

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **40241**_____

Trade Name **Methadone Hydrochloride Tablets USP 5mg**
and 10mg_____

Generic Name **Methadone Hydrochloride Tablets USP 5mg**
and 10mg_____

Sponsor **Eon Labs Manufacturing, Inc.**_____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40241

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	Included	Pending Completion	Not Prepared	Not Required
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40241

APPROVAL LETTER

1170-205

ANDA 40-241

MAY 29

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application dated January 10, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Methadone Hydrochloride Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendment dated April 16, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methadone Hydrochloride Tablets USP, 5 mg and 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dolophine Hydrochloride Tablets, 5 mg and 10 mg, respectively, of Roxane Laboratories Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40241

FINAL PRINTED LABELING

Mary

Final Printed Labeling

Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Iss. 9/97

NDC 0185-0021-01
Methadone 
Hydrochloride Tablets, USP

WARNING: May be habit forming.

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

 Eon Labs

Each tablet contains:
Methadone Hydrochloride 5 mg
APPROVED
KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

MAY 29 1998



Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Iss. 9/97

NDC 0185-0021-10
Methadone 
Hydrochloride Tablets, USP

WARNING: May be habit forming.

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

 Eon Labs

Each tablet contains:
Methadone Hydrochloride 5 mg
APPROVED
KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

MAY 29 1998



Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Iss. 9/97

NDC 0185-0131-01
Methadone 
Hydrochloride Tablets, USP

WARNING: May be habit forming.

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

 Eon Labs

Each tablet contains:
Methadone Hydrochloride 10 mg
APPROVED
KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

MAY 29 1998



Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Iss. 9/97

NDC 0185-0131-10
Methadone 
Hydrochloride Tablets, USP

WARNING: May be habit forming.

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

 Eon Labs

Each tablet contains:
Methadone Hydrochloride 10 mg
APPROVED
KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

MAY 29 1998



METHADONE HYDROCHLORIDE TABLETS, USP

WARNING : MAY BE HABIT FORMING

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.

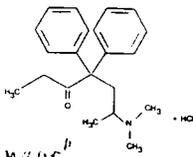
APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

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

Methadone Hydrochloride Tablets, USP 6-(dimethylamino)-4,4-diphenyl-3-heptanone, hydrochloride, is a white, crystalline material that is water soluble. It is represented by the following structural formula:



$C_{27}H_{37}NO \cdot HCl$

M.W. 345.91

Each tablet for oral administration contains 5 mg or 10 mg methadone hydrochloride. In addition each tablet contains the following inactive ingredients: anhydrous lactose, compressible (sucrose) cornstarch, magnesium stearate, microcrystalline cellulose, and talc.

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 the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE (see boxed Note below)

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 which has approval for maintenance treatment with methadone.

CONTRAINDICATIONS

Hypersensitivity to methadone.

WARNINGS

Methadone hydrochloride tablets are for oral administration only and *must not* be used for injection. It is recommended that Methadone Hydrochloride Tablets, 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 UPON 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 his/her 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 judgement 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 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.

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 light-headedness, 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

Symptoms-Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma; maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment-Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a nontolerant person, especially a child, takes a large dose of methadone, effective narcotic 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 the antagonists act for much shorter periods (1 to 3 hours). The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of

methadone, the use of respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered naloxone is the drug of choice 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.

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 hydrochloride 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 round, unscored, tablets imprinted \in over 21 on one side available in bottles of 100s, and 1000s.

Methadone Hydrochloride Tablets, USP, 10 mg - white round, unscored, tablets imprinted \in over 131 on one side available in bottles of 100s, and 1000s.

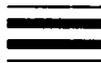
Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION Federal law prohibits dispensing without prescription.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Rev. 09/97
MF0131REV0997

Methadone
Hydrochloride
Tablets, USP



Rev 0997



Methadone
Hydrochloride
Tablets, USP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40241

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 40-241

3. NAME AND ADDRESS OF APPLICANT

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS for ANDA SUBMISSION

Basis for ANDA submission: Innovator product Dolophine®Hydrochloride/
Eli Lilly and Co.; patent - none; exclusivity - none

Patent and Exclusivity Certification: Pages #3,4,5

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Methadone Hydrochloride Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

10-Jan-1997: Original
25-Feb-1997: Amendment
12-Sept-1997: Amendment
16-April-1998: Amendment

