

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**06-134/S028**

***Trade Name:*** Dolophine Hydrochloride; 5 mg tablet and 10 mg tablet

***Generic Name:*** Methadone Hydrochloride

***Sponsor:*** Roxane

***Approval Date:*** November 17, 2006

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**06-134/S028**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**06-134/S028**

**APPROVAL LETTER**



NDA 06-134/S-028

Roxane Laboratories, Inc.  
P.O. Box 16532  
Columbus, OH 43216-6532

Attention: Robert Pfeifer, R.Ph., M.S.  
Associate Director, Medical Services  
Drug Regulatory Affairs, Approved Products

Dear Mr. Pfeifer:

Please refer to your supplemental new drug application dated October 17, 2006, received October 18, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dolophine tablets (methadone HCl).

This supplemental new drug application were submitted in response to the Agency's letter dated October 6, 2006, requesting extensive changes to the Package Insert and also to provide a Patient package Insert for Dolophine.

We have completed our review of this application, and it is approved effective on the date of this letter for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and patient package insert.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

*{See appended electronic signature page}*

Bob Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Bob Rappaport  
11/17/2006 05:42:06 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**06-134/S028**

**LABELING**

**ROXANE LABORATORIES, INC.**  
Columbus, OH 43216

**DOLOPHINE® HYDROCHLORIDE CII**  
(Methadone Hydrochloride Tablets, USP)  
5 mg, 10 mg  
Rx Only

**Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see DOSAGE AND ADMINISTRATION). Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.**

**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.**

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**Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction**

Code of Federal Regulations, Title 42, Sec 8

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

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

1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis).
2. During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07(b)).

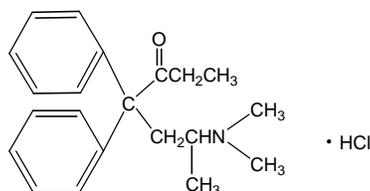
## DESCRIPTION

DOLOPHINE® HYDROCHLORIDE (Methadone Hydrochloride Tablets, USP), for oral administration, each contain 5 mg or 10 mg of methadone hydrochloride.

Methadone hydrochloride is a white, crystalline material that is water-soluble.

Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride. Its molecular formula is  $C_{21}H_{27}NO \cdot HCl$  and it has a molecular weight of 345.91. Methadone hydrochloride has a melting point of 235°C, and a pKa of 8.25 in water at 20°C. Its octanol/water partition coefficient at pH 7.4 is 117. A solution (1:100) in water has a pH between 4.5 and 6.5.

It has the following structural formula:



Other ingredients of DOLOPHINE include: magnesium stearate, microcrystalline cellulose, and starch.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Methadone hydrochloride is a mu-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

### Pharmacokinetics

#### Absorption

Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

#### Distribution

Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to  $\alpha_1$ -acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

#### Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, and CYP2C19 and to a

lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

#### Excretion

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the terminal half-life ( $T_{1/2}$ ) was highly variable and ranged between 8 to 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

#### Pharmacokinetics in Special Populations

##### Pregnancy

The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during 2nd and 3rd trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone. (See PRECAUTIONS: Pregnancy, Labor and Delivery, and DOSAGE AND ADMINISTRATION.)

##### Renal Impairment

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

##### Hepatic Impairment

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

##### Gender

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

##### Race

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

##### Geriatric

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

##### Pediatric

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

#### Drug Interactions (see PRECAUTIONS, Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some 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 before making a dosage adjustment.

### **INDICATIONS AND USAGE**

1. For the treatment of moderate to severe pain not responsive to non-narcotic analgesics.
2. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
3. For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

### **NOTE**

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

### **CONTRAINDICATIONS**

Methadone is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in DOLOPHINE.

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:**

#### **Respiratory Depression, Incomplete Cross-tolerance, and Iatrogenic Overdose**

**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.**

**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 (see DOSAGE AND ADMINISTRATION, Tables 1 and 2, for appropriate conversion schedules). A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.**

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 administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, 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.

