BlueCross BlueShield
Federal Employee Program

METHADONE

Dolophine (methadone oral tablets), Methadone Hydrochloride Intensol (methadone oral concentrate), Methadose Oral concentrate (methadone oral concentrate), Methadose Dispersible Tablets (tablets for oral suspension)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Methadone hydrochloride is a long-acting opioid agonist at mu-opioid receptors that is used to manage pain that requires long-term, daily opioid treatment when other pain treatments do not manage pain sufficiently or are not tolerated. It is also used for detoxification and maintenance treatment of opioid addiction, such as heroin or other morphine-like drugs, as part of a comprehensive plan that includes appropriate medical and social services. Methadone used to treat opioid addiction must only be dispensed by Opioid Treatment Programs approved by state authority and certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). Methadone must be used in accordance with the treatment requirements stipulated in the Federal Opioid Treatment Standards (1-5).

Maximum daily limit of methadone without a PA is 90 MME/day. Maximum daily limit of methadone with a PA is 200 MME/day.

Regulatory Status

FDA-approved indications: Methadone oral tablets (Methadose, Dolophine), methadone oral solution, methadone oral concentrate (Methadone Intensol Oral Concentrate) and methadone tablets for oral suspension are indicated for the following (1-3):

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

   Limitations of Use

   a. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioids, reserve methadone hydrochloride tablets, oral solution and oral concentrate for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

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b. Methadone hydrochloride tablets, oral solution, and oral concentrate are not indicated as an as needed (prn) analgesic.

2. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
3. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

Methadose Dispersible tablets and Methadose Oral Concentrate are indicated for the following (4-5):

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

Methadone tablets, oral solution, and oral concentrate include a boxed warning for the following (1-5):

- Respiratory depression is the chief hazard of opioid agonists, including morphine sulfate, which if not immediately recognized and treated, may lead to respiratory arrest and death. To reduce the risk of respiratory depression, proper dosing, titration, and monitoring are essential.
- All patients treated with opioids require careful monitoring for signs of abuse, misuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. The risk for opioid abuse increases in patients with a personal or family history of substance abuse or mental illness. Patients should be assessed for the risk of developing abuse prior to the start of treatment and should be routinely monitored during therapy.
- Prolonged use of opioid agonists during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening.
- Treatment with methadone may cause serious arrhythmia (torsades de pointes) and QT interval prolongation. Closely monitor patients for changes in cardiac rhythm during

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initiation and titration of methadone hydrochloride tablets, oral solution, and oral concentrate.

- When used to treat opioid addiction through detoxification or maintenance programs, methadone may only be dispensed by certified opioid treatment programs 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).

Methadone is contraindicated in patients who have significant respiratory depression, paralytic ileus, acute or severe bronchial asthma and hypersensitivity to any of its components or the active ingredient, methadone (1-5).

As with other opioids, physical dependence, respiratory depression, and overdose may also occur; hence monitoring and frequent patient evaluation should be used as part of an overall treatment plan (1-5).

The requires healthcare providers to go through the Risk Evaluation and Mitigation Strategy (REMS) program before prescribing methadone tablets, oral solution, or oral concentrate that are indicated for use as analgesics).

As of January 1, 2008, manufacturers of methadone hydrochloride tablets 40mg (dispersible) have voluntarily agreed to restrict distribution of this formulation to only those facilities authorized for detoxification and maintenance treatment of opioid addiction, and hospitals (7).

Methadone is a long-acting opioid whose duration of analgesic action (typically 4 to 8 hours) approximates that of morphine and has an elimination half-life that is substantially longer (typically 8 to 59 hours). Methadone's pharmacokinetic properties, coupled with high inter-patient variability in its absorption, metabolism, and relative analgesic potency necessitate a cautious and highly individualized approach to prescribing. The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

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Studies indicate that methadone-related fatalities were primarily related to respiratory depression during initial treatment along with poly-substance use (8-11).

CDC guidelines find that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%–61% of decedents (9). The FDA also states that benzodiazepines “are also commonly abused and misused, often together with opioid pain relievers and other medicines” (13).

CDC guidelines finds that given uncertain benefits and substantial risks that opioids should not be considered first-line or routine therapy for chronic pain (i.e., pain continuing or expected to continue longer than 3 months or past the time of normal tissue healing) outside of active cancer, palliative, and end-of-life care (9).

FDA warns that opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity (see Appendix 1 for list of drugs) (10).

The FDA has determined that a REMS is necessary for all opioid analgesics intended for outpatient use to ensure that the benefits of these drugs continue to outweigh the risks. The Opioid Analgesic REMS is a strategy to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics. Prescribers should counsel patients and caregivers about the use of naloxone for opioid overdose and consider prescribing naloxone if clinically indicated (12).

The safety and effectiveness of methadone hydrochloride in pediatric patients below the age of 18 have not been established (1-5).

Summary

Methadone hydrochloride is used in the treatment pain severe enough to require long-term, around-the-clock, daily opioid treatment for which alternative options are inadequate, detoxification

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treatment of opioid addiction, and maintenance treatment of opioid addiction in conjunction with appropriate social and medical services. Patients should be assessed for their risk of developing substance abuse prior to being prescribed methadone. When used for the detoxification and maintenance treatment of opioid addiction, methadone should only be prescribed by qualified physicians in conjunction with appropriate medical and social services, and should only be dispensed by certified treatment programs in accordance to the treatment requirements stipulated in the Federal Opioid Treatment Standards (1-7). The MME limits in this policy do not apply to medication supplied by SAMHSA certified methadone clinics. The safety and effectiveness of methadone hydrochloride in pediatric patients below the age of 18 have not been established (1-5).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of methadone while maintaining optimal therapeutic outcomes.

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