FDA:

14-Feb-1997: RF letter
17-Mar-1997: Acceptable for filing
28-Aug-1997: FDA Deficiency Letter
03-April-1998: FDA Minor Deficiency Letter

10. PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

11. Rx or OTC

Rx

2. RELATED IND/NDA/DMF(s)

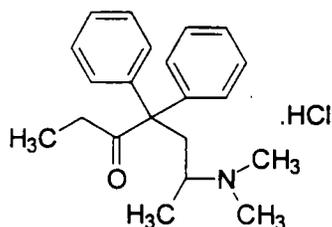
13. DOSAGE FORM

14. POTENCY

Tablets 5

mg and 10 mg

15. CHEMICAL NAME



AND STRUCTURE

345.91

C₂₁H₂₇NO.HCl

-(Dimethylamino)-4,4-diphenyl-3-heptanone hydrochlor

Methadone Hydrochloride USP

16. RECORDS AND REPORTS None

17. COMMENTS

This application was reviewed in accordance with OGD PPG Guide #29-90 since the initial review was performed by U.V. Venkataram. All deficiencies have been resolved satisfactorily.

18. CONCLUSIONS AND RECOMMENDATIONS

The ANDA is now satisfactory in CMC and is Approvable.

19. REVIEWER:

DATE COMPLETED:

Karen A. Bernard, Ph.D.

12-May-1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40241

BIOEQUIVALENCE REVIEW(S)

Methadone hydrochloride oral Tablets
5mg and 10mg
ANDA # 40-241
Reviewer: A.P. Patel
File: x:\wpfile\biofinal\40241w.297

Eon Labs.
Laurelton, NY
Submission Date:
Feb. 25, 1997

Review of Dissolution Data and a Request for Waiver

Introduction:

Methadone is indicated for relief of severe pain; for detoxification treatment of narcotic addiction and for temporary maintenance treatment of narcotic addiction.

Background:

The firm has requested waiver of the in-vivo bioequivalence requirements for its methadone hydrochloride oral tablets, 5mg and 10mg, per 21 CFR 320.24(b)(5). The firm has conducted dissolution testing comparing the test product versus the listed reference product, Dolophine® Hydrochloride Tablets, 5mg and 10mg, manufactured by Eli Lilly and Company for Roxane (Table 1). The product composition is given in Table

2.

Comments:

1. Methadone hydrochloride tablets are coded "AA" in the FDA Therapeutic Equivalence List and, therefore, no in-vivo study is needed to demonstrate bioequivalence.
2. There is a USP dissolution method for methadone hydrochloride tablets intended to be swallowed. Dissolution data are acceptable.

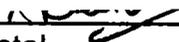
Deficiency: None

Recommendations:

1. The test product meets the Division of bioequivalence and CFR 320.24(b)(5) requirements for methadone hydrochloride oral tablets. The methadone hydrochloride oral tablets, 5mg and 10mg, manufactured by Eon Labs. are therefore deemed bioequivalent to Eli Lilly's Dolophine® Oral, 5mg and 10mg Tablets. The ANDA# 40241 is acceptable.
2. The dissolution testing conducted by the firm on its methadone HCl oral 5mg (lot#960804) and 10mg (lot#960805) tablets, are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml deaerated water at 37°C. using USP 23 apparatus 1 at 100 rpm. The test product should meet the following specifications:

Not less than _____ of the methadone hydrochloride in
the dosage form is dissolved in 45 minutes.

The firm should be informed of the above recommendations.



A.P. Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Date: 9/22/97

Concur: _____

Date: 11/20/97

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA# 40-241 (Original), HFD 650 (Director), HFD-658 (A.P. Patel), Drug File,
Division File.

Dissolution Testing: USP Method

The following USP 23 conditions were used:

Apparatus: 1 (basket) at 100 RPM

Medium: 500 mL water

Specifications: (Q) _____ of methadone hydrochloride dissolved in 45 minutes

Test product: Methadone Hydrochloride 5mg Tablets (lot#960804)

Methadone Hydrochloride 10mg Tablets (lot#960805)

Reference product:

Roxane's 5mg Dolophine® Tablets (lot#9MN13N) made by Eli Lilly.

Roxane's 10mg Dolophine® Tablets (lot#8NA93M) made by Eli Lilly.

