METHADONE HYDROCHLORIDE- methadone hydrochloride concentrate
ATLANTIC BIOLOGICALS CORP.

Methadone HCl Oral Concentrate

Methadone Hydrochloride Oral Concentrate, USP

and

Methadone Hydrochloride Oral Concentrate, USP

(dye-free, sugar-free, unflavored)

10 mg/mL

CII

Rx only

FOR ORAL USE ONLY

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION, LIFE-THREATENING QT PROLONGATION, ACCIDENTAL INGESTION, ABUSE, POTENTIAL INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES and TREATMENT FOR OPIOID ADDICTION

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, have been reported during initiation and conversion of patients to methadone, and even when the drug has been used as recommended and not misused or abused (*see*WARNINGS). Proper dosing and titration are essential and methadone hydrochloride oral concentrate should only be prescribed by healthcare professionals who are knowledgeable in the use of methadone for detoxification and maintenance treatment of opioid addiction. Monitor for respiratory depression, especially during initiation of methadone hydrochloride oral concentrate or following a dose increase. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak pharmacologic effect, especially during the initial dosing period (*see* WARNINGS).

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, is a risk factor for respiratory depression and death (*see*WARNINGS*and*PRECAUTIONS).

- **Reserve concomitant prescribing of benzodiazepines or other CNS depressants in patients in methadone treatment to those for whom alternates to benzodiazepines or other CNS depressants are inadequate.**
- **Follow patients for signs and symptoms of respiratory depression and sedation. If the patient is visibly sedated, evaluate the cause of sedation and consider delaying or omitting daily methadone dosing.**

Life-Threatening QT Prolongation

QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone (see WARNINGS). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients with risk factors for development of prolonged QT interval, a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction for changes in cardiac rhythm during initiation and titration of methadone hydrochloride oral concentrate (*see* WARNINGS).

Accidental Ingestion

Accidental ingestion of methadone hydrochloride oral concentrate, especially by children, can result in fatal overdose of methadone (*see*WARNINGS).

Misuse, Abuse, and Diversion of Opioids

Methadone hydrochloride oral concentrate contains methadone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit (*see*WARNINGS).

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The concomitant use of methadone hydrochloride oral concentrate with all cytochrome P450 3A4, 2B6, 2C19, 2C9 or 2D6 inhibitors may result in an increase in methadone plasma concentrations, which could cause potentially fatal respiratory depression. In addition, discontinuation of concomitantly used cytochrome P450 3A4 2B6, 2C19, or 2C9 inducers may also result in an increase in methadone plasma concentration. Follow patients

closely for respiratory depression and sedation, and consider dosage reduction with any changes of concomitant medications that can result in an increase in methadone levels (*see* WARNINGS *and* PRECAUTIONS, Drug Interactions).

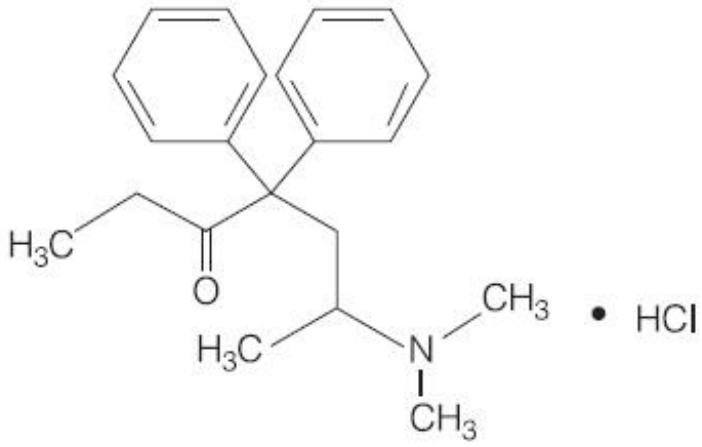
Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

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* DOSAGE AND ADMINISTRATION).

DESCRIPTION

Methadone Hydrochloride Oral Concentrate, USP, contains methadone, an opiate agonist, and is available as a cherry flavored liquid concentrate for oral administration. Methadone Hydrochloride Oral Concentrate, USP Sugar-free is a dye-free, sugar-free, unflavored liquid concentrate for oral administration. Each liquid concentrate contains 10 mg of methadone hydrochloride per mL.