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

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

### **Misuse, Abuse, and Diversion of Opioids**

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

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

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

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

### **Interactions with other CNS Depressants**

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

### **Interactions with Alcohol and Drugs of Abuse**

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

### **Head Injury and Increased Intracranial Pressure**

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

### **Hypotensive Effect**

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

## **DRUG ABUSE AND DEPENDENCE**

**DOLOPHINE 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 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.

### **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**).

## **PRECAUTIONS**

### 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.

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

### **Drug Interactions**

*In vitro* results 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.

### **Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists**

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

### **Anti-retroviral Agents**

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination – Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these antiretroviral 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 area under the concentration-time curve (AUC) of zidovudine which could result in toxic effects.

### **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 QD 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 upon 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<sub>max</sub> and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). The C<sub>max</sub> 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.

### **Others**

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

Desipramine – Blood levels of desipramine have increased with concurrent methadone administration.

### **Potentially Arrhythmogenic Agents**

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing 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.

### **Interactions with Alcohol and Drugs of Abuse**

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, 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.

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

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

### **Tolerance and Physical Dependence**

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and/or tolerance are not unusual during chronic opioid therapy.

If methadone is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

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

### **Special-Risk Patients**

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

### **Information for Patients**

- Patients should be cautioned that methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.
- Patients should be cautioned that methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.
- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking methadone.
- Patients initiating treatment with methadone for opioid dependence should be reassured that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Patients seeking to discontinue methadone maintenance treatment of opioid dependence should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.
- Patients should be instructed to keep methadone in a secure place out of the reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and their caregivers should be advised 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.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenesis – The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day

on a body surface area basis (mg/m<sup>2</sup>). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

**Mutagenesis** – There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. In contrast, methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E. coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

**Fertility** – Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for three consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naïve female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

#### **Pregnancy**

**Teratogenic Effects** – Pregnancy Category C. There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as “limited to fair”). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. In addition, reported studies generally compare the benefit of methadone to the risk of untreated addiction to illicit drugs; the relevance of these findings to pain patients prescribed methadone during pregnancy is unclear.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in the 3rd trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

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 overdose 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 overdose, 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 overdose 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 <b>Oral</b> Morphine Dose | Estimated Daily <b>Oral</b> 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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Company Logo

**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.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**06-134/S028**

**MEDICAL REVIEW(S)**



## FDA CENTER FOR DRUG EVALUATION AND RESEARCH

### MEMORANDUM

**To: File, NDA: 6-134 S-028**  
**From: Celia Winchell, M.D., Medical Team Leader**  
**SPONSOR: Roxane Pharmaceuticals**  
**DRUG: Dolophine (Methadone hydrochloride tablets USP)**  
**TYPE OF SUBMISSION: Labeling Supplement**  
**PM: Matthew Sullivan**

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#### 1. Background

##### 1.1. Methadone Regulatory History

Methadone HCl is a  $\mu$  agonist opiate which is used as an analgesic and in the treatment of opiate addiction. Methadone products were originally approved in the 1940's. In 1970, as part of the Drug Efficacy Study Implementation (DESI) process, methadone HCl was determined to be effective for the relief of moderate to severe pain; for the control of cough in patients in whom antitussives with less abuse liability have proven inadequate; and for suppressing the narcotic abstinence syndrome in the course of withdrawal therapy for narcotic dependence (FR Vol 35, No. 166, 8/26/70). This DESI notice applied to five NDAs, only one of which, Dolophine Hydrochloride (6-134) is still marketed. Subsequently, in 1972, through the rulemaking process, FDA proposed (4/6/72) and subsequently finalized (12/15/72) significant changes to the conditions of use for methadone, creating the system of methadone maintenance treatment and revoking the use of the drug as an antitussive, as the public health risk of unrestricted access to the drug for this indication exceeded the potential benefit. The FR notice (FR Vol. 37 No, 242, 12/15/72) stated that "the Commissioner concludes that there is a lack of substantial evidence that methadone is safe and effective for detoxification, analgesia, or antitussive use under the conditions of use that presently exist." The approval of all then-marketed methadone NDAs was withdrawn and manufacturers were required to resubmit, providing support for the maintenance treatment use, and conforming to labeling changes which addressed the new regulatory requirements for methadone use in addiction treatment. Roxane submitted the necessary supplement and Dolophine relabeled using Agency-provided language at that time.