Table 1

Time (min)	5mg Tablets				10mg Tablets			
	Test		Reference		Test		Reference	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
15	95.4	1.9	101.0	1.4	97.7	1.9	64.8	12.6
30	95.8	1.7	101.1	1.0	97.2	1.6	72.2	9.7
45	96.4	1.6	101.8	0.9	96.2	1.3	75.5	8.6
60	96.9	1.9	102.3	1.2	95.4	0.9	79.3	8.3
Potency	98.1%		102.6%		99.3%		100.3%	

Formulation: (Not to be released through FOI)

Eon's Methadone hydrochloride oral 5mg and 10mg tablets.

Table 2

Ingredients	mg per tablet (lot#960804)	mg per tablet (lot#960805)
Methadone hydrochloride, USP	5.0	10.0
Anhydrous Lactose, NF		
Compressible Sugar, NF		
Starch, NF (corn)		
Microcrystalline Cellulose, NF		
Talc, USP		
Magnesium Stearate, NF		
Total (theoretical)	134.0	268.0

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-241

APPLICANT: Eon Labs

DRUG PRODUCT: Methadone hydrochloride oral 5mg and 10 mg tablets.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40241

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-241

DRUG PRODUCT: Methadone
Hydrochloride Tablets, USP

FIRM: Eon Labs Manufacturing, Inc. DOSAGE FORM: Oral-Tablets

STRENGTH: 5 mg and 10 mg

CGMP STATEMENT/EIR UPDATE STATUS:
Acceptable 7/25/97

BIO INFORMATION:

The Division of Bioequivalence have determined that the bioequivalence review was found satisfactory on 11/20/97 by A. Patel.

VALIDATION- (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)

Analytical Methods: Page #565; The analytical methods for assay, content uniformity and dissolution assay are different from USP. However, the firm has submitted a comparative study to show that their in-house method is equivalent to the USP method. Additionally, the method was submitted by the document support staff for methods verification and was found to be satisfactory, NE Regional Labs, 6.16.97.

Methods Validation: Page #577; The assay method (# ARMR 067) and dissolution method (ARMR 068) were validated per the USP protocol and the results are satisfactory except as noted below.

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION?

Pre-approval Protocol:

Stability Stations: Accelerated Studies at 40°C/75% RH for 1, 2, 3 months; Long term studies at 25°C/60% RH for 0, 3, 6, 9, 12, 18, 24, and 36 months.

Container/Closure Attachment IV to review; Same as described in container section.

Tests, methods and Specifications: Attachment V to review; Same as finished product release certificate,

Post-approval Protocol: Page #642

Stability Batches: First three production lots and one lot yearly thereafter.

Stability Stations: Long term studies at 25°C - 30°C/ambient humidity for 0, 3, 6, 9, 12, 18, 24, and 36 months.

Container/Closure Attachment IV to review; Same as described in container section; smallest and largest size containers will be placed on stability.

Tests, methods and Specifications: Page #642; Attachment V to review; Same as finished product release certificate.

Stability Data: Page #646;

Lot# 960804 for 5 mg product, lot size tablets, 100's in 100 cc HDPE bottles, 1000's in 200 cc bottles and
0, 1, 2, and 3 months accelerated at 40°C/75% RH and 0,3 months 25°C - 30°C/ambient humidity.

Lot# 960805 for the 10 mg product, lot size is tablets, 100's in 100 cc HDPE bottles, 1000's in 400 cc bottles and
0, 1, 2, and 3 months accelerated at 40°C/75% RH and 0,3 months 25°C - 30°C/ambient humidity.

Stability Commitment: Page #639;

Commitments include

First 3 production batches to be placed on stability; smallest and largest packaging sizes or matrixing; data will be evaluated to support or extend expiration date; one-batch per year placed on stability thereafter; results will be submitted in annual report. Commitment to withdraw any lots from the market that do not meet specifications.

Expiration Date: Page #640; 24 months based on accelerated stability data at 40°C/75% RH/1,2,3 months of lot#s 960804 and 960805.

LABELING

The labeling review was found satisfactory by A. Veza on 4/29/98.

STERILIZATION VALIDATION

Not Applicable.

