CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75082

Trade Name Methadone Hydrochloride Tablets USP 40mg (Dispersable)

Generic Name Methadone Hydrochloride Tablets USP 40mg (Dispersable)

Sponsor Eon Labs Manufacturing, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75082

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75082

APPROVAL LETTER

ANDA 75-082

MAR 25 1998

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

Dear Madam:

This is in reference to your abbreviated new drug application dated February 25, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Methadone Hydrochloride Tablets USP, 40 mg (Dispersible).

Reference is also made to your amendments dated May 12, 1997, January 12, 1998 and February 5, 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, 40 mg (Dispersible) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Methadone Hydrochloride Tablets USP, 40 mg (Dispersible) of Roxane Laboratories, Inc.]. Your disintegration testing should be incorporated into the stability and quality control programs 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. 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/25/98

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75082

FINAL PRINTED LABELING

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

Iss. 11/96

NDC 0185-0132-01

Methadone Hydrochloride Tablets, USP (C II)

WARNING: May be habit forming.

40 mg

DISPERSIBLE TABLETS
FOR METHADONE TREATMENT PROGRAMS

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Methadone
Hydrochloride .....40 mg

KEEP TIGHTLY CLOSED.

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

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

N 3 0185-0132-01 0

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.

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

N 3 0185-0132-01 0

METHADONE HYDROCHLORIDE TABLETS, USP
Dispersible Tablets
For Methadone Treatment Programs

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:

Code of Federal Regulations, Title 21, Sec. 291.505

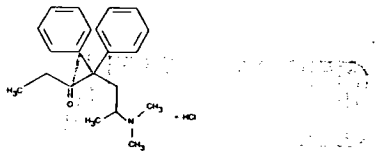
METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

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.

DESCRIPTION

Methadone Hydrochloride Tablets, USP (6-(Dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride), is a white, crystalline material that is water soluble. However, the dispersible tablet preparation of methadone hydrochloride has been specially formulated with insoluble excipients to deter the use of this drug by injection. Methadone hydrochloride has the molecular formula $C_{21}H_{27}NO \cdot HCl$ and its molecular weight is 345.91.



Methadone Hydrochloride Tablets, USP (Dispersible) are intended for dispersion in a liquid prior to oral administration of the prescribed dose. Each tablet also contains the following inactive ingredients: colloidal silicon dioxide, corn starch, magnesium stearate, and microcrystalline cellulose.

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 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.

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

1. Detoxification treatment of narcotic addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of narcotic addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

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. This preparation contains insoluble excipients and therefore *must not* be injected. 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 stock 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 judgement of the physician, the potential benefits outweigh the possible hazards.

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.

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

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.

ADVERSE REACTIONS

Heroin Withdrawal - During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, "sleepy yen," weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration - Initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects.

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 in the ambulatory patient if he 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.

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

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, an effective narcotic antagonist is 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 antagonist acts 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. This agent should be given repeatedly until the patient's status remains satisfactory. The hazard that the narcotic antagonist will further depress respiration is less likely with the use of naloxone. 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 THAT 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

Methadone Hydrochloride Tablets USP (Dispersible) are intended for dispersion in a liquid prior to oral administration of the prescribed dose.

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.

For Maintenance Treatment - In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of narcotic drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the narcotic tolerance of the new patient. If such a patient has been a heavy user of heroin up to the day of admission, he/she may be given 20 mg 4 to 8 hours later or 40 mg in a single oral dose. If the patient enters treatment with little or no narcotic tolerance (eg, if he/she has recently been released from jail or other confinement), the initial dosage may be one half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional 10-mg doses may be administered as needed. Subsequently, the dosage should be adjusted individually, as tolerated and required, up to a level of 120 mg daily. The patient will initially ingest the drug under observation daily, or at least 6 days a week, for the first 3 months. After demonstrating satisfactory adherence to the program regulations for a least 3 months, the patient may be permitted to reduce to 3 times weekly the occasions when he must ingest the drug under observation. He shall receive no more than a 2-day take-home supply. With continuing adherence to the program's requirements for at least 2 years, he/she may then be permitted twice-weekly visits to the program for drug ingestion under observation, with a 3-day take-home supply. A daily dose of 120 mg or more shall be justified in the medical record. Prior approval from state authority and the Food and Drug Administration is required for any dose above 120 mg administered at the clinic and for any dose above 100 mg to be taken at home. A regular review of dosage level should be made by the responsible physician, with careful consideration given to reduction of dosage as indicated on an individual basis. A new dosage level is only a test level as stability is achieved.

