LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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August 29, 2001

(OVERNIGHT COURIER)

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Methadone Hydrochloride Tablets, USP, 15 mg, 20 mg, 30 mg, and 40 mg are suitable for consideration in abbreviated new drug applications (ANDAs).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Methadone Hydrochloride Tablets, USP, 15 mg, 20 mg, 30 mg, and 40 mg are suitable for submission as ANDAs. The listed reference drug product upon which this petition is based is Dolophine® Tablets (methadone hydrochloride), 5 mg and 10 mg approved under NDA 06-134 (Attachment 1). Therefore, the petitioner seeks a change in strength (from 5 mg and 10 mg to include 15 mg, 20 mg, 30 mg, and 40 mg strengths) from that of the listed drug product.

B. Statement of Grounds

The reference listed drug (RLD) product is currently available in tablets containing either 5 mg or 10 mg of methadone hydrochloride. The proposed drug product represents tablets that will contain higher strengths of the drug (15 mg, 20 mg, 30 mg, and 40 mg). These additional strengths are believed to be consistent with the currently approved RLD product's labeling and will provide a more convenient single dosage unit to provide the specific dose prescribed by the physician for the individual patient. The petition is thus seeking a change in strength (from 5 mg and 10 mg to include a 15 mg, 20 mg, 30 mg, and 40 mg strength) from that of the reference listed drug.

The approved labeling of the RLD lists three indications for methadone hydrochloride, pain, detoxification treatment, and temporary maintenance treatment of narcotic addiction. The dosage and administration section of the labeling reads as follows for each of the indications:

> "For relief of pain – Dosage should be adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual

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dosage recommended in cases of exceptionally severe pain or in those patients who have become tolerant to the analgesic effects of narcotics.

The usual adult dose is 2.5 mg to 10 mg every three or four hours as necessary".

"For detoxification treatment – The drug shall be administered daily under close supervision as follows:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than four weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgement. Initially, a single oral dose of **15 to 20 mg** of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses it may be necessary to exceed these levels. **40 mg / day** in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for two to three days, and then the amount of methadone normally will be gradually decreased." (Emphasis added).

There are no specific dosage instructions for narcotic maintenance, which is to be conducted only under approved treatment programs and for which dosage is to be individualized for the specific patient.

It is clear from the labeling of the approved drug product that dosage strengths of 15 mg, 20 mg, 30 mg, and 40 mg are clearly contemplated for the approved indications. For pain management, the patient must be titrated to the appropriate dose to relieve the pain. The labeling clearly acknowledges that doses above the recommended 10 mg level are appropriate for certain patients. In addition, it is clear that for detoxification treatment doses of 15 mg, 20 mg, and up to 40 mg as a single dose are appropriate.

In further support of the change in strength requested in this petition, we refer to other petitions that have been approved over the years to revise upwards the quantity of narcotic component of both hydrocodone bitartrate and oxycodone containing products. These petitions have allowed increases in the strength of a single dose, recognizing the need to titrate a patient to pain relief by using doses that while clearly contemplated in the labeling of their respective RLD products, have exceeded the quantity of drug previously available in a single dosage unit.

The petitioner is seeking the requested changes in strength from the RLD drug product to provide the physician greater flexibility in administering alternate dosage strengths that are consistent with doses contemplated in the approved labeling of the RLD. The goal being to reduce the number of tablets a patient would need to take for a single dose. This will improve patient convenience, compliance, and make it easier to achieve the required dose for those patients that either have difficulty in swallowing multiple tablets or because of their illness makes multiple-tablet administration difficult.

Copies of labeling of the reference listed drug product upon which this petition is based and draft labeling for the proposed product are included in Attachment 2. The proposed labeling is the "same as" the approved RLD labeling with the exception of changes allowed because the manufacturer of the generic product differs from that of the RLD and in the How Supplied Section which lists the additional available strengths sought by this petition. There are no changes in the indications or dosage and administration sections necessary, as the approved labeling of the RLD already contemplates the use of the proposed dosage strengths.

