ינואר 2019

רופא/ה ורוקח/ת נכבד/ה,

## עדכון עלון לרופא – Methadone Oral Solution

**מעבדות רפא מבקשת להביא לידיעתכם כי עודכן העלון לרופא של התכשיר**

**המרכיב הפעיל:** Methadone HCl

**התוויה:**

Relief of severe pain. Detoxification and withdrawal treatment in narcotic addiction.

בהתאם לדרישת משרד הבריאות להוסיף לכל התכשירים מקבוצת האופיואידים Black box לגבי אינטראקציה עם בנזודיאזפינים, הוסף בעלון לפני ההתוויה המידע הבא:

**WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see section 'Interactions'].
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

מצ"ב קישור לעלון לרופא – השינוי מסומן בצבע.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות (www.health.gov.il), וניתן גם לקבלו מודפס ע"י פניה לחברת מעבדות רפא בע"מ בטל': 02-5893939 או בדוא"ל שכתובתו RA@rafa.co.il.

בכבוד רב,

מגר' מיכל וויקוביץ
רוקחת ממונה

Doctor Leaflet

# Methadone

*Narcotic prescription required.

## COMPOSITION

Active ingredient: Methadone HCl Concentrated Solution 50 mg/ml

To be diluted before administration. The solution should be diluted by the pharmacist to the requested concentration and volume into a new bottle, according to the physician's instructions.

Inactive Ingredients: Methyl paraben, propyl paraben, purified water.

**WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see 'Drug Interactions'].

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists and during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration. Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration.

Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.
In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.
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 is considered and outweighs the risks.

## ACTION

Methadone hydrochloride is a synthetic opioid agent with analgesic and antitussive properties equal to those of morphine, but with lower sedative and addictive effects. The onset of action occurs 30-60 minutes after an oral dose, with peak effect after 90-120 minutes. The duration of action is 4-6 hours. Methadone is readily absorbed from the gastrointestinal tract. It is widely distributed in the tissues and diffuses across the placenta. It is highly plasma-bound, with a half-life of 15-25 hours.
Methadone is metabolized in the liver mainly by N-demethylation and cyclization. The metabolites are excreted in the bile and urine. A variable amount of the dose appears in the urine unchanged. Some metabolites are active. With repeated administration, the half-life may be greatly prolonged and duration of action may increase to 22-48 hours, possibly because of accumulation of methadone or of active metabolites. Renal excretion is dependent on urinary pH, and is higher in acidic urine.

## INDICATIONS

Relief of severe pain.
Detoxification and withdrawal treatment in narcotic addiction.

## CONTRAINDICATIONS

Known hypersensitivity to methadone or to any other ingredient in this preparation.
Methadone 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.
Methadone is contraindicated in any patient who has or is suspected of having a paralytic ileus.

## WARNINGS

**Concentrated solution.**

**Do not dispense the medicine to the patient in this bottle.**
**The solution should be diluted by the pharmacist to the requested concentration and volume into a new bottle, according to the physician's instructions.**
**For oral administration only. The preparation must not be injected**.

## Respiratory depression

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly during the initial dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation or dose titration. Respiratory depression is of particular concern 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 should be used with extreme caution in 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, and 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 used at the lowest effective dose and only under careful medical supervision.

## Incomplete Cross-tolerance between Methadone and other Opioids

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 who are being converted to treatment with methadone, thus making determination of dosing during opioid treatment 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. A high dose of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

## Drug abuse and Dependence

Methadone is, a mu-agonist opioid with an abuse liability similar to other opioid agonists. Methadone and other opioids used in analgesia can be abused and are subject to criminal diversion. Abuse of methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of lost prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. However, it should be important to note that preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

## 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 is expected during opioid agonist therapy of opioid addiction.

Physical dependence and/or tolerance are not unusual during chronic opioid therapy.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Methadone, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests 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.

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.

However, most patients who receive opiates for medical reasons do not develop dependence syndromes.

**Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms.**

### Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of methadone and its 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, narcotics produce effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

### Acute Abdominal Conditions

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

### Hypotension

Hypotension may result in the postoperative patient or in any individual whose ability to maintain blood pressure is compromised by hypovolemia or concurrent administration of phenothiazines or general anesthetics. Narcotics may produce orthostatic hypotension in ambulatory patients.

### 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. In most of the cases seen at typical maintenance doses, 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.

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 potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opiate dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone should be weighed against the substantial morbidity and mortality associated with untreated opioid addiction.

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 should be performed.

## GENERAL

When treating pain, 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 with methadone outweigh the known potential risks of cardiac conduction abnormalities, respiratory depression, altered mental states and postural hypotension. Methadone 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 or reduced ventilatory drive.