Methadone hydrochloride is chemically described as 3-heptanone, 6-(dimethylamino)-4,4-diphenyl-, hydrochloride. Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. It is present in methadone hydrochloride oral concentrate as the racemic mixture. Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 part per 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water. Its structural formula is:



$C_{21}H_{27}NO•HCl$ MW = 345.91

Other ingredients of methadone hydrochloride oral concentrate, USP: artificial cherry flavor, sorbic acid, potassium sorbate, FD&C red no. 40, D&C red no. 33, poloxamer 188, propylene glycol, glycerin, sucrose, and purified water.

Other ingredients of Methadone Hydrochloride Oral Concentrate, USP (Dye-Free, Sugar-Free, Unflavored): citric acid anhydrous, purified water, and sodium benzoate.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown.

Pharmacodynamics

Effects on the Central Nervous System

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

Methadone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

Effects on the Cardiovascular System

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

Effects on the Endocrine System

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

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

Effects on the Immune System

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

Concentration–Adverse Reaction Relationships

There is a relationship between increasing methadone plasma concentration and increasing frequency of

dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

Pharmacokinetics

Absorption

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

Distribution

Methadone 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 α_1-acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1, 5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion

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

Specific Populations

Use During Pregnancy

The disposition of oral methadone has been studied in approximately 30 pregnant patients in the second and third trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (*see* **PRECAUTIONS, Pregnancy, Labor and Delivery,** *and* **DOSAGE AND ADMINISTRATION**).

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 accumulating methadone after multiple dosing.

Renal Impairment

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

Sex

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

Race

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

Age

Geriatric Population

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

Pediatric Population

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

Drug Interaction Studies

Cytochrome P450 Interactions

Methadone undergoes hepatic N-demethylation by cytochrome P450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. 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 their CYP induction activity.

Cytochrome P450 Inducers

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

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

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

St. John's Wort, Phenobarbital, Carbamazepine -Administration of methadone with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 Inhibitors

Voriconazole - Voriconazole can inhibit the activity of CYP3A4, CYP2C9 and CYP2C19. Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 4 days) increased

the C_{max} and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). 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.

Anti-Retroviral Agents

Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, and lopinavir+ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity.

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination – Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone.

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

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

INDICATIONS AND USAGE

1. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
2. For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

Limitations of Use

Methadone products used for the treatment of opioid addiction in detoxification or maintenance programs are subject to the conditions for distribution and use required under 21 CFR, Title 42, Sec 8 (*see* **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Methadone hydrochloride is contraindicated in patients with:

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

WARNINGS

Methadone hydrochloride oral concentrate and Methadone hydrochloride oral concentrate Sugar-Free are for oral administration only. The preparation must not be injected. Methadone hydrochloride oral concentrate and Methadone hydrochloride oral concentrate Sugar-Free, if dispensed, should be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of methadone, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status (*see* **OVERDOSAGE**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of methadone hydrochloride oral concentrate, 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 pharmacologic effect, especially during the initial dosing period. Monitor patients closely for respiratory depression, when initiating therapy with methadone hydrochloride oral concentrate and following dose increases.

Instruct patients against use by individuals other than the patient for whom methadone was prescribed and to keep methadone out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of methadone are essential (*see* **DOSAGE AND ADMINISTRATION**). Overestimating the methadone dosage when initiating treatment can result in fatal overdose with the first dose.

To further reduce the risk of respiratory depression, consider the following:

- Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other mu-opioid agonists. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. Follow induction directions closely to avoid inadvertent overdose (*see* **DOSAGE AND ADMINISTRATION**).
- Proper dosing and titration are essential and methadone should be overseen only by healthcare professionals who are knowledgeable in the pharmacokinetics and pharmacodynamics of methadone.

Risks from Concomitant Use of Benzodiazepines or Other CNS Depressants with Methadone

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

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

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

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

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

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

Life-Threatening QT Prolongation

Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most patients on the lower doses typically used for maintenance, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients. The effects of methadone on the QT interval have been confirmed in *in vivo* laboratory studies, and methadone has been shown to inhibit cardiac potassium channels in *in vitro* studies.