Special Considerations for a Pregnant Patient - Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels shall be kept as low as possible if continued methadone treatment is deemed necessary. It is the responsibility of the program sponsor to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone.

Special Limitations - Treatment of Patients Under Age 18

1. The safety and effectiveness of methadone for use in the treatment of adolescents have not been proved by adequate clinical study. Special procedures are therefore necessary to assure that patients under age 16 will not be admitted to a program and that patients between 16 and 18 years of age will be admitted to maintenance treatment only under limited conditions.
2. Patients between 16 and 18 years of age who were enrolled and under treatment in approved programs on December 15, 1972, may continue in maintenance treatment. No new patients between 16 and 18 years of age may be admitted to a maintenance treatment program after March 15, 1973, unless a parent, legal guardian, or responsible adult designated by the state authority completes and signs Form FD 2635, "Consent for Methadone Treatment."
   Methadone treatment of new patients between the ages of 16 and 18 years of age will be permitted after December 15, 1972, only with a documented history of 2 or more unsuccessful attempts at detoxification and a documented history of dependence on heroin or other morphine-like drugs beginning 2 years or more prior to application for treatment. No patient under age 16 may be continued or started on methadone treatment after December 15, 1972, but these patients may be detoxified and retained in the program in a drug-free state for follow-up and aftercare.
3. Patients under age 18 who are not placed on maintenance treatment may be detoxified. Detoxification may not exceed 3 weeks. A repeat episode of detoxification may not be initiated until 4 weeks after the completion of the previous detoxification.

HOW SUPPLIED

Methadone Hydrochloride Tablets, USP 40 mg are supplied as white dispersible tablets, quadrisected on one side and imprinted ℰ over "132" on the other side. They are available in bottles of: 100.

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

Rx only.

Issued 02/98

MF 0132ISS0298

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75082

CHEMISTRY REVIEW(S)

5.12.97
Sudam

ANDA 75-082

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-082

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Methadone Hydrochloride Tablets USP 40 mg (Dispersible Tablets); Eli Lilly and Company.
The applicant certifies that to the best of their knowledge there are no effective patents or exclusivity associated with NDA 17-058 (Methadone Hydrochloride, Lilly)

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Methadone Hydrochloride Tablets USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: February 25, 1997
Amendment: May 12, 1997

FDA:
Refusal to File Letter: May 1, 1997
Letter (Acceptable for Filing): June 2, 1997

10. PHARMACOLOGICAL CATEGORY
Detoxification of narcotic addiction

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

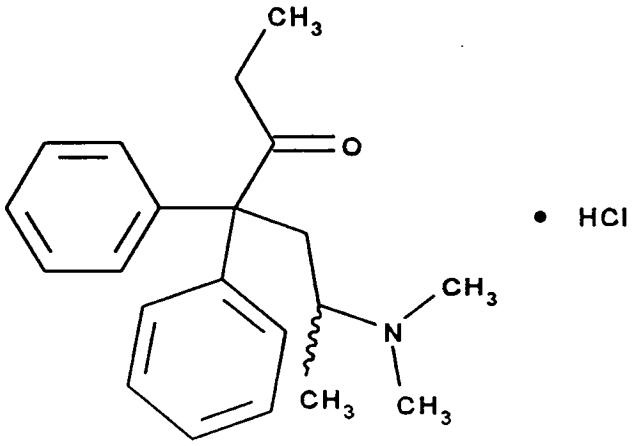
13. DOSAGE FORM
Tablet (Dispersible)

14. POTENCY
40 mg

15. CHEMICAL NAME AND STRUCTURE

Methadone Hydrochloride

$C_{21}H_{27}NO.HCl$; M.W. = 345.91



(±)-6-(Dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride.
CAS [1095-90-5]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
   a. Minor deficiencies regarding the stability testing protocol remain.
   b. Label review is pending as of 10/15/97.
   c. The Div. Of Bioequivalence has requested dissolution data for informational purposes.
   d. EIR for all firms is satisfactory as of 6/4/97.
   e. Method validation is not required as the drug substance and drug product are USP. Method verification has been performed and found satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is NOT APPROVABLE. The amendment will be a MINOR FACSIMILE.

