Methadone Hydrochloride Oral Solution (methadone hydrochloride) - Drug Summary

Roxane Laboratories, Inc.

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Methadone Oral Solution
(methadone hydrochloride)

BOXED WARNING

Exposes patients and other users to the risk of opioid addiction, abuse, and misuse, leading to overdose and death; assess each patient's risk prior to prescribing and monitor all patients regularly for the development of these behaviors/conditions. Serious, life-threatening, or fatal respiratory depression may occur; monitor for respiratory depression, especially during initiation or following a dose increase. Accidental ingestion, especially in children, can result in fatal overdose. QT interval prolongation and serious arrhythmia (torsades de pointes) reported; closely monitor for changes in cardiac rhythm during initiation and titration. Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome; advise pregnant women of the risk and ensure availability of appropriate treatment. For detoxification and maintenance of opioid dependence, methadone should be administered in accordance w/ treatment standards, including limitations on unsupervised administration.

THERAPEUTIC CLASS

Opioid analgesic

DEA CLASS

CII

ADULT DOSAGE & INDICATIONS

Severe Pain (Daily, Around-the-Clock Management)

Requiring long-term opioid treatment for which alternative treatment options are inadequate

1st Opioid Analgesic:
Initial: 2.5mg q8-12h

Titration and Maint:
Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions
Titrate slowly, with dose increases no more frequent than every 3-5 days; some patients may require longer intervals of up to 12 days
If breakthrough pain is experienced, patient may require a dose increase or need rescue medication w/ an appropriate dose of an immediate-release medication

Conversions

D/C all other around-the-clock opioid drugs when therapy is initiated

From Parenteral Methadone:
Use conversion ratio of 1:2mg for parenteral to oral methadone (eg, 5mg parenteral to 10mg oral)

Conversion Factors to Methadone:
Total Daily Baseline Oral Morphine Equivalent Dose: Estimated Daily Oral Methadone as Percent of Morphine Equivalent Dose
<100mg: 20-30%
100-300mg: 10-20%
300-600mg: 8-12%
600-1000mg: 5-10%
>1000mg: <5%

Calculation for Estimated Daily Dose for Oral Methadone:
Always round down, if necessary, to the appropriate methadone strength(s) available

On a Single Opioid: Sum the total daily dose of opioid, convert to morphine equivalent dose, then multiply the morphine equivalent dose by the corresponding percentage to calculate approximate daily oral methadone dose
On >1 Opioid: Calculate approximate oral methadone dose for each opioid and sum the totals to obtain approximate daily total methadone dose
On Fixed-Ratio Opioid/Nonopioid Analgesics: Only use the opioid component of these products in the conversion

Detoxification/Maintenance Treatment of Opioid Addiction

Induction/Initial:
Initial: 20-30mg single dose; use lower initial doses for patients whose tolerance is expected to be low at treatment entry
Max Initial: 30mg
May administer an additional 5-10mg if withdrawal symptoms are not suppressed or if symptoms reappear
Max Total Day 1 Dose: 40mg
Adjust dose over the 1st week of treatment based on control of withdrawal symptoms at the time of expected peak activity (eg, 2-4 hrs after dosing)

Short-Term Detoxification:
Titrate to a total daily dose of 40mg in divided doses to achieve an adequate stabilizing level
Gradually decrease methadone dose on a daily basis or at 2-day intervals, 2-3 days after stabilization
Hospitalized patients may tolerate a daily reduction of 20% of the total daily dose; ambulatory patients may need a slower schedule

Titration and Maint:
Usual: 80-120mg/day

Medically Supervised Withdrawal After a Period of Maint Treatment:
Dose reductions should be <10% of the established tolerance or maint dose w/ 10- to 14-day intervals

Management of Acute Pain During Methadone Maint Treatment:
May require somewhat higher and/or more frequent doses than in nontolerant patients

DOSING CONSIDERATIONS

Renal Impairment
Start on lower dose and w/ longer dosing intervals and titrate slowly

Hepatic Impairment
Start on lower dose and titrate slowly

Pregnancy
May need to increase dose or decrease dosing interval

Elderly
Start at lower end of dosing range

Discontinuation
Avoid abrupt discontinuation; use a gradual downward titration every 2-4 days

ADMINISTRATION

Oral route

HOW SUPPLIED

Sol: 5mg/5ml, 10mg/5ml [500mL]

CONTRAINDICATIONS

Significant respiratory depression, acute or severe bronchial asthma in unmonitored setting or in the absence of resuscitative equipment, and known or suspected paralytic ileus.

WARNINGS/PRECAUTIONS

Reserve for use in patients for whom alternative analgesic treatment options (eg, nonopioid or IR opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Not indicated as a prn analgesic. Deaths reported during conversion from chronic, high dose treatment w/ other opioid agonists and during initiation of treatment of addiction in subjects previously abusing high doses of other agonists. Retained in the liver and then slowly released, prolonging the duration of potential toxicity, w/ repeated dosing. Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients; monitor closely when initiating and titrating, and when given w/ drugs that depress respiration. May decrease respiratory drive to the point of apnea, even at therapeutic doses, in patients w/ significant COPD or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression; monitor for respiratory depression and consider alternative nonopioid analgesics. May cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients; increased risk in patients w/ compromised ability to maintain BP. Monitor for signs of sedation and respiratory depression in patients susceptible to the intracranial effects of carbon dioxide retention (eg, those w/ increased intracranial pressure, or brain tumors). May obscure clinical course in patients w/ head injury. Avoid w/ GI obstruction and impaired consciousness or coma. May cause spasm of the sphincter of Oddi or increase serum amylase. May aggravate convulsions in patients w/ convulsive disorders and may induce or aggravate seizures. May impair mental/physical abilities. Abrupt discontinuation may lead to opioid withdrawal symptoms. Infants born to opioid-dependent mothers may be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms.