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

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

Only initiate therapy with methadone hydrochloride oral concentrate 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.

Accidental Ingestion

Accidental ingestion of even one dose of methadone hydrochloride oral concentrate, especially by children, can result in respiratory depression and death due to an overdose. Keep methadone hydrochloride oral concentrate out of reach of children to prevent accidental ingestion.

Misuse, Abuse, and Diversion of Opioids

Methadone hydrochloride oral concentrate contain methadone, an opioid agonist and a Schedule II controlled substance. Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

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.

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. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly (*see***PRECAUTIONS, Pregnancy**).

Advise pregnant women receiving opioid addiction treatment with methadone hydrochloride oral concentrate of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. This risk must be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

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

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

Addition of CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuation of a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors in patients treated with methadone hydrochloride oral concentrate may decrease methadone plasma concentrations, reducing efficacy or, and may, lead to a withdrawal symptoms in patients physically dependent on methadone. When using methadone hydrochloride oral concentrate with CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers or discontinuing CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors, follow patients for signs or symptoms of opioid withdrawal and consider increasing the methadone hydrochloride oral concentrate dosage as needed.

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

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

Patients with Chronic Pulmonary Disease - Methadone hydrochloride oral concentrate-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of methadone hydrochloride oral concentrate (*see* **WARNINGS, Life-Threatening Respiratory Depression**).

Elderly, Cachectic, or Debilitated Patients - Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients (*see* **WARNINGS, Life-Threatening Respiratory Depression**).

Monitor such patients closely, particularly when initiating and titrating methadone hydrochloride oral concentrate and when methadone hydrochloride oral concentrate is given concomitantly with other drugs that depress respiration.

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 concentrate with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (*see* **PRECAUTIONS, Drug Interactions**). This may occur within the recommended dosage range.

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

Adrenal Insufficiency

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

Severe Hypotension

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

Use in Patients with Head Injury or Increased Intracranial Pressure

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), methadone hydrochloride oral concentrate may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with methadone.

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

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

Risks of Use in Patients with Gastrointestinal Conditions

Methadone hydrochloride oral concentrate is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The methadone in methadone hydrochloride oral concentrate may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum

amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risks of Seizure in Patients with Seizure Disorders

Methadone may increase frequency of seizures in patients with seizure disorders, and increase the risks of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during methadone hydrochloride oral concentrate therapy.

Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist, including methadone hydrochloride oral concentrate. In these patients, mixed agonists/antagonist and partial agonist analgesics may precipitate withdrawal symptoms (*see* **PRECAUTIONS, Drug Interactions**).

When discontinuing methadone hydrochloride oral concentrate, gradually taper the dosage (*see* **DOSAGE AND ADMINISTRATION**). Do not abruptly discontinue methadone hydrochloride oral concentrate.

Use in Ambulatory Patients

Driving or Operating Heavy Machinery

Inform patients that methadone hydrochloride oral concentrate may impair the ability to perform potentially hazardous activities such as driving or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication (*see* **PRECAUTIONS, Information for Patients**).

Laboratory Test Interactions

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

PRECAUTIONS

Information for Patients

Life-Threatening Respiratory Depression

Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting methadone hydrochloride oral concentrate or when the dose is increased (*see* **WARNINGS**). Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal addictive effects may occur if methadone hydrochloride oral concentrate is used with benzodiazepines or other CNS depressants, including alcohol. Counsel patients that such medications should not be used concomitantly unless supervised by a healthcare provider (*see* **WARNINGS** *and* **PRECAUTIONS, Drug Interactions**).

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 hydrochloride oral concentrate (*see* **WARNINGS**).

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death (*see* **WARNINGS**). Instruct patients to take steps to store methadone hydrochloride oral concentrate securely. Advise patients to dispose of unused methadone hydrochloride oral concentrate by flushing down the toilet.

Abuse Potential

Inform patients that methadone hydrochloride oral concentrate contains methadone, a Schedule II controlled substance that is subject to abuse (*see* **WARNINGS**). Instruct patients not to share methadone hydrochloride oral concentrate with others and to take steps to protect methadone hydrochloride oral concentrate from theft or misuse.