19. REVIEWER: Donald Shostak

DATE COMPLETED: October 16, 1997

ANDA 75-082

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-082

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Methadone Hydrochloride Tablets USP 40 mg (Dispersible Tablets); Eli Lilly and Company.
The applicant certifies that to the best of their knowledge there are no effective patents or exclusivity associated with NDA 17-058 (Methadone Hydrochloride, Lilly)

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Methadone Hydrochloride Tablets USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: February 25, 1997
Amendment: May 12, 1997
Amendment (Facsimile): January 12, 1998
Amendment (Label): February 5, 1998

FDA:
Refusal to File Letter: May 1, 1997
Letter (Acceptable for Filing): June 2, 1997
Chem Rev # 1: November 12, 1997
Label Review: December 17, 1997
Chem. Facsimile: December 24, 1997

10. PHARMACOLOGICAL CATEGORY
Detoxification of narcotic addiction

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

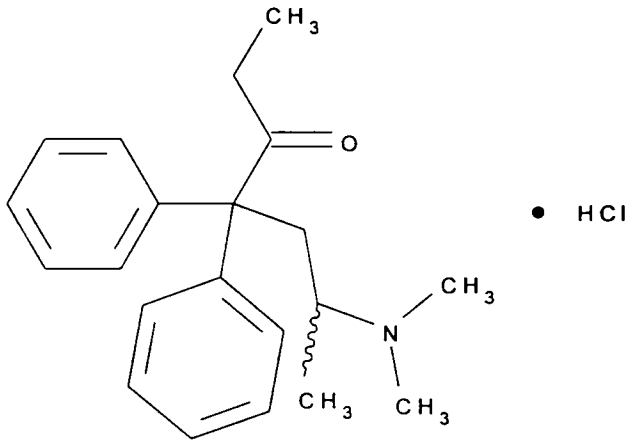
13. DOSAGE FORM
Tablet (Dispersible)

14. POTENCY
40 mg

15. CHEMICAL NAME AND STRUCTURE

Methadone Hydrochloride

$C_{21}H_{27}NO.HCl$; M.W. = 345.91



(±)-6-(Dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride.
CAS [1095-90-5]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
a. Chemistry, manufacturing and controls procedures are satisfactory.
b. Label review of the 2/5/98 amendment is satisfactory.
c. The Div. Of Bioequivalence has requested dissolution data for informational purposes only. Bio acceptable and waiver is granted - 10/9/97.
d. EIR for all firms is satisfactory as of 6/4/97.
e. Method validation is not required as the drug substance and drug product are USP. Method verification has been performed and found satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application can be approved.

19. REVIEWER:
Donald Shostak

DATE COMPLETED:
January 14, 1998
(Revised - labeling 2/10/98)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75082

BIOEQUIVALENCE REVIEW(S)

OCT -9 1997

Methadone Hydrochloride Tablets, Dispersible	Eon
40 mg Tablets	Laurelton, NY
ANDA #75-082	Submission Date: 5/12/97
Reviewer: Moo Park	
Filename: 75082w.597	

Review of a Waiver Request

I. Objective

Review of Eon's waiver request on its Methadone Hydrochloride Tablets, Dispersible, 40 mg strength. Reference product is Roxane's Methadone Hydrochloride Tablets, Dispersible, 40 mg strength.

II. Background

Methadone Hydrochloride Tablets, Dispersible, 40 mg strength, is AA rated in the Orange Book. USP does not require dissolution testing for Methadone Hydrochloride Tablets, Dispersible. USP requires disintegration test.

III. Comments

1. Methadone Hydrochloride Tablets, Dispersible, 40 mg strength is an AA rated drug product. *In vivo* bioequivalence study is not required.

2. Test formulation is shown in Table 1. Roxane's reference product contains the following inactive ingredients: cellulose, magnesium stearate, potassium phosphate, silicon dioxide, cornstarch, stearic acid, color, and flavors.