ADVERSE REACTIONS

Respiratory depression, QT prolongation, arrhythmia, systemic hypotension, lightheadedness, dizziness, sedation, N/V, sweating.

DRUG INTERACTIONS

Concomitant use w/ other CNS depressants (eg, sedatives, tranquilizers, phenothiazines) may result in hypotension, profound sedation, coma, respiratory depression, and death; reduce dose of one or both drugs when combined therapy is considered. Deaths reported when therapy has been abused in conjunction w/ benzodiazepines. CYP3A4 inhibitors may cause decreased clearance, leading to an increase in plasma levels and increased or prolonged opioid effects; these effects could be more pronounced w/ concomitant use of CYP2C9 and 3A4 inhibitors. CYP3A4 inducers may induce metabolism and, therefore, may increase clearance, leading to a decrease in plasma concentrations, lack of efficacy, or (possibly) development of a withdrawal syndrome in a patient who had developed physical dependence to therapy. Antiretroviral agents w/ CYP3A4 inhibitory activity (eg, abacavir, darunavir + ritonavir [RTV], efavirenz, lopinavir + RTV) may increase clearance or decrease plasma levels. May decrease levels of didanosine and stavudine. May increase AUC of zidovudine. Monitor for cardiac conduction changes w/ drugs known to have potential to prolong QT interval. Pharmacodynamic interactions may occur w/ potentially arrhythmogenic agents (eg, Class I and III antiarrhythmics, neuroleptics, TCAs, calcium channel blockers). Monitor closely w/ drugs capable of inducing electrolyte disturbances that may prolong QT interval, including diuretics, laxatives, mineralocorticoid hormones. Mixed agonist/antagonist (eg, pentazocine, nalbuphine, butorphanol), and partial agonist (buprenorphine) analgesics may reduce the analgesic effect or precipitate withdrawal symptoms; avoid use. Meperidine w/ or w/in 14 days of MAOI use may precipitate severe reactions; if use of methadone w/ an MAOI is necessary, a sensitivity test should be performed. May increase levels of desipramine. Anticholinergics may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

PREGNANCY AND LACTATION

Category C, caution in nursing.

MECHANISM OF ACTION

Synthetic opioid analgesic; mu-agonist. Produces actions similar to morphine; acts on CNS and organs composed of smooth muscle. May also act as an N-methyl-D-aspartate receptor antagonist.

PHARMACOKINETICS

Absorption: Bioavailability (36-100%); C_{max}=124-1255ng/mL; T_{max}=1-7.5 hrs. **Distribution:** V_d=1-8L/kg; plasma protein binding (85-90%); found in breast milk. **Metabolism:** Hepatic N-demethylation via CYP3A4, 2B6, 2C19 (major); 2C9, 2D6 (minor). **Elimination:** Urine, feces; $T_{1/2}$=8-59 hrs.

ASSESSMENT

Assess for personal/family history or risk factors for drug abuse or addiction, general condition and medical status, opioid/experience/tolerance, pain type/severity, previous opioid daily dose, potency, and type of prior analgesics used, respiratory depression, cardiac conduction abnormalities, COPD or other respiratory complications, GI obstruction, paralytic ileus, hepatic/renal impairment, previous hypersensitivity to drug, pregnancy/nursing status, possible drug interactions, and any other conditions where treatment is contraindicated or cautioned.

MONITORING

Monitor for respiratory depression (especially w/in the first 24-72 hrs), QT prolongation and arrhythmias, orthostatic hypotension, syncope, symptoms of worsening biliary tract disease, aggravation/induction of seizure, tolerance, physical dependence, mental/physical impairment, withdrawal syndrome, hypersensitivity reactions, and other adverse reactions. Monitor for signs of misuse, abuse, and addiction. Periodically reassess the continued need for therapy during chronic therapy.

PATIENT COUNSELING

Inform that use of medication, even when taken as recommended, may result in addiction, abuse, and misuse. Instruct not to share w/ others and to take steps to protect from theft or misuse. Inform of the risks of life-threatening respiratory depression; advise how to recognize respiratory depression and to seek medical attention if breathing difficulties develop. Inform that accidental ingestion, especially in children, may result in respiratory depression or death. Instruct to dispose of unused methadone by flushing the drug down the toilet. Instruct to seek medical attention immediately if patient experiences symptoms suggestive of an arrhythmia. Inform female patients of reproductive potential that prolonged use of drug during pregnancy may result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated. Inform that potentially severe additive effects may occur if drug is used w/ alcohol or other CNS depressants, and instruct not to use such drug unless supervised by a healthcare provider. Advise to use drug exactly ud and not to d/c w/o 1st discussing the need for tapering regimen w/ prescriber. Inform that drug may impair ability to perform potentially hazardous activities (eg, driving a car, operating heavy machinery). Advise about potential for severe constipation, including management instructions and when to seek medical attention. Inform that anaphylaxis may occur; advise how to recognize such a reaction and when to seek medical attention. Instruct nursing mothers to watch for signs of methadone toxicity in their infants (eg, increased sleepiness [more than usual], difficulty breastfeeding, breathing difficulties, limpness); instruct to inform physician immediately if these signs occur.

STORAGE

20-25°C (68-77°F).

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