Important Administration Instructions (*see* DOSAGE AND ADMINISTRATION)

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

- Methadone hydrochloride oral concentrate is for oral administration only. The preparation must not be injected.
- Inform patients that methadone hydrochloride oral concentrate should be taken only as directed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression), and the dose should not be adjusted without consulting a physician or other healthcare professional.
- Reassure patients initiating treatment with methadone hydrochloride oral concentrate for opioid dependence that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Apprise patients seeking to discontinue treatment with methadone for opioid dependence of the high risk of relapse to illicit drug use associated with discontinuation of methadone hydrochloride oral concentrate maintenance treatment.
- Advise patients not to discontinue methadone hydrochloride oral concentrate without first discussing the need for a tapering regimen with the prescriber.

Serotonin Syndrome

Inform patients that methadone hydrochloride oral concentrate 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, Drug Interactions**).

MAOI Interaction

Inform patients to avoid taking methadone hydrochloride oral concentrate while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking methadone hydrochloride oral concentrate (*see* **WARNINGS** *and* **PRECAUTIONS, Drug Interactions**).

Adrenal Insufficiency

Inform patients that methadone hydrochloride oral concentrate 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**).

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in methadone hydrochloride oral concentrate. Advise patients how to recognize such a reaction and when to seek medical attention (*see* **ADVERSE REACTIONS**).

Neonatal Opioid Withdrawal

Advise women that if they are pregnant while being treated with methadone hydrochloride oral concentrate, the baby may have signs of withdrawal at birth and that withdrawal is treatable (*see* **WARNINGS**).

Lactation

Instruct nursing mothers using methadone hydrochloride oral concentrate 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 their baby's healthcare provider immediately if they notice these signs. If they cannot reach the healthcare provider right away, instruct them to take the baby to the emergency room or call 911 (or local emergency services) (*see* **PRECAUTIONS, Pregnancy**).

Constipation

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

Drug Interactions

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments (*see* **WARNINGS**).
Examples:	Alcohol, benzodiazepines, and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids.
Inhibitors of CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6	
Clinical Impact:	Methadone undergoes hepatic N-demethylation by several cytochrome P450 (CYP) isoforms, including CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6. The concomitant use of methadone and CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitors can increase the plasma concentration of methadone, resulting in increased or prolonged opioid effects, and may result in a fatal overdose, particularly when an inhibitor is added after a stable dose of methadone is achieved. These effects may be more pronounced with concomitant use of drugs that inhibit more than one of the CYP enzymes listed above. After stopping a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor, as the effects of the inhibitor decline, the methadone plasma concentration can decrease, resulting in decreased opioid efficacy or withdrawal symptoms in patients physically dependent on methadone.
Intervention:	If concomitant use is necessary, consider dosage reduction of methadone until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4, CYP2B6, CYP2C19, CYP2C9, or CYP2D6 inhibitor is

	discontinued, follow patients for signs of opioid withdrawal and consider increasing the methadone dosage until stable drug effects are achieved.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), fluconazole, fluvoxamine, some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine)
Inducers of CYP3A4, CYP2B6, CYP2C19, or CYP2C9	
Clinical Impact:	The concomitant use of methadone and CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducers can decrease the plasma concentration of methadone, resulting in decreased efficacy or onset of withdrawal symptoms in patients physically dependent on methadone. These effects could be more pronounced with concomitant use of drugs that can induce multiple CYP enzymes. After stopping a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer, as the effects of the inducer decline, the methadone plasma concentration can increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, sedation, or death.
Intervention:	If concomitant use is necessary, consider increasing the methadone dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4, CYP2B6, CYP2C19, or CYP2C9 inducer is discontinued, consider methadone dosage reduction and monitor for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin, St. John's Wort, Phenobarbital
Potentially Arrhythmogenic Agents	
Clinical Impact:	Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents or drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia).
Intervention:	Monitor patients closely for cardiac conduction changes.
Examples:	Drugs known to have potential to prolong QT interval: Class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. Drugs capable of inducing electrolyte disturbances: Diuretics, laxatives, and, in rare cases, mineralocortocoid hormones.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome (*see* **WARNINGS**).
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue methadone hydrochloride oral concentrate if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) (*see* **WARNINGS**).
Intervention:	The use of methadone hydrochloride oral concentrate is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	Patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Methadone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of methadone hydrochloride oral concentrate and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when methadone hydrochloride oral concentrate is used concomitantly with anticholinergic drugs.