Therefore, the petitioner requests that the Commissioner find that a change in strength from 5 mg and 10 mg tablets to include 15 mg, 20 mg, 30 mg, and 40 mg strength tablets for this product raises no questions of safety or effectiveness, and the Agency should then approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert Pollock cc

Robert. W. Pollock
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

RP/cc

Attachments:

1. Page 3-233, *Approved Drug Products with Therapeutic Equivalence Evaluations, 21st Edition*
2. Dolophine® Hydrochloride (Methadone Hydrochloride) Tablets Package Insert Labeling Draft Insert Labeling for the Proposed Drug Product

cc: G. Davis (OGD), L. Lachman

14p1214

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

METARAMINOL BITARTRATE

INJECTABLE; INJECTION

	ARAMINE			
AP	+ MERCK	**EQ 10MG BASE/ML**	**N09509 002**	
			DEC 22, 1987	
	METARAMINOL BITARTRATE			
AP	AM PHARM PARTNERS	**EQ 10MG BASE/ML**	**N80722 001**	

METAXALONE

TABLET; ORAL

	SKELAXIN		
+	CARNRICK	400MG	N13217 001

METFORMIN HYDROCHLORIDE

TABLET; ORAL

	GLUCOPHAGE		
	BRISTOL MYERS SQUIBB	500MG	N20357 001
			MAR 03, 1995
		850MG	N20357 002
			MAR 03, 1995
+		1GM	N20357 005
			NOV 05, 1998

TABLET, EXTENDED RELEASE; ORAL

	GLUCOPHAGE XR		
+	BRISTOL MYERS SQUIBB	500MG	N21202 001
			OCT 13, 2000

METFORMIN HYDROCHLORIDE; *MULTIPLE*
SEE GLYBURIDE; METFORMIN HYDROCHLORIDE

METHACHOLINE CHLORIDE

FOR SOLUTION; INHALATION

	PROVOCHOLINE		
	METHAPHARM	100MG/VIAL	N19193 001
			OCT 31, 1986

METHADONE HYDROCHLORIDE

CONCENTRATE; ORAL

	METHADONE HCL			
AA	ROXANE	**10MG/ML**	**N40180 001**	
			APR 30, 1998	
AA	UDL	**10MG/ML**	**N40088 001**	
			NOV 30, 1994	
	METHADONE HCL INTENSOL			
AA	ROXANE	**10MG/ML**	**N89897 001**	
			SEP 06, 1988	
	METHADOSE			
AA	+ MALLINCKRODT	**10MG/ML**	**N17116 002**	

INJECTABLE; INJECTION

	DOLOPHINE HCL		
+	ROXANE	10MG/ML	N06134 006

POWDER; FOR RX COMPOUNDING

	METHADONE HCL		
	MALLINCKRODT	50GM/BOT	N06383 002
		100GM/BOT	N06383 003
		500GM/BOT	N06383 004

SOLUTION; ORAL

	METHADONE HCL		
+	ROXANE	5MG/5ML	N87393 001
+		10MG/5ML	N87997 001
			AUG 30, 1982

SYRUP; ORAL

	DOLOPHINE HCL		
+	ROXANE	10MG/30ML	N06134 004

TABLET; ORAL

	DOLOPHINE HCL			
AA	+ ROXANE	**5MG**	**N06134 002**	
AA	+	**10MG**	**N06134 010**	
	METHADONE HCL			
AA	EON	**5MG**	**N40241 001**	
			MAY 29, 1998	
AA		**10MG**	**N40241 002**	
			MAY 29, 1998	
AA	ROXANE	**5MG**	**N88108 001**	
			MAR 08, 1983	
AA		**10MG**	**N88109 001**	
			MAR 08, 1983	
	METHADOSE			
AA	MALLINCKRODT	**5MG**	**N40050 001**	
			APR 15, 1993	

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 2

PV 0820 UCP

TABLETS DOLOPHINE® HYDROCHLORIDE

Ⓒ II

METHADONE HYDROCHLORIDE TABLETS, USP

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:
Code of Federal Regulations, Title 21, Sec. 291.505

METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

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.

A METHADONE PRODUCT, WHEN USED AS AN ANALGESIC, MAY BE DISPENSED IN ANY LICENSED PHARMACY.

DESCRIPTION

Dolophine® Hydrochloride (Methadone Hydrochloride Tablets, USP, Lilly) (3-heptanone, 6-(dimethylamino)-4,4-diphenyl-, hydrochloride), is a white, crystalline material that is water soluble. Its molecular weight is 345.91.

Each tablet contains 5 mg (0.015 mmol, No. 1712) or 10 mg (0.029 mmol, No. 1730) methadone hydrochloride. The tablets also contain cellulose, cornstarch, lactose, magnesium stearate, sucrose, and talc. The 10-mg tablet also contains acacia.

ACTIONS

Methadone hydrochloride is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or temporary maintenance in narcotic 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.

A parenteral dose of 8 to 10 mg of methadone is approximately equivalent in analgesic effect to 10 mg of morphine. With single-dose administration, the onset and duration of analgesic action of the 2 drugs are similar.