SIZE OF DEMONSTRATION BATCH

PROPOSED PRODUCTION BATCH-MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Blank Production Record:

5 mg: Page 238; batch size tablets; includes formula card, process description with equipment and parameters identified; identified; yield calculation and limits included;

10 mg: Page 244; batch size tablets; includes formula card, process description with equipment and parameters identified; identified; yield calculation and limits included;

10 mg: Page 250; batch size .ablets; includes formula card, process description with equipment and parameters identified; yield calculation and limits included;

Comparison between executed and production batches:

5 mg tablets production batch size
tablets executed batch size, lot# 960804

10 mg tablets production batch size
tablets executed batch size, batch # 960805

10 mg tablets production batch size
tablets executed batch size, batch # 960805 (Note: the
executed batch data is the same as above).

RECOMMENDATION: Approve

SIGNATURE:

DATE: May 12, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40241

CORRESPONDENCE



Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

April 16, 1998

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

Reference: Minor Amendment
Methadone Hydrochloride Tablets USP, 5 mg and 10 mg
ANDA # 40-241

Dear Dr. Holcombe:

Reference is made to your April 3, 1998 letter commenting on our original abbreviated new drug application submitted January 10, 1997 for Methadone Hydrochloride Tablets, USP, 5 mg and 10 mg. The following are our responses to the deficiencies noted in your letter:

- 1. The application cannot be approved until deficiencies regarding are addressed satisfactorily by the holder.**

Response:

We have been informed by _____ our
that they have satisfied the deficiencies regarding _____ on March 19, 1998.

2.

Dr. F. Holcombe

April 16, 1998

APR 17 1998

Page 1 of 2

GENERIC DRUGS

Response:

We commit to performing testing for Methadone Hydrochloride Tablets USP, 5 mg and 10 mg until we gather enough data to ensure consistent results. At that time we will discontinue further in-process testing. Three samples will be taken from the

A diagram from our sampling SOP showing the locations of the samples is included (*Attachment #1*).

If there are any comments or questions regarding this submission, please contact me at (718) 276-8607, extension 235.

Sincerely,
Eon Labs Manufacturing, Inc.



Amal Shaker
Regulatory Affairs Associate

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-241

APPLICANT: Eon Labs

DRUG PRODUCT: Methadone hydrochloride oral 5mg and 10 mg tablets.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

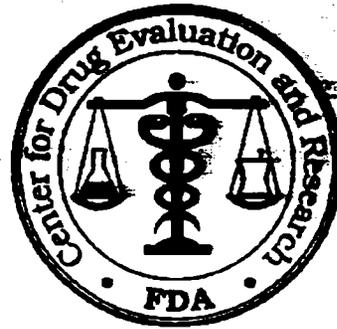
Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 40-241

APR 3 1998



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Eon Labs Manufacturing, Inc.
ATTN: Sadie M. Ciganek

PHONE: 718-276-8600

FAX: 718-276-8635

FROM: Kassandra Sherrod

PROJECT MANAGER (301) 827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated January 10, 1997, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for ~~Hydrochloride~~ Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendment dated September 12, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CDC and Bioequivalency comments attached.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

X:\new\ogdadmin\macros\faxmin.frm

September 12, 1997

Frank O. Holcombe, Jr., Ph. D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

*PI # contains labels
manufacturing for approval
labeling
revised drafted
4/28/98*

no sig
AMENDMENT

RECEIVED

SEP 10 1997

Re: **MAJOR AMENDMENT**
Methadone Hydrochloride Tablets, USP, 5 mg and 10 mg
ANDA 40-241

GENERIC DRUGS

Dear Dr. Holcombe:

Reference is made to your August 28, 1997 letter commenting on our original abbreviated new drug application submitted January 10, 1997 for Methadone Hydrochloride Tablets, USP, 5 mg and 10 mg. The following are our responses to the deficiencies noted in your letter:

1. **The blank production records do not include blank packaging/labeling record. Please submit.**

Response:

Included for your review are the blank packaging records for the proposed marketed packages (*attachment 1*).

PAGES 2-6 REDACTED
CMC

Dr. F. Holcombe

September 12, 1997

Labeling Deficiencies:

1. CONTAINER; 5 mg and 10 mg - 100's and 1000's

- a. We encourage you to differentiate the two strengths of your product by using boxing and/or contrasting colors.**

Response:

As can be seen on the attached final printed labels we use color to differentiate between the two strengths of the product.

b. Front panel

- i. Relocate the statement "WARNING: MAY BE HABIT FORMING" to appear immediately following the established name. We refer you to 21 CFR 329.10 (c) for further guidance.**
- ii. Add the word "POISON" in red uppercase bold print in a box with bold lines to be consistent with the approved labeling of the listed drug.**

Response:

As per our recent conversation with the Division of Labeling, the word Poison will not be included on the final printed labels.

c. Side panel

Revise to read, "... in a tight, light ...".