Paradoxical Effects of Antiretroviral Agents on Methadone

Concurrent use of certain protease inhibitors 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 hydrochloride oral concentrate and could precipitate a withdrawal syndrome. Monitor patients receiving methadone hydrochloride oral concentrate and any of these antiretroviral therapies closely for evidence of withdrawal effects and adjust the methadone hydrochloride oral concentrate dose accordingly.

Effects of Methadone on Antiretroviral Agents

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

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

Desipramine – Plasma levels of desipramine have increased with concurrent methadone administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (HDD). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These

doses were approximately 1.3 and 2.3 times the HDD. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times the HDD. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis - There are several published reports on the potential genetic toxicity of methadone. Methadone tested 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. In contrast, 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.

Impairment of Fertility - Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces decreased sexual activity (mating) of male rats at 10 mg/kg/day (corresponding to 0.3 times the human daily oral dose of 120 mg/day based on body surface area). Methadone also produces a significant regression of sex accessory organs and testes of male mice and rats at 0.2 and 0.8 times the HDD, respectively. Methadone treatment of pregnant rats from Gestation Day 14 to 19 reduced fetal blood testosterone and androstenedione in male. Decreased serum levels of testosterone were observed in male rats that were treated with methadone (1.3 to 3.3 mg/kg/day for 14 days, corresponding to 0.1 to 0.3 times the HDD) or 10 to 15 mg/kg/day for 10 days (0.8 to 1.2 times the HDD).

Pregnancy

Pregnancy Category C. Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy(*see* **WARNINGS**).

There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by 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). 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 complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs.

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

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the second trimester or premature delivery in the third trimester.

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

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

Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with methadone hydrochloride oral concentrate.

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

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Data

Animal Data

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

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

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

Additional animal data demonstrates evidence for neurochemical changes in the brains of offspring from methadone-treated pregnant rats, including changes to the cholinergic, dopaminergic, noradrenergic and

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

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

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

Labor and Delivery

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

Lactation

Risk Summary

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

Clinical Considerations

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

Data

In a study of ten breastfeeding women maintained on oral methadone doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk were reported, which, in the majority of

samples, were lower than maternal serum drug concentrations at steady state.

In a study of twelve breastfeeding women maintained on oral methadone doses of 20 to 80 mg/day, methadone concentrations from 39 to 232 mcg/L in milk were reported. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day, which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone.

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

Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible(*see* **ADVERSE REACTIONS**). Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported.

Pediatric Use

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

Geriatric Use

Clinical studies of methadone 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, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

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

Hepatic Impairment

The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing. Start these patients on lower doses and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression.

Renal Impairment

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

ADVERSE REACTIONS

The 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. In such individuals, lower doses are advisable.

Other adverse reactions include the following: (listed alphabetically under each subsection)

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

Cardiovascular (*see* **WARNINGS, Cardiac Conduction Effects**) – arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Digestive – abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic and Lymphatic – reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain

Nervous – agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures

Respiratory – pulmonary edema, respiratory depression (*see* **WARNINGS, Respiratory Depression**)

Skin and Appendages – pruritus, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses – hallucinations, visual disturbances

Urogenital – amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of methadone hydrochloride oral concentrate.

Serotonin syndrome - Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs (*see* **WARNINGS***and* **PRECAUTIONS, Drug Interactions**).

Adrenal insufficiency - Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use (*see* **WARNINGS**).

Anaphylaxis - Anaphylactic reaction has been reported with ingredients contained in methadone hydrochloride oral concentrate (*see* **CONTRAINDICATIONS**).

Androgen deficiency - Cases of androgen deficiency have occurred with chronic use of opioids(*see* **CLINICAL PHARMACOLOGY**).

DRUG ABUSE AND DEPENDENCE

Methadone hydrochloride oral concentrate contains methadone, a Schedule II opioid agonist. Schedule II opioid substances, which also include hydromorphone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Abuse of methadone hydrochloride oral concentrate poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone hydrochloride oral concentrate with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Because methadone hydrochloride oral concentrate may be diverted for non-medical use, careful

record keeping of ordering and dispensing information, including quantity and frequency is strongly advised.