### 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.

### Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

**Anxiety** – Since methadone as used by tolerant patients at a constant maintenance dosage does not act as a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the

dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and 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 acute pain cannot be expected to derive analgesia from their existing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. 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 non-tolerant patients.

## 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 should be observed and the possibility of respiratory depression requires added vigilance.

## Use in Pregnancy

Safety of use in pregnancy has not been established. The placental transfer of narcotics is very rapid. Maternal addiction with subsequent neonatal withdrawal is well documented following illicit use. Withdrawal symptoms include irritability, excessive crying, yawning, sneezing, increased respiratory rate, tremors, hyperreflexia, fever, vomiting, increased stools and diarrhea. Symptoms usually appear during the first days of life.

## 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.

## Nursing Mothers

Methadone is secreted into human milk. The safety of breastfeeding while taking oral methadone is controversial. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state.

Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low

plasma concentrations in some infants whose mothers were taking methadone. Caution should be exercised when methadone is administered to a nursing woman. There have been rare cases of sedation and respiratory depression in infants exposed to methadone through breast milk.
Mothers using methadone should receive specific information about how to identify respiratory depression and sedation in their babies. They should know when to contact their healthcare provider or seek immediate medical care. A healthcare provider should weigh the benefits of breastfeeding against the risks of infant exposure to methadone and possible exposure to other medicines.
Women on high dose methadone maintenance, who are already breast feeding, should be counseled to wean breast-feeding gradually in order to prevent neonatal abstinence syndrome. Methadone-treated mothers considering nursing an opioid-naïve infant should be counseled regarding the presence of methadone in breast milk.
Because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In patients being treated for opioid dependence, this should include weighing the risk of methadone against the risk of maternal illicit drug use.

### Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and caregivers should be instructed to keep methadone in a secure place out of the reach of children and to discard unused methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

## ADVERSE REACTIONS

### Heroin Withdrawal

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore 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.

### Initial Administration

The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

### Major Hazards

Respiratory depression, apnea, and to a lesser degree, systemic hypotension, circulatory depression, respiratory arrest, shock and cardiac arrest, and death have occurred.

### Most Frequent

Lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects are more prominent in ambulatory patients and in those not experiencing severe pain. They can be alleviated by lowering the dosage.

### Allergic

Pruritis, urticaria, other skin rashes, diaphoresis, laryngospasm, edema, and rarely, haemorrhagic urticaria.

### Central Nervous System

Euphoria, dysphoria, delirium, weakness, headache, edema, drowsiness, miosis, coma, insomnia, agitation, tremor, seizures, impairment of mental and physical performance, lethargy, anxiety, fear, psychic dependence, mood changes, hallucinations, disorientation, confusion, and visual disturbances. Choreic movements have been induced by methadone.

### Cardiovascular

Facial flushing, peripheral circulatory collapse, arrhythmias, bigeminal rhythms, cardiomyopathy, ECG abnormalities, extrasystoles, heart failure, phlebitis, QT interval prolongation, T-wave inversion, torsade de pointes, tachycardia, bradycardia, palpitations, hypotension, syncope, ventricular fibrillation.

### Gastrointestinal

Dry mouth, glossitis, abdominal pain, anorexia, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility and toxic dilation. Concomitant administration of laxatives may counteract narcotic-induced constipation.

### Genitourinary

Ureteral spasm and spasm of vesical sphincters, urinary retention or hesitancy, oliguria, antidiuretic effect, reduced libido or potency, amenorrhea.

### Haematologic and Lymphatic

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

### Metabolic and Nutritional

Hypokalemia, hypomagnesemia, weight gain.

### Respiratory

Pulmonary edema, respiratory depression.

### Other

Muscular rigidity.

Maintenance on a stabilized dose - during prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

## PRECAUTIONS

Acute abdominal conditions (diagnosis or clinical course) may be obscured by narcotics.

Exercise caution in elderly and debilitated patients and in patients sensitive to CNS depressants, including those with cardiovascular disease, myxedema, acute alcoholism, delirium tremens, cerebral arteriosclerosis, fever, kyphoscoliosis, Addison's disease, prostatic hypertrophy or urethral stricture, toxic psychosis, severe CNS depression or coma.

Renal and hepatic dysfunction may cause a prolonged duration of action and cumulative effects.

Use with caution in atrial flutter and other supraventricular tachycardias, because vagolytic action may produce an increase in the ventricular response rate.

If dosage is substantially increased because of tolerance to the drug, seizures may be aggravated or occur in individuals without a history of convulsive disorders. Cough reflex is suppressed. Exercise caution when using postoperatively and in patients with pulmonary disease.