2. **INSERT**

a. **TITLE**

Add the statement "Warning: May be habit forming" to appear immediately beneath the established name.

b. **BOXED WARNING**

To be consistent with the reference listed drug, enclose the text, "CONDITIONS FOR DISTRIBUTION . . . IN ANY LICENSED PHARMACY" in a box with bold lines.

c. **DESCRIPTION**

i. Include the molecular formula and structural formula. We refer you to USP 23 for further guidance.

ii. Revise the second paragraph to read, "Each tablet for oral administration contains . . . In addition each tablet contains the following inactive ingredients . . .".

iii. Delete the text "0.025 mmol, 0.029 mmol". Note this text does not appear in the approved labeling of the reference listed drug.

iv. Make the following revisions:

- "microcrystalline cellulose" instead of "cellulose"
- "anhydrous lactose" instead "lactose"
- "compressible sugar" instead of "sucrose"

d. **CLINICAL PHARMACOLOGY**

To be in accord with 21 CFR 201.57, revise the section heading "ACTIONS" to read "CLINICAL PHARMACOLOGY".

e. **INDICATIONS AND USAGE**

i. To be in accord with 21 CFR 201.57, revise the section heading "INDICATIONS" to read "INDICATIONS AND USAGE".

ii. Revise "(see boxed Note)" to read "(see boxed Note below)".

iii. Add a period at the end of the third sentence.

iv. Note

A) Enclose the entire text of the Note in a box with bold lines.

B) Revise to read as follows:

. . . verified in a program which has approval for maintenance treatment with methadone.

f. To be in accord with 21 CFR 201.57, revise "CONTRAINDICATION" to read "CONTRAINDICATIONS".

g. WARNINGS

i. Enclose the first paragraph in a box with bold lines.

ii. Revise the first sentence to read, "Methadone hydrochloride tablets are for oral . . .".

iii. DRUG DEPENDENCE

Revise to read as follows:

. . . DEVELOP UPON REPEATED ADMINISTRATION . . .

iv. Hypotensive Effect

Revise the first sentence to read, ". . . maintain his/her blood pressure . . ."

h. PRECAUTIONS (Drug Interactions)

i. Pentazocine

Revise the last sentence to read ". . . when given pentazocine".

ii. Delete the text "Desipramine-Blood . . . therapy". Please note, this text does not appear in the approved labeling of the reference listed drug.

i. ADVERSE REACTIONS (Hematologic)

Delete the hyphen from the word "thrombocytopenia".

j. OVERDOSAGE

i. Revise the first subsection heading to read "symptoms".

ii. Revise this section to be in accord with the enclosed copy of the OVERDOSAGE section from the insert labeling of the reference listed drug.

k. DOSAGE AND ADMINISTRATION (For Detoxification Treatment)

- i. **Revise to read "... THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:".**
- ii. **In the penultimate paragraph revise the third sentence to read, "... 15 to 20 mg of methadone hydrochloride ...",**

I. HOW SUPPLIED

- i. **Include the established name of your drug product. .**
- ii. **Indicate that your tablets are unscored.**
- iii. **Caution - Federal . . . without prescription. (delete "a")**
- iv. **Capitalize the "M" in your corporate name appearing in the "Manufactured by" statement.**

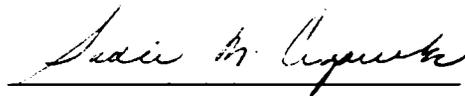
Please revise your labels and labeling, as instructed above, and submit in final print.

Response:

Final Printed labels and labeling have been revised to include your observations and are being submitted (*attachment 10*). To facilitate review of this submission. included is a side by side comparison of the current insert and the last submission with all differences annotated and explained (*attachment 11*).

We hope that our responses satisfactorily address the deficiencies noted in your letter. If you need further clarification or information please do not hesitate to call me at (718) 276-8600 ext.330.

Sincerely,
Eon Labs Manufacturing Inc.



