not change your dose. Take methadone exactly as prescribed by your healthcare provider.
- Always use a calibrated measuring device for Methadone Hydrochloride Oral Solution to correctly measure your dose. A household teaspoon or tablespoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device.
- Do not take more than your prescribed dose in 24 hours. If you take methadone for pain and miss a dose, take methadone as soon as possible and then take your next dose 8 or 12 hours later as directed by your healthcare provider. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.
- If you take methadone for opioid addiction and miss a dose, take your next dose the following day as scheduled. Do not take extra doses. Taking more than the prescribed dose may cause you to overdose because methadone builds up in your body over time.

- Do not crush, dissolve, snort or inject methadone because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking methadone without talking to your healthcare provider.**
- After you stop taking methadone, flush any unused methadone down the toilet.

While taking Methadone Hydrochloride Oral Solution DO NOT:

- Drive or operate heavy machinery, until you know how methadone affects you. Methadone can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with methadone may cause you to overdose and die.

The possible side effects of Methadone Hydrochloride Oral Solution are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of Methadone Hydrochloride Oral Solution. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

Distr. by: **West-Ward**
Pharmaceuticals Corp.
Eatontown, NJ 07724
For more information, please call 1-800-962-8364.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

4056301//09

Revised March 2017

METHADONE HYDROCHLORIDE SOLUTION

METHADONE HCL
5 MG/5 ML
ORAL SOLUTION
RX ONLY
DELIVERS 5 ML

17856355505

DISTRIBUTED BY ATLANTIC BIOLOGICALS CORP.
Exp:03/09/2020
Lot#lot1
Mfg:DIST BY: WEST-WARD
MFG LOT#AA5916A
Pkg by UDS
Morrisville, NC 27560
CII

METHADONE HCL
2MG/2ML
ORAL SOLUTION
RX ONLY
DELIVERS 2 ML

17856355501

DISTRIBUTED BY ATLANTIC BIOLOGICALS CORP.
Exp:03/09/2020
Lot#lot1
Mfg:DIST.BY WEST-WARD
MFG LOT#AA9011A
Pkg by UDS
Morrisville, NC 27560
CII

17856-3555-04
Methadone
Hydrochloride
Oral Solution, USP
1mg/1mL
Delivers 1mL

UDOSE

See package insert for indications and dosage schedule

Store at 25°C(77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.] Each 5mL contains methadone hcl USP 5mg, alcohol 8%.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN

17856355504

17856-3555-04 **Dosage: 1mg/1mL**

Methadone Hcl Oral Solution **Qty: 60 ENFit SRN**

GTIN: 00117856355540
S/N: 01015001
Exp: 10/16/20
Lot: 010150

CII

Packaged by Unit Dose Solutions
Morrisville, NC 27560

Distributed by: AtlanticBiologicals Corp.
Miami Fl 33179

Rev.09/19 **Call to Reorder: 800.509.7592**

17856-3555-02
METHADONE HYDROCHLORIDE ORAL SOLUTION 1 mg per 1 mL
FOR ORAL USE ONLY

UDOSE

See package insert for indications and dosage schedule

17856355502

Store at 20° to 25°C (68° to 77°F); with excursions permitted between 15° to 30°C (59° to 86°F).[See USP Controlled Room Temperature.]
KEEP OUT OF THE REACH OF CHILDREN

17856-3555-02 **Dosage: 1 mL**

METHADONE **Qty: 120 ENFIT SYRINGES**

GTIN: 00117856355526
S/N: 00919201
Exp: 07/16/20
Lot: 009192

CII

Packaged by:Unit Dose Solutions
Morrisville, NC 27560

Distributed by: AtlanticBiologicals Corp,
Miami Fl 33179

Rev.09/19 **Call to Reorder: 800.509.7592**

METHADONE HCL
20MG/10ML
ORAL SOLUTION
RX ONLY
DELIVERS 10ML

17856355605

DISTRIBUTED BY ATLANTIC BIOLOGICALS CORP.
Exp:03/09/2020
Lot#lot1
Mfg:DIST BY: WEST-WARD MFG LOT#AA9014A
Pkg by UDS
Morrisville, NC 27560
CII

METHADONE HCL
10 MG/5 ML
ORAL SOLUTION
RX ONLY
DELIVERS 5 ML

17856355606

DISTRIBUTED BY ATLANTIC BIOLOGICALS CORP.
Exp:03/09/2020
Lot#lot1
Mfg:WEST-WARD MFG LOT#AA9014A
Pkg by UDS
Morrisville, NC 27560
CII

METHADONE HYDROCHLORIDE

methadone hydrochloride solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:17856-3555(NDC:0054-3555)
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METHADONE HYDROCHLORIDE (UNII: 229809935B) (METHADONE - UNII:UC6VBE7V1Z)	METHADONE HYDROCHLORIDE	5 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
ALCOHOL (UNII: 3K9958V90M)	
BENZOIC ACID (UNII: 8SKN0B0MIM)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
GLYCERIN (UNII: PDC6A3C0OX)	
SORBITOL (UNII: 506T60A25R)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:17856-3555-2	120 in 1 CASE	04/27/2020	
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:17856-3555-4	60 in 1 BOX, UNIT-DOSE	04/27/2020	
2		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
3	NDC:17856-3555-5	5 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product	04/27/2020	
4	NDC:17856-3555-1	2 mL in 1 CUP; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)	04/27/2020	
5	NDC:17856-3555-8	120 in 1 BOX, UNIT-DOSE	08/06/2020	
5		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA087393	05/22/1981	

METHADONE HYDROCHLORIDE

methadone hydrochloride solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:17856-3556(NDC:0054-3556)

Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METHADONE HYDROCHLORIDE (UNII: 229809935B) (METHADONE - UNII:UC6VBE7V1Z)	METHADONE HYDROCHLORIDE	10 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
ALCOHOL (UNII: 3K9958V90M)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
BENZOIC ACID (UNII: 8SKN0B0MIM)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
SORBITOL (UNII: 506T60A25R)	
GLYCERIN (UNII: PDC6A3C0OX)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:17856-3556-5	72 in 1 CASE	04/27/2020	
1		10 mL in 1 CUP; Type 0: Not a Combination Product		
2	NDC:17856-3556-6	72 in 1 CASE	04/27/2020	
2		5 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA087997	08/30/1982	

Labeler - ATLANTIC BIOLOGICALS CORP. (047437707)

Establishment

Name	Address	ID/FEI	Business Operations
ATLANTIC BIOLOGICALS CORP.		047437707	REPACK(17856-3555, 17856-3556)