Methadone may cause drowsiness or dizziness. Patients should be cautioned against engaging in potentially hazardous activities requiring mental or physical alertness, such as driving a car or operating machinery.

## DRUG INTERACTIONS

### Methadone/Alcohol/General Anesthetics/Tricyclic Antidepressants/CNS Depressants

Concomitant use may result in increased CNS depression, respiratory depression, and hypotensive effects. Caution is recommended, and the dosage of one or both agents should be reduced. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines. In addition, some phenothiazines increase, while others decrease, methadone-induced analgesia.

### Methadone/Anticholinergics

Concomitant use may result in increased risk of severe constipation and/or urinary retention.

### Methadone/Anti-retroviral agents

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination

Concomitant use of these anti retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these anti-retroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine

Experimental evidence demonstrated 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.

Zidovudine

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

### Methadone/Cytochrome P450

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with CYP inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

### Cytochrome P450 Inducers

Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. 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 b.i.d. initially for 1 day followed by 300 mg per day 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 along with other CYP3A4 inducers may result in withdrawal symptoms.

### Cytochrome P450 Inhibitors

Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4, such as azole antifungal agents (e.g., ketoconazole) and macrolide antibiotics (e.g., erythromycin), with methadone should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels up on coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole

Repeat dose administration of oral voriconazole (400mg Q12h for 1 day, then 200mg 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 Cmax 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.

### Methadone/Levallorphan/Naloxone

Antagonism of the analgesic, CNS and respiratory depressant effects of methadone may occur, and may precipitate withdrawal symptoms in physically dependent patients. The dosage of levallorphan, naloxone, naltrexone should be carefully titrated when used to treat overdosage in dependent patients.

### Methadone/Other Opioid Drugs

Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently. Patients who are addicted to heroin or who are on a methadone maintenance program may experience withdrawal symptoms when given pentazocine, butorphanol, nalbuphine or buprenorphine.

### Methadone/Monoamine Oxidase Inhibitors/Furazolidone

Methadone should be used cautiously and in reduced dosage in patients receiving monoamine oxidase inhibitors or furazolidone. It is recommended that a small test dose, or several incremental test doses over a period of several hours, should first be administered to permit observation of any interaction.

### Methadone/Desipramine

Blood levels of desipramine have increased with concurrent methadone administration.

### Methadone/Arrythmogenic 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 arrythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing methadone concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives and, in rare cases, mineralocorticoid hormones.

### Methadone/Neuromuscular Blocking Agents

Respiratory depressant effects of neuromuscular blocking agents may be additive to central respiratory depressant effects of opioid analgesics. Caution is recommended when methadone is administered in the immediate post-operative period to patients who have received a neuromuscular blocking agent.

### Diagnostic Interference

Because narcotics may increase biliary tract pressure with resultant increases in plasma amylase or lipase, levels may be unreliable for 24 hours after narcotic administration.

## DOSAGE AND ADMINISTRATION

For oral use only.

Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another and during dose titration.**

While methadone’s duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone’s plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours). **Methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects.** Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations.

For these reasons steady-state plasma concentrations and full analgesic effects are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

### Treatment of Pain

Optimal methadone initiation and dose titration strategies for the treatment of pain have not been determined. Published equianalgesic conversion ratios between methadone and other opioids are imprecise, providing at best, only population averages that cannot be applied consistently to all patients. It should be noted that many commonly cited equianalgesia tables only present relative analgesic potencies of single opioid doses in non-tolerant patients, thus greatly underestimating methadone’s analgesic potency and its potential for adverse effects in repeated-dose settings.

Regardless of the dose determination strategy employed, methadone is most safely initiated and titrated using small initial doses and gradual dose adjustments.

As with all opioid drugs, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient’s prior analgesic treatment experience. The following dosing recommendations should only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient. Prescribers should always follow appropriate pain management principles of careful assessment and ongoing monitoring.

In the selection of an initial dose of methadone, attention should be given to the following:

1. The total daily dose, potency and specific characteristics of the opioid the patient had been taking previously, if any.
2. The relative potency estimate used to calculate an equianalgesic starting methadone dose, in particular, whether it is intended for use in acute or chronic methadone dosing.
3. The patient's degree of opioid tolerance.
4. The age, general condition and medical status of the patient.
5. Concurrent medications, particularly other CNS and respiratory depressants.
6. The type, severity and expected duration of the patient's pain.
7. The acceptable balance between pain control and adverse side effects.

Initiation of Therapy in Opioid Non-Tolerant Patients

When oral methadone is used as the first analgesic in patients who are not already being treated with, and tolerant to, opioids, the usual oral methadone starting dose is 2.5 mg to 10 mg every 8 to 12 hours, slowly titrated to effect.