Sadie M. Ciganek
Vice President Regulatory Affairs



Eon Labs
A Health Care Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

February 25, 1997

Mr. Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish place
Rockville, Maryland 20855

AMENDMENT

AC
505(x)(2)(a)(ok)

3/7/97

Re: ANDA 40-241- AMENDMENT
METHADONE HYDROCHLORIDE TABLETS, USP, 5 MG AND 10 MG

Dear Mr. Phillips;

We refer to your letter of February 14, 1997 **refusing to file** our ANDA 40-241 submitted January 10, 1997, for Methadone Hydrochloride Tablets, USP, 5 mg and 10 mg. The deficiencies noted in the letter made reference to the lack of certificates of analysis for the 5 mg and 10 mg finished products of the Methadone hydrochloride tablets, USP.

In accordance with the provisions outlined in the letter, we are amending our submission with the enclosed information which includes the completed **"Quality Control Finished Tablet Specification and Report Form"** for Methadone hydrochloride tablets, USP, 5 mg and 10 mg.

If additional information is required, please contact me at (718) 276-8600, extension:404.

Sincerely,
Eon Labs Manufacturing, Inc.

Eva Sultana Khan
Eva S. Khan
Regulatory Affairs Associate

RECEIVED

FEB 20 1997

OFFICE OF GENERAL COUNSEL

ANDA 40-241

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, New York 11413

MAR 17 1997

|||||

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated February 14, 1997, and your amendment dated February 25, 1997.

~~NAME OF DRUG: Methadone Hydrochloride Tablets, 5 mg and~~

DATE OF APPLICATION: January 10, 1997

DATE OF RECEIPT: January 13, 1997

DATE ACCEPTABLE FOR FILING: February 26, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 28 1997

ANDA 40-241/Eon Labs

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-241 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Methadone Hydrochloride Tablets USP, 5 mg and 10 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

ANDA 40-241/Eon Labs

ANDA 40-241/Eon Labs

Sincerely yours,

[Handwritten signature]

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 40-241

Date of Submission: February 25, 1997

Applicant's Name: Eon Labs Manufacturing, Inc.

Established Name: Methadone Hydrochloride Tablets USP,
5 mg and 10 mg

Labeling Deficiencies:

1. CONTAINER: 5 mg and 10 mg - 100s and 1000s
 - a. We encourage you to differentiate the two strengths of your product by using boxing and/or contrasting colors.
 - b. Front panel
 - i. Relocate the statement "WARNING: MAY BE HABIT FORMING" to appear immediately following the established name. We refer you to 21 CFR 329.10(c) for further guidance.
 - ii. Add the word "POISON" in red uppercase bold print in a box with bold lines to be consistent with the approved labeling of the listed drug.
 - c. Side panel
Revise to read, "... in a tight, light ...".
2. INSERT
 - a. TITLE
Add the statement "Warning: May be habit forming" to appear immediately beneath the established name.
 - b. BOXED WARNING
To be consistent with the reference listed drug,

enclose the text, "CONDITIONS FOR DISTRIBUTION ...
IN ANY LICENSED PHARMACY" in a box with bold
lines.

c. DESCRIPTION

- i. Include the molecular formula and structural formula. We refer you to USP 23 for further guidance.
- ii. Revise the second paragraph to read, "Each tablet for oral administration contains... In addition each tablet contains the following inactive ingredients ...".
- iii. Delete the text "0.025 mmol, 0.029 mmol". Note this text does not appear in the approved labeling of the reference listed drug.
- iv. Make the following revisions:
 - "microcrystalline cellulose" instead of "cellulose"
 - "anhydrous lactose" instead "lactose"
 - "compressible sugar" instead of "sucrose"

d. CLINICAL PHARMACOLOGY

To be in accord with 21 CFR 201.57, revise the section heading "ACTIONS" to read "CLINICAL PHARMACOLOGY".

e. INDICATIONS AND USAGE

- i. To be in accord with 21 CFR 201.57, revise the section heading "INDICATIONS" to read "INDICATIONS AND USAGE".
- ii. Revise "(see boxed Note)" to read "(see boxed Note below)".
- iii. Add a period at the end of the third sentence.
- iv. NOTE
 - A) Enclose the entire text of the NOTE in a box with bold lines.

