


METHADONE HYDROCHLORIDE INJECTION, USP

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| METHADONE HYDROCHLORIDE INJECTION, USP Rx only |  |
| CONDITIONS FOR DISTRIBUTION AND USE | |
| CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS FOR THE TREATMENT OF OPIOID ADDICTION | |
| Code of Federal Regulations, Title 42, Sec 8 | |
| METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS OR INSTITUTIONS BY FORMAL AGREEMENT WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY. CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. | |
| FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM. | |

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

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis). For patients unable to take oral medication, parenteral methadone may be used.
- 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)).

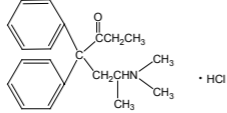
DESCRIPTION

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

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

Methadone hydrochloride is a white, crystalline material that is water-soluble. Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-hepatanone hydrochloride. 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:



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

CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a μ agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe. Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Pharmacokinetics

Absorption:

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

Distribution:

Methadone is a lipophilic drug and the steady state volume of distribution ranges between 2 -6 L/kg. In plasma, methadone is predominantly bound to α₁-acid glycoprotein (85% - 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 and to a lesser extent CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.

Excretion:

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

Pharmacokinetics in Special Populations:

Pregnancy

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

Renal Impairment

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

Hepatic Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

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

Race

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

Geriatric

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

Pediatric

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

Drug Interactions (see PRECAUTIONS, Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, and to a lesser extent 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 CYP3A4 or CYP2D6 inhibitors may reduce metabolism and potentiate methadone's effects. Therefore, drugs

administered concomitantly with methadone should be evaluated for interaction potential (see **Drug Interactions**)

INDICATIONS AND USAGE

- For the treatment of moderate to severe pain not responsive to non-narcotic analgesics.
- For use in temporary treatment of opioid dependence in patients unable to take oral medication.

Outpatient maintenance and outpatient detoxification treatment may be provided only by opioid treatment programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of hospitalization, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

NOTE: INJECTABLE METHADONE PRODUCTS ARE NOT APPROVED FOR THE OUTPATIENT TREATMENT OF OPIOID DEPENDENCE. IN THIS PATIENT POPULATION, PARENTERAL METHADONE IS TO BE USED ONLY FOR PATIENTS UNABLE TO TAKE ORAL MEDICATION, SUCH AS HOSPITALIZED PATIENTS.

CONTRAINDICATIONS

Methadone Hydrochloride Injection is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadone Hydrochloride Injection. Methadone Hydrochloride Injection is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

WARNINGS

Cardiac Conduction Effects

Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. For use of methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone has been considered to outweigh the risk of QT prolongation that has been reported with high doses of methadone.

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

In using methadone an individualized benefit to risk assessment should be carried out and should include evaluation of patient presentation and complete medical history. For patients judged to be at risk, careful monitoring of cardiovascular status, including QT prolongation and dysrhythmias and those described previously should be performed.

Respiratory Depression

Respiratory depression is the chief hazard from methadone hydrochloride. Respiratory depression is a particular potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

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

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

Incomplete Cross-Tolerance Between Methadone and Other Opioids

Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is a particular concern for patients tolerant to other μ-opioid agonists when converting to methadone, making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high dose treatment with other opioid agonists. Therefore, it is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see **DOSAGE AND ADMINISTRATION**, Tables 1 and 2, for appropriate conversion schedules). A high degree of "opioid tolerance" does not eliminate the possibility of methadone toxicity.

Misuse, Abuse, and Diversion of Opioids

Methadone is a μ-agonist opioid with an abuse liability similar to that of morphine and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when dispensing Methadone Hydrochloride Injection in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion.

Concerns about abuse, addiction, diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (see **PRECAUTIONS**)

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone have frequently involved concomitant benzodiazepine abuse.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, opioids must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis of clinical course of patients with acute abdominal conditions.

Hypotensive Effect

The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (i.e., severe volume depletion).

PRECAUTIONS

General

Methadone given on a fixed-dose schedule may have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of cardiac conduction abnormalities, respiratory depression, altered mental states and postural hypotension. Methadone Hydrochloride Injection should be used with caution in elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia.

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

Drug Interactions

In vitro results indicate that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, and to a lesser extent CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with inhibitors may reduce metabolism and potentate methadone's effects. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Opioid antagonists, mixed agonist/antagonists, and partial agonists: As with other μ-agonists, patients maintained on methadone may experience withdrawal symptoms when given these agents. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine

Anti-retroviral agents:

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

Efavirenz: Coadministration of efavirenz in HIV-infected methadone-maintenance patients has resulted in decreased methadone plasma concentrations of methadone associated with signs of opiod withdrawal, and necessitating increases in methadone dose.

Ritonavir and Ritonavir/Lopinavir: Reduced plasma methadone levels have been observed after administration of ritonavir alone or ritonavir/lopinavir combination. Withdrawal symptoms were however, inconsistently observed. Caution is warranted when administering methadone to patients receiving ritonavir-containing regimens in addition to other drugs known to decrease methadone plasma levels.

Zidovudine: Experimental evidence suggests that methadone increases the area under the concentration-time curve (AUC) of zidovudine with possible toxic effects.

Didanosine and Stavudine: Experimental evidence suggests that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

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

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

Phenytoin: In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d initially for 1 day followed by 300 mg QD for 3-4 days) resulted in ~50% reduction in methadone exposure and concurrently withdrawal symptoms occurred. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and the methadone exposure increased and was comparable to pre-phenytoin dose scenario.

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

Cytochrome P450 inhibitors: Since the metabolism of methadone is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus patients coadministered with inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), while receiving methadone should be carefully monitored and dosage adjustment made if warranted. Some selective serotonin reuptake inhibitors (SSRI's) (i.e., sertraline, fluvoxamine) upon coadministration may increase methadone plasma levels and result in increased opiate effects or toxicity.

Others:

Monoamine Oxidase (MAO) Inhibitors: Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone, but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

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

Potentially Arrhythmogenic Agents: Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. Caution should also be exercised when prescribing concomitant drugs capable of inducing electrolyte disturbances that may prolong the QT interval (hypomagnesemia, hypokalemia). These include diuretics, laxatives, and in rare cases mineralocorticoid hormones.

Interactions with other CNS Depressants: Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma.

Use with Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist, such as Methadone Hydrochloride Injection. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of Methadone Hydrochloride Injection and/or may precipitate withdrawal symptoms.

Anxiety

Methadone, used by tolerant patients at a constant maintenance dosage, is not a tranquilizer. Patients who are maintained on this drug will react to life problems and stresses as do other individuals. Anxiety in a patient on methadone should not be confused with narcotic abstinence and should not prompt treatment by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of symptoms of opioid dependence or pain. Methadone is ineffective for relief of general anxiety.

Acute Pain

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

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

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

Tolerance and Physical Dependence

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). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and/or tolerance are not unusual during chronic opioid therapy.

If methadone is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: 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.

In general, chronically administered methadone should not be abruptly discontinued.

Special-Risk Patients

Methadone should be given with caution and the initial dose reduced in certain patients, such as the elderly and debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions appropriate to the use of parenteral opioids should be observed and the possibility of respiratory depression should always be kept in mind.

Information for Patients

Methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery. The patient should be cautioned accordingly.