At the time, the FDA also intended to place extensive restrictions on the use of methadone for pain, requiring that it be distributed only to certain pharmacies and prescribed only by specially registered physicians. These measures were intended to limit the amount of methadone available to be diverted for illicit use. The original plan for restricted access to methadone as an analgesic was abandoned after it was challenged

in court; however, the stigma of association with addiction treatment served to discourage use of methadone as an analgesic for several decades, a trend which has only recently reversed.

## **1.2. Dolophine Labeling History**

The Dolophine label has remained essentially unchanged since the approval of the methadone maintenance indication in the late 1970's. The label addressed the use of Dolophine for pain and for addiction treatment, and the NDA provided for both oral and parenteral formulations. The parenteral formulation was manufactured by Lilly and marketed by Roxane under NDA 6-134. In 2002, Lilly and Roxane decided to discontinue the manufacture and marketing of parenteral methadone. Parenteral methadone was judged to be a medically necessary drug, used for the treatment of pain primarily in palliative care settings, and the Agency identified an alternative manufacturer, aaIPharma, who agreed to manufacture and market parenteral methadone. The *parenteral formulation* portion of the Dolophine NDA (6-134) was sold to aaIPharma and was administratively separated from 6-134 and designated NDA 21-624. (This NDA was since sold to Xanodyne, which markets the product.) The Division worked with aaIPharma to develop a label for the parenteral product and requested a labeling supplement from Roxane to revise the Dolophine label to omit reference to the parenteral product. In addition, the Division requested that Roxane update the label to reflect the extensive revisions to the methadone label which the Agency had made in reviewing labeling supplements for other methadone products. These revisions incorporated new information about methadone's pharmacology, drug-drug interactions, arrhythmogenic potential, and emphasized the risk of iatrogenic overdose. The Agency also asked that Roxane revise the dosage and administration section to reflect current knowledge about the use of methadone.

Roxane did not respond to this supplement request, and the Dolophine label remained unrevised. A second supplement request letter was sent on October 6, 2006, and this submission (S028) was received in response.

## **1.3. Methadone Used in Treatment of Pain**

Recently, as part of an overall growth in the use of opioids for chronic pain, has the use of methadone as an analgesic experienced a resurgence. According to IMS data, prescriptions of methadone are up dramatically in the past few years. There has also been a concurrent increase in reports of methadone-associated fatalities or other serious adverse events. In some cases, reported adverse events appear to have been attributable to a lack of understanding on the part of the prescriber or the patient of methadone's pharmacokinetics and the necessary precautions that must be undertaken when administering this drug, particularly during initiation of treatment and titration to effective dose, and in converting patients from other opioid analgesics to methadone.

In response to concerns about adverse events associated with the use of methadone for the treatment of pain, the Agency contacted Roxane again and provided language to be used in the revised labeling.

## 2. Labeling Changes in this Supplement

This supplement represents a complete revision of the labeling for Dolophine. In most respects, it resembles the label for NDA 21-624.

A fully re-written clinical pharmacology section, based on literature review, was created in the course of revising the labels for Methadose (NDA 17-116, oral syrup indicated for addiction treatment) and Diskets (NDA 17-058, dispersible tablets indicated for addiction treatment)<sup>1</sup>. This section was included in the revised Dolophine label.

Like previously-revised labels, this label includes the addition of a warning concerning possible cardiac conduction effects of methadone, rewording of several label sections to emphasize the risk of iatrogenic overdose, and a revised Pregnancy and Nursing section.

Sections on Drug Abuse and Dependence have been revised to reflect current wording of these sections in other opioid analgesics.

The Dosing and Administration section for the pain indication has been revised based on an extensive literature review on dosing and dose conversion which was undertaken in the course of developing the label for NDA 21-624. Like the labels for Methadose and Diskets, the Dosing and Administration section for the addiction treatment indication was revised to reflect current recommendations in the Treatment Improvement Protocols issued by the Substance Abuse and Mental Health Services Administration.