B) Revise to read as follows:

... verified in a program which has approval for maintenance treatment with methadone.

f. To be in accord with 21 CFR 201.57, revise "CONTRAININDICATION" to read "CONTRAININDICATIONS".

g. WARNINGS

i. Enclose the first paragraph in a box with bold lines.

ii. Revise the first sentence to read, "Methadone hydrochloride tablets are for oral ...".

iii. DRUG DEPENDENCE

Revise to read as follows:

... DEVELOP UPON REPEATED ADMINISTRATION ...

iv. *Hypotensive Effect*

Revise the first sentence to read, "...maintain his/her blood pressure..."

h. PRECAUTIONS (Drug Interactions)

i. Pentazocine

Revise the last sentence to read "... when given pentazocine".

ii. Delete the text "Desipramine-Blood ... therapy". Please note, this text does not appear in the approved labeling of the reference listed drug.

i. ADVERSE REACTIONS (*Hematologic*)

Delete the hyphen from the word "thrombocytopenia".

j. OVERDOSAGE

i. Revise the first subsection heading to read "Symptoms".

- ii. Revise this section to be in accord with the enclosed copy of the OVERDOSAGE section from the insert labeling of the reference listed drug.

- k. DOSAGE AND ADMINISTRATION (*For Detoxification Treatment*)
 - i. Revise to read "... THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:".

 - ii. In the penultimate paragraph revise the third sentence to read, "... 15 to 20 mg of methadone hydrochloride ...",

- l. HOW SUPPLIED
 - i. Include the established name of your drug product.

 - ii. Indicate that your tablets are unscored.

 - iii. Caution - Federal... without prescription. (delete "a")

 - iv. Capitalize the "M" in your corporate name appearing in the "Manufactured by" statement.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

M L
Jerry Phillips

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: OVERDOSAGE section of the insert labeling from
reference listed drug.

OVERDOSAGE

Symptoms—Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment—Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a nontolerant person, especially a child, takes a large dose of methadone, effective narcotic 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 the antagonists act for much shorter periods (1 to 3 hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered naloxone is the drug of choice 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.

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.

HOW SUPPLIED

Tablets:

5 mg (No. 1712) (100's), NDC 0002-1064-02

10 mg (No. 1730) (100's), NDC 0002-1072-02

CAUTION—Federal (U.S.A.) law prohibits dispensing without prescription.

MAJOR AMENDMENT

AUG 28 1997

ANDA/~~ADA~~: 40-241



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TO: APPLICANT Eon Labs
ATTN: Sadie Cigonek

PHONE 718-276-8600
FAX 718-276-8635

FROM: Tim Ames PROJECT MANAGER (301-827-5849)

Dear ~~Sir~~ Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated Jan 10, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methadone Hydrochloride Tabs USP; 5mg and 10mg. Reference is also made to your amendment(s) dated February 25, 1997.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (9 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You ~~have been~~/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
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ANDA 40-241

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

FEB 14 1997

|||||

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated January 10, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methadone Hydrochloride Tablets USP, 5 mg and 10 mg.

We have given your application a preliminary review, and we find ~~that it is not sufficiently complete to merit a critical technical review.~~

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

The application lacks certificates of analysis for your 5 mg and 10 mg finished products. Please provide this information in an amendment to your application.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 594-0315

Sincerely yours,

Jerry Phillips *J* 2/17/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Eon Labs
A Health Care Company

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January 10, 1997

Douglas L. Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Refuse to file
2/13/97

**RE: Original ANDA
Methadone Hydrochloride Tablets, USP, 5 mg and 10 mg**

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Methadone Hydrochloride Tablets, USP, 5 mg and 10 mg. This application consists of the following volumes:

- Volume 1 Debarment, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, certificates of analysis, and components and composition.
- Volume 2 Raw material control data, manufacturing and packaging data including executed batch records.
- Volume 3 Container/closure, finished product control, methods validation, stability data, control numbers, samples, and environmental impact statement.

A full table of content precedes each appropriately paginated volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Brooklyn, New York. Subsequent amendments or supplements containing chemistry, manufacturing and controls data to be submitted to the District Field Office.

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GENERIC DRUGS

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If there are any comments or questions about this application, please contact me at (718) 276-8600, extension 330.

Sincerely,
Eon Labs Manufacturing, Inc.



Sadie M. Ciganek
Vice President Regulatory Affairs