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

Methadone hydrochloride oral concentrate, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs certified by the Substance Abuse and Mental Health Services Administration (and agencies, practitioners or institutions by formal agreement with the program sponsor).

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

Physical dependence can develop during chronic opioid therapy.

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 (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 significant dose reduction of a drug. Withdrawal is also precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) or mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. Physical dependence is expected during opioid agonist therapy of opioid addiction.

Methadone hydrochloride oral concentrate should not be abruptly discontinued (*see* **DOSAGE AND ADMINISTRATION**). If methadone hydrochloride oral concentrate is abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other 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(*see* **DOSAGE AND ADMINISTRATION, Medically Supervised Withdrawal After a Period of Maintenance Treatment**).

OVERDOSAGE

Clinical Presentation

Acute overdosage with methadone can be manifested by respiratory depression somnolence progressing to stupor or coma, skeletal-muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment of Overdose

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

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

administered in the absence of clinically significant respiratory or circulatory depression secondary to methadone overdose.

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

In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

DOSAGE AND ADMINISTRATION

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

Code of Federal Regulations, Title 42, Sec 8.

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

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

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

During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 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 21 CFR 1306.07(b)).

Important General Information

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

- The peak respiratory depressant effect of methadone occurs later and persists longer than its peak pharmacologic effect.
- A high degree of opioid tolerance does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other opioid agonists.
- There is high interpatient variability in absorption, metabolism, and relative analgesic potency. Population-based conversion ratios between methadone and other opioids are not accurate when

applied to individuals.

- With repeated dosing, methadone is retained in the liver and then slowly released, prolonging the duration of potential toxicity.
- Steady-state plasma concentrations are not attained until 3 to 5 days after initiation of dosing.
- Methadone hydrochloride oral concentrate has a narrow therapeutic index, especially when combined with other drugs.

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

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

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg.

If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear.

The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

During the induction phase of methadone maintenance treatment, patients may show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness 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.

Short-Term Detoxification

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

Titration and Maintenance Treatment of Opioid Dependence

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

Medically Supervised Withdrawal After a Period of Maintenance Treatment

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

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

Abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms (*see* **DRUG ABUSE AND DEPENDENCE**). Opioid withdrawal symptoms have been associated with an increased risk of relapse to illicit drug use in susceptible patients.

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 nonmethadone-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.

Dosage Adjustment During Pregnancy

Methadone clearance may be increased during pregnancy. During pregnancy, 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* **CLINICAL PHARMACOLOGY, Pharmacokinetics, Specific Populations,***and* **PRECAUTIONS, Pregnancy**).

HOW SUPPLIED

Methadone hydrochloride oral concentrate USP 10 mg/mL is supplied as a red, cherry flavored liquid concentrate, as follows:

1 fl. oz. Bottle (30 mL) ……NDC 66689-694-30 (Supplied with calibrated dropper);

1 Liter Bottle (1000 mL) ……..NDC 66689-694-79

Methadone Hydrochloride Oral Concentrate, USP 10 mg/mL, is supplied as a dye-free, sugar-free, unflavored liquid concentrate, as follows:

1 fl. oz. Bottle (30 mL) ……NDC 66689-695-30 (Supplied with calibrated dropper);

1 Liter Bottle (1000 mL) ……..NDC 66689-695-79

Dispense in tight containers, protected from light. Store at 20° to 25°C (68° to 77°F) ***[see USP Controlled Room Temperature].***

DISTRIBUTED BY:

ATLANTIC BIOLOGICALS CORP.

