

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately 2 times a human daily oral dose of 120 mg/day on a mg/m<sup>2</sup> basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and "various other lesions." The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m<sup>2</sup> basis) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m<sup>2</sup> basis) administered during days 6 to 15 and 6 to 18, respectively.

**Nonteratogenic Effects** – Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

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

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone prior to mating. In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Further, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

**Clinical Pharmacology for Pregnancy** – Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with methadone. [See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION].

**Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.**

#### 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. 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.

#### Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

#### Renal Impairment

The use of methadone has not been extensively evaluated in patients with renal insufficiency.

#### Hepatic Impairment

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

#### Gender

The use of methadone has not been evaluated for gender specificity.

### **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.

**The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.**

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following:

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

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

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

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

Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain

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

Respiratory – pulmonary edema, respiratory depression

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

Special Senses – hallucinations, visual disturbances

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

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.

#### **DRUG ABUSE AND DEPENDENCE**

**Methadone contains methadone, a mu-agonist opioid with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. Methadone and other opioids used in analgesia have the potential for being abused and are subject to criminal diversion.**

#### Abuse

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.

#### Physical Dependence and Tolerance

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.

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (See PRECAUTIONS; Pregnancy, Labor and Delivery).

### OVERDOSAGE

#### Signs and Symptoms

Serious overdosage of methadone 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, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

#### Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid antagonists act for much shorter periods (one to three hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of other respiratory stimulants is not indicated.

Opioid antagonists should not be administered 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.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

### DOSAGE AND ADMINISTRATION

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 DOLOPHINE, 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 <u>Oral</u> Morphine Dose	Estimated Daily <u>Oral</u> 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

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

#### 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.

### HOW SUPPLIED

**DOLOPHINE® HYDROCHLORIDE**  
Methadone Hydrochloride Tablets, USP

5 mg white scored tablets (Identified 54 162)  
NDC 0054-4218-25: Bottles of 100 tablets.

10 mg white scored tablets (Identified 54 549)  
NDC 0054-4219-25: Bottles of 100 tablets.

Dispense in a tight, light-resistant container as defined in the USP/NF.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

component number/version  
Revised October 2006  
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**PATIENT INFORMATION**  
**DOLOPHINE® HYDROCHLORIDE CII**  
**(Methadone Hydrochloride Tablets), 5 mg and 10 mg**

**WARNINGS:**

**Keep DOLOPHINE out of the reach of children. Accidental overdose by a child is a medical emergency and can result in death. If a child accidentally takes DOLOPHINE, get emergency help right away.**

**Do not take a higher dose of DOLOPHINE or take it more often than prescribed. This can lead to an overdose and possible death.**

Read the Patient Information that comes with DOLOPHINE before you take it and each time you get a new prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment. Share the important information in this leaflet with members of your household.

**What is The Most Important Information I Should Know About DOLOPHINE?**

- **DOLOPHINE can cause life threatening breathing problems which can lead to death.** These problems are more likely to happen when DOLOPHINE is first started or in someone who is not already taking other narcotic (opioid) pain medicines.
  - **Breathing problems from DOLOPHINE may not happen right away after taking a dose. Sometimes breathing problems will happen a while after you take a dose, even after pain has returned. It is very important that you take DOLOPHINE exactly as your doctor has prescribed. Talk to your doctor about your pain. Your doctor can decide if your DOLOPHINE dose needs to be changed.**
- **DOLOPHINE can cause life-threatening heart beat problems that can lead to death.** Most heart beat problems have happened in people using large doses of DOLOPHINE for pain treatment. Some heart beat problems have happened in people using smaller doses of DOLOPHINE for treatment of narcotic drug addiction.

**What is DOLOPHINE?**

DOLOPHINE is a prescription medicine that contains methadone, which is a narcotic pain medicine similar to morphine. **DOLOPHINE is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.**

- **Prevent theft and misuse. Keep your DOLOPHINE tablets in a safe place to protect them from theft. Never give DOLOPHINE to anyone else even if they have the same symptoms you have. It may harm them and even cause death. Selling or giving away this medicine is dangerous and against the law.**

**DOLOPHINE is used:**

1. to treat moderate to severe pain in people that do not respond to non-narcotic pain medicines;
2. to control withdrawal symptoms in patients being treated for narcotic drug addiction;
3. for maintenance treatment of narcotic drug addiction along with other social and medical services. Stopping maintenance treatment of narcotic drug addiction with DOLOPHINE may result in a return to narcotic drug use.



## **Who Should Not Take DOLOPHINE?**

**Do not take DOLOPHINE if you:**

- have severe asthma or severe lung problems.
- have a blockage or obstruction in your intestines.
- are allergic to methadone or anything else in DOLOPHINE. See the end of this leaflet for a complete list of ingredients.