The Dolophine label also presents risk/benefit information addressing both the pain treatment and the addiction treatment population.

The most notable difference between the Dolophine label and the previously-approved labels for the injectable product (NDA 21-624) and Methadose (17-116) is the addition of language to the boxed warning at the beginning of the label. The methadone products have carried a boxed warning concerning the regulatory requirements for the use of methadone in the treatment of addiction since the early 1970's. In approving the new label for NDA 21-624, the Division also added a boxed warning to the Warnings section of the label, highlighting the potential for QT prolongation and Torsade de Pointes. In the Methadose label, this information was included but not boxed, because of the different risk/benefit assessments for the pain and addiction populations, and the unintended adverse consequences of adding a similar warning to the label for Orlaam, another product indicated for addiction treatment<sup>2</sup>. However, in view of the increasing reports of accidental overdoses involving methadone, the Agency determined that the prominence of warnings about methadone-associated deaths, potentially attributable to its

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<sup>1</sup> "Approvable" actions were taken on these supplements in 2003 and revised labeling for Methadose was approved in 2005. Final revised labeling for Diskets is being approved concurrently with revised Dolophine labeling.

<sup>2</sup> After a boxed warning concerning cardiac conduction was added to the Orlaam label, clinics discontinued providing the product and eventually marketing was discontinued for business reasons. Because it offered some unique advantages for certain patients, the loss of this product from the armamentarium was a concern to the treatment community.

respiratory or cardiac effects, should be increased for all products used in outpatients. Language has been added to the boxed warning for Dolophine and slightly different language is being added to the labels for Methadose and Diskets. (b) (5)

Finally, a patient package insert for pain patients has been developed. (b) (5)

The information may be disseminated effectively by treatment providers once it is fully appreciated by the treatment community. (b) (5)

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/s/

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Celia Winchell  
11/14/2006 05:02:25 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**06-134/S028**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## **Division of Anesthesia, Analgesia and Rheumatology Products**

### **Regulatory Project Manager Review**

**Application Number:** NDA 06-134/S-028

**Name of Drug:** Dolophine tablets (methadone hydrochloride)

**Sponsor:** Roxane Pharmaceutical, Inc

#### **Material Reviewed**

Original Labeling Supplement (S-028)

**Submission Date(s):** October 17, 2006

**Receipt Date(s):** October 18, 2006

**Background and Summary Description:** A Supplement Request (SR) letter was sent to the Sponsor on October 6, 2006, containing a completely revised label. This label was created by the Division, largely from sections of the Methadose label (NDA 17-116).

The Sponsor made only minor changes, noted below, and returned it to the Division in the form of Labeling Supplement 028.

The SR letter also requested the creation of a Patient Package Insert (PPI), and one was included in S-028. The PPI was review by DSCRCS and returned to the Sponsor with numerous changes. The Sponsor accepted all the revisions on November 16, 2006.

Of note, no changes are made to the carton or container.

#### **Status Report**

**Reviews Completed:** Matt Sullivan, RPM, November 16, 2006.

**Review Concurrence:**

#### **RPM Review**

Changes noted here are additions or deletions that the Sponsor made to the label included with the Division's October 6, 2006, SR letter. Please note that a strikethrough indicates deletion and an underline indicates addition to the SR letter label.

ROXANE LABORATORIES, INC.  
Columbus, OH 43216

DOLOPHINE® HYDROCHLORIDE CII  
(Methadone Hydrochloride Tablets, USP)  
5 mg, 10 mg  
Rx Only

**BOX WARNING:**  
No changes noted

**DESCRIPTION:**  
DOLOPHINE® HYDROCHLORIDE (Methadone Hydrochloride Tablets, USP), for oral administration, each contain 5 mg or 10 mg of methadone hydrochloride.

Other ingredients of DOLOPHINE include: magnesium stearate, microcrystalline cellulose, and starch.