More frequent administration may be required during methadone initiation in order to maintain adequate analgesia, and extreme caution is necessary to avoid overdosage, taking into account methadone's long elimination half-life.

Conversion from Parenteral Methadone to Oral Methadone

Conversion from parenteral methadone to oral methadone should initially use a 1:2 dose ratio (e.g., 5 mg parenteral methadone to 10 mg oral methadone).

Switching Patients to Methadone from other Chronic Opioids

Switching a patient from another chronically administered opioid to methadone requires caution due to the uncertainty of dose conversion ratios and incomplete cross-tolerance. **Deaths have occurred in opioid tolerant patients during conversion to methadone.**

Conversion ratios in many commonly used equianalgesic dosing tables do not apply in the setting of repeated methadone dosing. Although with single-dose administration the onset and duration of analgesic action, as well as the analgesic potency of methadone and morphine, are similar methadone's potency increases over time with repeated dosing. Furthermore, the conversion ratio between methadone and other opiates varies dramatically depending on baseline opiate (morphine equivalent) use as shown in the table below.

The dose conversion scheme below is derived from various consensus guidelines for converting chronic pain patients to methadone from morphine. Clinicians should consult published conversion guidelines to determine the equivalent morphine dose for patients converting from other opioids.

Table 1. Oral Morphine to Oral Methadone Conversion for Chronic Administration

| Total Daily Baseline **Oral** Morphine Dose | Estimated Daily **Oral** Methadone Requirement as percent of Total Daily |
|---|---|

| | Morphine Dose |
|---|---|
| < 100 mg | 20% to 30% |
| 100 to 300 mg | 10% to 20% |
| 300 to 600 mg | 8% to 12% |
| 600 mg to 1000 mg | 5% to 10% |
| > 1000 mg | < 5 % |

The total daily methadone dose derived from the table above may then be divided to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).

Note: Equianalgesic methadone dosing varies not only between patients, but also within the same patient, depending on baseline morphine (or other opioid) dose. Table 1 has been included in order to illustrate this concept and to provide a safe starting point for opioid conversion. Methadone dosing should not be based solely on these tables.

Methadone conversion and dose titration methods should always be individualized to account for the patient's prior opioid exposure, general medical condition, concomitant medication and anticipated breakthrough medication use.

The endpoint of titration is achievement of adequate pain relief, balanced against tolerability of opioid side effects. If a patient develops intolerable opioid related side effects, the methadone dose or dosing interval may need to be adjusted.

Dosage Adjustment during Pregnancy

Methadone clearance may be increased during pregnancy. Several small studies have demonstrated significantly lower trough methadone plasma concentrations and shorter methadone half-lives in women during their pregnancy compared to after their delivery. During pregnancy a woman's methadone dose may need to be increased or their dosing interval decreased. Methadone should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Detoxification and Maintenance Treatment of Opiate Dependence

### Induction/Initial Dosing

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.

### For 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.

### For Maintenance Treatment

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.

### For 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. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

## OVERDOSAGE

### Manifestations

In severe overdosage, apnea, circulatory collapse, convulsions, cardiopulmonary arrest and even death may occur. The less severely poisoned patient often presents the triad of central nervous system depression, miosis and respiratory depression.

Serious overdosage is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, constricted pupils, skeletal muscle flaccidity, and cold and clammy skin. Hypotension, bradycardia, hypothermia, pulmonary edema, pneumonia or shock occurs in up to 40% of patients.

### Treatment

Primary attention should be given to the maintenance of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent may be required.
After assessing the pulmonary status of the patient, administer a narcotic antagonist (naloxone is the antagonist of choice). Narcotic antagonists are specific antidotes for overdosage. The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), where opioid antagonist act for much shorter periods (one to three hours).
Since the duration of action of most narcotics exceeds that of narcotic antagonists, administration of the antagonist should be repeated to maintain adequate respiration and the patient should be kept under surveillance. Do not administer an antagonist in the absence of clinically-significant respiratory or cardiovascular depression.
In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.
Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication.
Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.
Employ oxygen, intravenous fluids, vasopressors and other supportive measures as indicated. In cases of oral overdose, and where treatment can be instituted within 2 hours following ingestion, evacuate the stomach by emesis or gastric lavage. Closely observe the patient for a rise in temperature or pulmonary complications that may require institution of antibiotic therapy.

## SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Once the bottle is opened, it should be stored below 25°C and the solution can be used within 6 months, but no later than the expiration date printed on the package.

## PRESENTATION

Bottles of 200 ml.

## REGISTRATION HOLDER

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