20101 N.E 16TH PLACE

MIAMI, FL 33179

PRINCIPAL DISPLAY PANEL (CHERRY FLAVOR)

NDC 17856-0694-1

METHADONE HYDROCHLORIDE

ORAL CONCENTRATE, USP CII

2.5mg/0.25mL

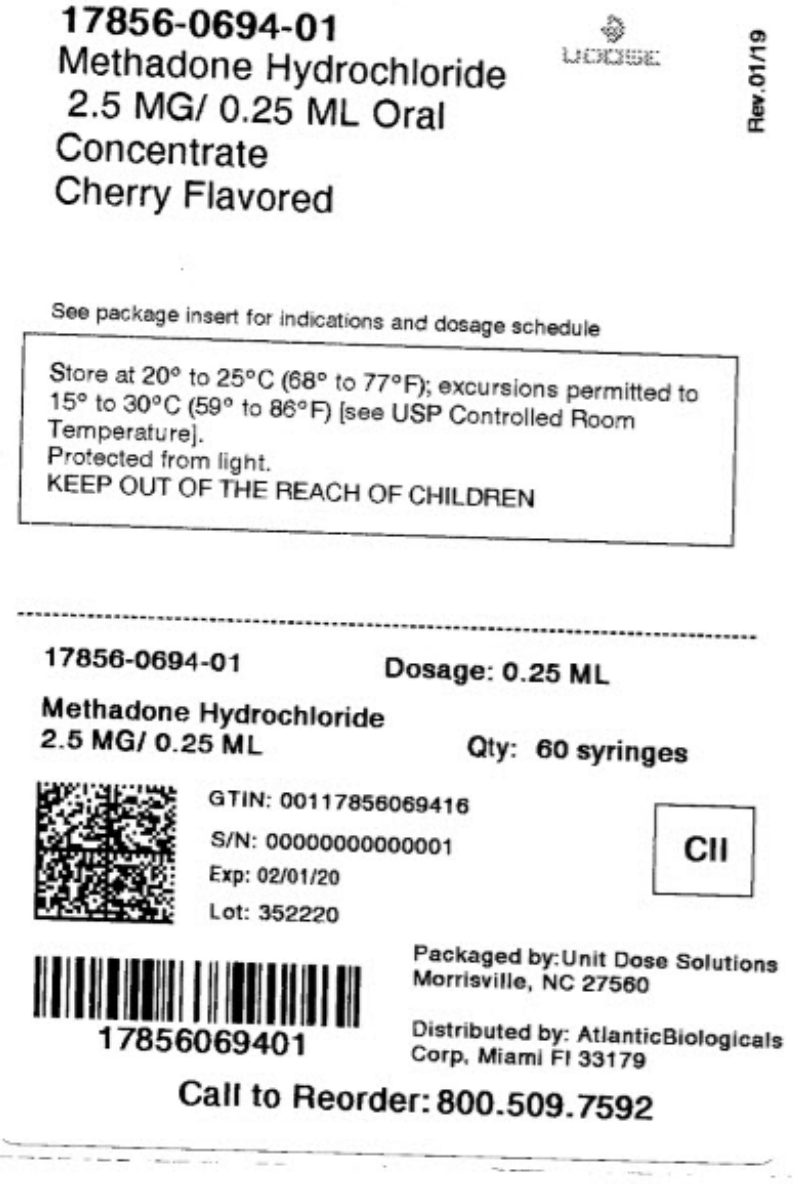
(Cherry Flavored)

STORAGE: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight container protected from light.

At the time of dispensing, replace cap with safety cap dropper.

Rx Only



NDC 17856-0694-2

METHADONE HYDROCHLORIDE

ORAL CONCENTRATE, USP CII

5mg/0.5mL

(Cherry Flavored)

STORAGE: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight container protected from light.

At the time of dispensing, replace cap with safety cap dropper.

Rx Only

17856-0694-02
Methadone Hydrochloride
5 mg/ 0.5mL Oral Concentrate
Cherry Flavored

UNIDOSE

Rev.01/19

See package insert for indications and dosage schedule

Store at 20 to 25 C (68 to 77 F); excursions permitted to 15 to 30 C (59 to 86 F) [See USP Controlled room temperature]. Protected from light.
Keep this and all medications out of the reach of children.