When administered orally, methadone is approximately one half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS (*see* boxed Note)

For relief of severe pain.
For detoxification treatment of narcotic addiction.
For temporary maintenance treatment of narcotic addiction.

NOTE

If methadone is administered for treatment of heroin dependence for more than 3 weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his/her stay or whose enrollment has been verified in a program approved for maintenance treatment with methadone.

CONTRAINDICATION

WARNINGS

Tablets Dolophine Hydrochloride are for oral administration only and *must not* be used for injection. It is recommended that Tablets Dolophine Hydrochloride, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE—METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

Interaction With Other Central Nervous System Depressants—Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Anxiety—Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not 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 dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure—The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions—Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect—The administration of methadone may result in severe hypotension in an individual whose ability to maintain normal blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients—Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy—Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn.

Use in Children—Methadone is not recommended for use as an analgesic in children, since documented clinical experience has been insufficient to establish a suitable dosage regimen for the pediatric age group.

PRECAUTIONS

Drug Interactions:

Pentazocine—**Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given an opioid agonist-antagonist, such as pentazocine.**

Rifampin—The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

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; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses

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 therapy.

Special-Risk Patients—Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

Acute Abdominal Conditions—The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

ADVERSE REACTIONS

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST 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. Some adverse reactions may be alleviated if the ambulatory patient lies down.

Other adverse reactions include the following:

Central Nervous System—Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal—Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular—Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary—Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic—Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic—Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

OVERDOSAGE

Signs and Symptoms—Methadone is an opioid and produces effects similar to those of morphine. Symptoms of overdose begin within seconds after intravenous administration and within minutes of nasal, oral, or rectal administration. Prominent symptoms are miosis, respiratory depression, somnolence, coma, cool clammy skin, skeletal muscle flaccidity that may progress to hypotension, apnea, bradycardia, and death. Noncardiac pulmonary edema may occur and monitoring of heart filling pressures may be helpful.

Treatment—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Initial management of opioid overdose should include establishment of a secure airway and support of ventilation and perfusion. Naloxone may be given to antagonize opioid effects, but the airway must be secured as vomiting may ensue. The duration of methadone effect is much longer (36 to 48 hours) than the duration of naloxone effect (1 to 3 hours) and repeated doses (or continuous intravenous infusion) of naloxone may be required.

If the patient has chronically abused opioids, administration of naloxone may precipitate a withdrawal syndrome that may include yawning, tearing, restlessness, sweating, dilated pupils, piloerection, vomiting, diarrhea, and abdominal cramps. If these symptoms develop, they should abate quickly as the effects of naloxone dissipate.

If methadone has been taken by mouth, protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of methadone.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL 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. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT 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.

DOSAGE AND ADMINISTRATION

For Relief of Pain—Dosage should be adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual dosage recommended in cases of exceptionally severe pain or in those patients who have become tolerant to the analgesic effect of narcotics.

The usual adult dosage is 2.5 to 10 mg every 3 or 4 hours as necessary.

For Detoxification Treatment—THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than 4 weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2 to 3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will 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 shall always be 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 and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

If the patient is unable to ingest oral medication, parenteral administration may be substituted.

HOW SUPPLIED

Tablets:

5 mg debossed on one side with 54
162 (UC5020)—(100s)
NDC 0054-4216-25

10 mg debossed on one side with 54
549 (UC5021)—(100s)
NDC 0054-4217-25

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

CAUTION—Federal (USA) law prohibits dispensing without prescription.

Literature issued April 27, 1995

Manufactured for **Roxane Laboratories, Inc.**
Columbus, OH 43216
by **Eli Lilly and Company**
Indianapolis, Indiana 46285

PV 0820 UCP

PRINTED IN USA

METHADONE HYDROCHLORIDE TABLETS, USP

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:
Code of Federal Regulation, Title 21, Sec. 291.505
METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATION (21 CFR 291.505).

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.

A METHADONE PRODUCT, WHEN USED AS AN ANALGESIC, MAY BE DISPENSED IN ANY LICENSED PHARMACY.

DESCRIPTION

Methadone Hydrochloride Tablets, USP 6-(dimethylamino)-4, 4-diphenyl-3-hepatonone hydrochloride, is a white, crystalline material that is water soluble. Its molecular weight is 345.91.

Each Methadone Hydrochloride Tablet contains: 5 mg (0.0145 mmol), 10 mg (0.029 mmol), 15 mg (0.0435 mmol), 20 mg (0.058 mmol), 30 mg (0.087 mmol), or 40 mg (0.116 mmol) Methadone Hydrochloride, USP.

Each Tablet also contains Colloidal Silicone Dioxide NF, Lactose Monohydrate NF, Microcrystalline Cellulose NF, and Magnesium Stearate NF.

CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or temporary maintenance in narcotic 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.

A parenteral dose of 8 to 10 mg of methadone is approximately equivalent in analgesic effect to 10 mg of morphine. With single-dose administration, the onset and duration of analgesic action of the 2 drugs are similar.

When administered orally, methadone is approximately one half as potent as when given parenterally. Oral administration results in a delay of onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE *(see boxed Note)*

1. For the relief of severe pain.

2. For detoxification treatment of narcotic addiction.

3. For temporary maintenance treatment of narcotic addition.

NOTE

If methadone is administered for treatment of heroin dependence for more than 3 weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his/her stay or whose enrollment has been verified in a program which has approval for maintenance treatment with methadone.

CONTRAINDICATION

Hypersensitivity to methadone.

WARNINGS

Methadone Hydrochloride Tablets USP are for oral administration only and *must not* be used for injection. It is recommended that Methadone Hydrochloride Tablets USP, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE **- METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING**

ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

Interaction With Other Central Nervous System Depressants - Methadone should be used with caution and in reduce dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Anxiety - Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not 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 dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure - The respiratory depressant effects of the methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions - Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect - The administration of methadone may result in severe hypotension in an individual whose ability to maintain normal blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients - Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy - Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn.

Use in Children - Methadone is not recommended for use as an analgesic in children, since documented clinical experience has been insufficient to establish a suitable dosage regimen for the pediatric age group.

PRECAUTIONS

Drug Interactions:

Pentazocine - **Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given an opioid agonist-antagonist such as pentazocine.**

Rifampin - The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Monoamine Oxidase (MAO) Inhibitors - Therapeutic doses of meperidine have precipitated sever 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; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses 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 therapy.

Special-Risk Patients - Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

Acute Abdominal Conditions - The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

ADVERSE REACTIONS

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST 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. Some adverse reactions may be alleviated if the ambulatory patient lies down.

Other adverse reactions include the following:

Central Nervous System - Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal - Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary - Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic - Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

OVERDOSAGE

Signs and Symptoms – Methadone is an opioid and produces effects similar to those of morphine. Symptoms of overdose begin within seconds after intravenous administration and within minutes of nasal, oral or rectal administration. Prominent symptoms are miosis, respiratory depression, somnolence, coma, cool clammy skin, skeletal muscle flaccidity that may progress to hypertension, apnea, bradycardia, and death. Noncardiac pulmonary edema may occur and monitoring of heart filling pressures may be helpful.

Treatment – To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Initial management of opioid overdose should include establishment of a secure airway and support of ventilation and perfusion. Naloxone may be given to antagonize opioid effects, but the airway must be secured as vomiting may ensue. **The duration of methadone effect is much longer (36 to 48 hours) than th duration of naloxone effect (1 to 3 hours) and repeated doses (or continuous intravenous infusion) of naloxone may be required.**

If the patient has chronically abused opioids, administration of naloxone may precipitate a withdrawal syndrome that may include yawning, tearing , restlessness, sweating, dilated pupils, piloerection, vomiting, diarrhea, and abdominal cramps. If these symptoms develop, they should abate quickly as the effects of naloxone dissipate.

If the methadone has been taken by mouth, protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gasses, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emtying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of methadone.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL 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. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT 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.

DOSAGE AND ADMINISTRATION

For Relief of Pain - Dosage should be adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual dosage recommended in cases of exceptionally severe pain or in those patients who have become tolerant to the analgesic effect of narcotics.

The usual adult dosage is 2.5 mg to 10 mg every three or four hours as necessary.

For Detoxification Treatment - THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than four weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2 to 3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will 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 shall always be 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 and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

If the patient is unable to ingest oral medication, parenteral administration may be substituted.

HOW SUPPLIED

METHADONE HYDROCHLORIDE TABLETS, USP:

5 mg white, scored tablets NDC 0406-6974-34: Bottles of 100 tablets
10 mg white, scored tablets NDC 0406-3454-34: Bottles of 100 tablets
15 mg white, scored tablets NDC 0406-XXXX-XX: Bottles of 100 tablets
20 mg white, scored tablets NDC 0406-XXXX-XX: Bottles of 100 tablets
30 mg white, scored tablets NDC 0406-XXXX-XX: Bottles of 100 tablets
40 mg white, scored tablets NDC 0406-XXXX-XX: Bottles of 100 tablets

Rx only.

Keep tightly closed. Dispense in a tight, light-resistant container. Store at controlled room temperature, 15° to 30°C (59° to 86°F).

8/23/01