**CLINICAL PHARMACOLOGY:**

Methadone hydrochloride is a  $\mu$  mu-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the terminal half-life ( $T_{1/2}$ ) was highly variable and ranged between <sup>(b)</sup> 8 to 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some

CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their (b) (4) 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 before making a dosage adjustment.

[PM Note: These changes in this section have been concurred with by Dr Srikanth Nallani, the Clinical Pharmacology Reviewer]

#### INDICATIONS AND USAGE:

(b) (4)

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

(b) (4)

(b) (4)

#### CONTRAINDICATIONS:

Methadone is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in (b) (4) DOLOPHINE.

#### WARNINGS:

**Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other  $\mu$  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 (see DOSAGE AND ADMINISTRATION, Tables 1 and 2, for appropriate conversion schedules). A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.**

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history

who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. For use of methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

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

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

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

[PM Note: This text was inadvertently left out of the SR letter that was sent to the Sponsor. The Sponsor, however, noted that it was missing when they compared the label with that of Methadose. They therefore chose to include it in this label.]

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing (b) (4) DOLOPHINE in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion.

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

(b) (4) DOLOPHINE 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 can be abused and are subject to criminal diversion.

“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 (b) (4) 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.

#### **PRECAUTIONS:**

### **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 upon coadministration with methadone and result in increased opiate effects and/or toxicity.

**Anxiety** – Since methadone as used by tolerant (b) (4) 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 (b) (4) 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.

### **Pregnancy**

**Teratogenic Effects – Pregnancy Category C.** There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as “limited to fair”). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial

**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].

#### 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.

#### 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.

#### **ADVERSE REACTIONS:**

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

Respiratory – pulmonary edema, respiratory depression

Special Senses – hallucinations, visual disturbances

[PM Note: Other sections within adverse reactions were reordered in alphabetical order, but no additions or deletions were made.]

#### **DRUG ABUSE AND ADDICTION:**

**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 <sup>(b) (4)</sup> 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 (b) (4) 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.

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:**

No changes noted

#### **DOSAGE AND ADMINISTRATION:**

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  $\mu$  mu -opioid agonists makes determination of dosing during opioid conversion complex.

In the selection of an initial dose of (b) (4) 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.

**SAFETY AND HANDLING INSTRUCTIONS:**

No changes noted

**HOW SUPPLIED:**

DOLOPHINE® HYDROCHLORIDE  
Methadone Hydrochloride Tablets, USP

5 mg white scored tablets (Identified 54 (b) (4)).  
NDC 0054-421 (b) (4)-8-25: Bottles of 100 tablets.

10 mg white scored tablets (Identified 54 (b) (4)).  
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  
© RLI, 2006

Company Logo

[PM Note: During the course of the review, the Sponsor notified the Division that some errors were made in the 'How Supplied' section of the label. The Sponsor provided the corrected information informally, and requested that the Division simply incorporate the new information in the label when it is approved. Therefore the following changes will be made:

**HOW SUPPLIED:**

5 mg white scored tablets (Identified 54 (b) (4) 162).  
NDC 0054-421 (b) (4)-8-25: Bottles of 100 tablets.

10 mg white scored tablets (Identified 54 (b) (4) 549).  
NDC 0054-4219-25: Bottles of 100 tablets.

**The Sponsor concurred with this change, and the label in its entirety, on November 16, 2006. ]**

## **RECOMMENDATIONS**

Issue an Approval letter to the Sponsor for this S-028.

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this page is the manifestation of the electronic signature.**  
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/s/

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Matthew Sullivan  
11/17/2006 04:23:10 PM  
CSO

Parinda Jani  
11/17/2006 04:30:16 PM  
CSO

## Sullivan, Matthew

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**From:** rpfeifer@col.boehringer-ingelheim.com  
**Sent:** Friday, November 17, 2006 11:49 AM  
**To:** Sullivan, Matthew  
**Subject:** Re: Roxane comments on Dolophine PPI  
**Attachments:** emfinfo.txt

Hi Matt

Those changes are fine with us.

I appreciate the opportunity to review all these items. It has been a pleasure to work in this fashion with you folks. I appreciate your willingness to openly discuss these issues.