17856-0694-02 **Dosage: 0.5 mL**

Methadone Hydrochloride 5 mg/ 0.5mL **Qty: 60 syringes**

GTIN: 00117856069423
S/N: 00779700000001
Exp: 02/14/20
Lot: 007797

CII

17856069402

Packaged by:Unit Dose Solutions Morrisville, NC 27560

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Call to Reorder: 800.509.7592

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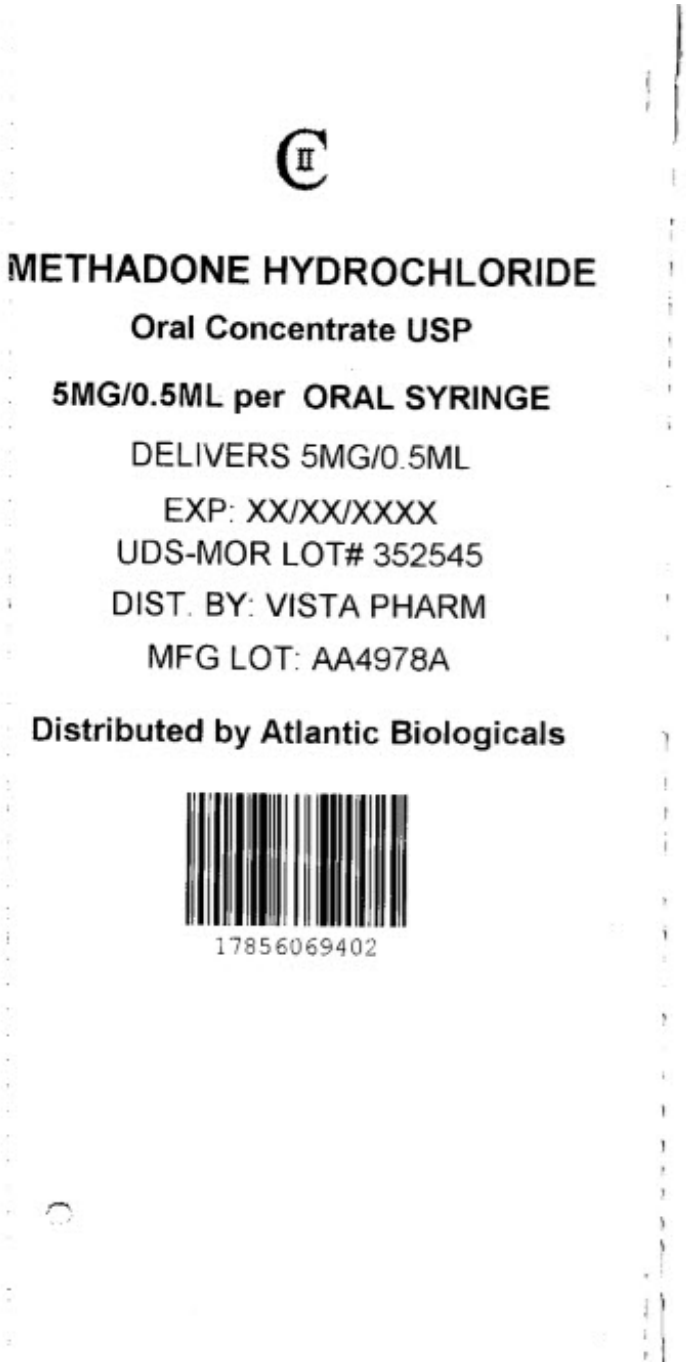

METHADONE HYDROCHLORIDE

methadone hydrochloride concentrate

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:17856-0694(NDC:66689-694)
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 1 mL

Inactive Ingredients	
Ingredient Name	Strength
SORBIC ACID (UNII: X045WJ989B)	
POTASSIUM SORBATE (UNII: 1VPU26JZZ4)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
GLYCERIN (UNII: PDC6A3C0OX)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SUCROSE (UNII: C151H8M554)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics			
Color	RED	**Score**	
Shape		**Size**	
Flavor	CHERRY	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:17856-0694-1	60 in 1 BOX, UNIT-DOSE	01/26/2021	
1		0.25 mL in 1 SYRINGE; Type 0: Not a Combination Product		
2	NDC:17856-0694-2	60 in 1 BOX, UNIT-DOSE	01/26/2021	
2		0.5 mL in 1 SYRINGE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040088	08/28/2019	

Labeler - ATLANTIC BIOLOGICALS CORP. (047437707)

Establishment

Name	Address	ID/FEI	Business Operations
ATLANTIC BIOLOGICALS CORP.		047437707	relabel(17856-0694) , repack(17856-0694)

Revised: 1/2021 ATLANTIC BIOLOGICALS CORP.