## **What Should I Tell my Doctor Before I Start Taking DOLOPHINE?**

**DOLOPHINE may not be right for you. Before starting DOLOPHINE, tell your doctor about all your medical and mental conditions including a history of drug or alcohol abuse or addiction.**

**Tell your doctor if you:**

- **are pregnant or plan to become pregnant.** DOLOPHINE may harm your unborn baby.
- **are breast feeding.** DOLOPHINE passes through your breast milk and may harm your baby. You should choose to use DOLOPHINE or breastfeed, but not both.

**Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with DOLOPHINE. Be especially careful about other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers. Sometimes, the doses of certain medicines (including DOLOPHINE) may need to be changed if they are used together.**

**Do not take any medicine while using DOLOPHINE until you have first talked to your doctor or pharmacist. They will be able to tell you if it is safe to take other medicines while you are using DOLOPHINE.**

**Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist each time you get a new medicine.**

## **How Should I Take DOLOPHINE?**

- **Take DOLOPHINE exactly as prescribed. Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. **Do not take a higher dose of DOLOPHINE or take it more often than prescribed. This can lead to an overdose and possibly death.**
- **If you take too much DOLOPHINE or overdose, call 911 or your local emergency number right away.**
- Review your medical conditions regularly with your doctor to determine if you still need DOLOPHINE, or if the dose needs to be adjusted.
- When starting treatment with DOLOPHINE for narcotic drug dependence, you should be aware that your dose of methadone will "hold" for longer periods of time as treatment goes on.

- **Stopping DOLOPHINE.** Ask your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking DOLOPHINE all at once if you have been taking it for more than a few days.
- Tell all health professionals that treat you that you take DOLOPHINE.
- After stopping treatment with DOLOPHINE, flush the unused tablets down the toilet.

#### **What Should I Avoid While Taking DOLOPHINE?**

- **Do not drive, operate heavy machinery, or do other possible dangerous activities** until you know how DOLOPHINE affects you. DOLOPHINE can make you sleepy. Ask your doctor when it is okay to do these activities.
- **Do not drink alcohol while using DOLOPHINE.** It may increase the chance of having dangerous side effects.
- **Do not take other medicines with DOLOPHINE without first talking with your doctor.**

#### **What are the Possible Side Effects of DOLOPHINE?**

- **DOLOPHINE can cause life threatening breathing and heart problems which can lead to death** See "What Is The Most Important Information I Should Know About DOLOPHINE?"
  - **Call your doctor or get medical help right away if you:**
    - have trouble breathing
    - have extreme drowsiness and breathing slows down
    - have slow shallow breathing (little chest movement with breathing)
    - fast or slowed heartbeat
    - feel faint, very dizzy, confused, have palpitations (irregular heart beat) or any other unusual symptoms

These can be symptoms that you have taken too much (overdose of) DOLOPHINE, or the dose is too high for you. They can also be symptoms of a serious heart reaction. **These symptoms can lead to serious problems or death if not treated right away.**

- **DOLOPHINE can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.
- **DOLOPHINE can cause physical dependence.** Do not stop taking DOLOPHINE or any other opioid without first talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Talk to your doctor about slowly stopping DOLOPHINE to avoid getting sick with withdrawal symptoms. Physical dependency is not the same as drug addiction.
- **For patients using DOLOPHINE for pain treatment, there is a chance of abuse or addiction with DOLOPHINE.** The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

Some common side effects of DOLOPHINE are lightheadedness, dizziness, drowsiness, nausea, vomiting and sweating. Other side effects include weakness, headache, constipation, itching, and dry mouth.

Talk to your doctor about any side effects that bother you or that do not go away.

These are not all the possible side effects of DOLOPHINE. For a complete list, ask your doctor or pharmacist.

#### **How Should I Store DOLOPHINE Tablets?**

- **Keep DOLOPHINE in a safe place away from children. Accidental use by a child is a medical emergency that can result in death. If a child accidentally takes DOLOPHINE, get emergency help right away.**
- Keep DOLOPHINE at room temperature, 59 to 86°F (15 to 30°C).
- Always keep DOLOPHINE in a secure place to protect from theft.
- Dispose of any unused DOLOPHINE remaining from a prescription as soon as they are no longer needed. Unused tablets should be flushed down the toilet.

#### **General Information About DOLOPHINE.**

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflet. Do not use DOLOPHINE for a condition for which it was not prescribed. **Do not give DOLOPHINE to other people, even if they have the same symptoms you have. DOLOPHINE can harm other people and even cause death. Sharing DOLOPHINE is against the law.**

This leaflet summarizes the most important information about DOLOPHINE. If you would like more information, talk with your doctor. You can also ask your pharmacist or doctor for information about DOLOPHINE that is written for healthcare professionals, or you can visit [www.Roxane.com](http://www.Roxane.com) or call 1-800-962-8364.

#### **What are the Ingredients in DOLOPHINE?**

**Active Ingredient:** methadone hydrochloride, USP

**Inactive Ingredients:** magnesium stearate, microcrystalline cellulose, and starch.