Best regards,

Bob

----- Original Message -----

From: Sullivan, Matthew <Matthew.Sullivan@fda.hhs.gov>  
To: Pfeifer,Bob ROX-US-C  
Sent: Fri Nov 17 11:27:42 2006  
Subject: RE: Roxane comments on Dolophine PPI

Bob –

So much for me not bothering you on Friday. We're considering two changes to the PI, and want to see what your thoughts are:

1. (b) (4) (but leave all the text intact) for this paragraph under Indications:

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

2. (b) (4) (but leave all the text intact) for this paragraph under Warnings:

### Cardiac Conduction Effects

Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose

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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.

I tried to put this in blackberry friendly text so hopefully you can share your thoughts without having to go back to your office.

Thanks

Matt

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From: rpfeifer@col.boehringer-ingelheim.com [<mailto:rpfeifer@col.boehringer-ingelheim.com>]  
Sent: Thursday, November 16, 2006 3:58 PM  
To: Sullivan, Matthew  
Cc: rpfeifer@col.boehringer-ingelheim.com  
Subject: FW: Roxane comments on Dolophine PPI

Hi Matt,

These look fine. One comment (extremely minor): in the PPI, last section titled "General Information About DOLOPHINE," the "comma" after the word "professionals" is (for some reason) bolded, italicized and underlined. You may want to correct that.

We, of course, when laying this out in a production size leaflet may modify some of the headings/subheadings/subsubheadings/etc (bold/underline/italics) to conform with our standard Roxane Corporate requirements, but of course, none of the boxing or bolding of critical text will be modified.

We await the official approval!

Thanks very much,

Bob Pfeifer

-----Original Message-----

From: Sullivan, Matthew [<mailto:Matthew.Sullivan@fda.hhs.gov>]  
Sent: Thursday, November 16, 2006 12:43 AM  
To: Pfeifer, Bob ROX-US-C  
Subject: RE: Roxane comments on Dolophine PPI

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Bob –

I think we're all set to provide you with the copies for your final review and concurrence.

The PPI is the same as we've previously shared – no changes there.

The PI is the same as well, except that I incorporated the NDC number change that we had from a week or two ago. I didn't include tracked changes on it, because it's only the NDC information – nothing else.

Please let me know if you agree with these. Assuming you do, I shouldn't have to bother you on Friday....unless we come up with a last minute change on our end!

Thanks

Matt

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From: rpfeifer@col.boehringer-ingelheim.com [<mailto:rpfeifer@col.boehringer-ingelheim.com>]  
Sent: Friday, November 03, 2006 10:54 AM  
To: Sullivan, Matthew  
Subject: Roxane comments on Dolophine PPI

Hi Matt,

We had no comments on your PPI edits for Dolophine. We added some Roxane-specific contact info on the last page as requested. I attach that document here.

Please let us know how you would like to move forward.

Thanks

Bob

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-----Original Message-----

From: Sullivan, Matthew [<mailto:Matthew.Sullivan@fda.hhs.gov>]

Sent: Thursday, November 02, 2006 3:58 PM

To: Pfeifer,Bob ROX-US-C

Subject: following-up on methadone

Bob –

Just following up on the voicemail I left you the other day. Any updates on the Dolophine PPI and/or the Diskets label?

Also, I noticed this in the how supplied section of the Dolophine label:

5 mg white scored tablets (Identified 54 (b)).

NDC 0054 (b) (4)25: Bottles of 100 tablets.

Could you check the NDC? It looks like there might be an extra (b) in the middle.

Thanks

Matt

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Matthew W. Sullivan, M.S.

Regulatory Project Manager

Division of Anesthesia, Analgesia

and Rheumatology Products

Food and Drug Administration

Phone 301-796-1245

Fax 301-796-9722 / 9723

[matthew.sullivan@fda.hhs.gov](mailto:matthew.sullivan@fda.hhs.gov)

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✓ Draft Labeling (b4)

     Draft Labeling (b5)

     Deliberative Process (b5)

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/s/

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Matthew Sullivan  
11/27/2006 03:10:25 PM  
CSO