Table 1. Test Formulation

Ingredient	Amount/tablet mg
Methadone Hydrochloride	40
Starch	
Microcrystalline Cellulose	
Colloidal Silicon Dioxide	
Magnesium Stearate	
Total Weight	1690

3. Disintegration testing was performed on 12 units of Eon's test product, lot #960806, and Roxane's reference product, lot #9MN84N. All test and reference products showed disintegration time of less than one minute under the following USP method:

Apparatus	USP 23 disintegration apparatus without disk
Frequency	30 cycles per min
Medium	water
Volume	1000 mL
Temperature	37°C
Specification	NMT minutes

4. Waiver is granted for Eon's Methadone Hydrochloride Tablets, Dispersible, 40 mg strength. However, comparative dissolution testing is requested for information purposes. Quick disintegration does not warrant fast and complete dissolution. Records show that Roxane and Mallinckrodt submitted comparative dissolution testing data for the approval of their ANDA's.

IV. Recommendations

1. The Division of Bioequivalence agrees that the information submitted by Eon demonstrates that its Methadone Hydrochloride Tablets, Dispersible, 40 mg strength, falls

under 21 CFR 320.22(c) of the Bioavailability/Bioequivalence Regulations. Waiver of *in vivo* bioequivalence study requirements for Eon's Methadone Hydrochloride Tablets, Dispersible, 40 mg strength, is granted. The firm's test product, Methadone Hydrochloride Tablets, Dispersible, 40 mg strength, is, therefore, deemed bioequivalent to Roxane's Methadone Hydrochloride Tablets, Dispersible, 40 mg strength.

2. The firm is advised to submit comparative dissolution testing using USP method for information purposes.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D. 10/9/97
Team Leader, Review Branch III
Division of Bioequivalence

Concur: _____ Date: 10/9/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #75-082 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

File history: Draft (7/11/97); 2nd Draft (10/9/97); Final (10/9/97)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75082

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **75-082** Date of Submission: **May 12, 1997**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Methadone Hydrochloride Tablets USP, 40 mg (Dispersible)**

Labeling Deficiencies:

1. CONTAINER 100s

   a. Relocate the "WARNING: May be habit forming." statement to between the established name and the strength.

   b. Add the following statement to the main panel:

      FOR METHADONE TREATMENT PROGRAMS

2. INSERT

   a. TITLE

      Add the following statement immediately below the title:

      For Methadone Treatment Programs

   b. Box the section entitled "CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS".

   c. DESCRIPTION

      i. Revise the chemical name to be the same as the second USP 23 name.

      ii. Second sentence

      However, the dispersible tablet preparation of ...

iii. Third sentence

"molecular formula" rather than "empirical formula".

iv. Include the structural formula for methadone hydrochloride.

v. Second paragraph

A). Add the following as the new first sentence:

Methadone Hydrochloride Tablets USP (Dispersible) are intended for dispersion in a liquid prior to oral administration of the prescribed dose.

B). Current second sentence - Each tablet also contains the following inactive ingredients: colloidal ...

C). We encourage you to alphabetize your listing of inactive ingredients.

d. CLINICAL PHARMACOLOGY

"CLINICAL PHARMACOLOGY" rather than "ACTIONS".

e. INDICATIONS AND USAGE

i. "INDICATIONS AND USAGE" rather than "INDICATIONS".

ii. NOTE

A). Box the text in this subsection.

B). Last sentence - ... in a program which has approval for ...

f. CONTRAINDICATIONS

The section title is plural.

g. WARNINGS

Box the text of the first paragraph.

h. PRECAUTIONS

i. Drug Interactions, Pentazocine -

... when given pentazocine.

ii. Relocate the "Acute Abdominal Conditions" subsection to be the penultimate subsection.

i. ADVERSE REACTIONS

Fourth paragraph, last sentence -

Some adverse reactions may be alleviated in the ambulatory patient if he lies down.

j. OVERDOSAGE

i. Revise the text which precedes the "NOTE" text as follows:

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, an effective narcotic antagonist is 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 antagonist acts 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. This agent should be given repeatedly until the patient's status remains satisfactory. The hazard that the narcotic antagonist will further depress respiration is less likely with the use of naloxone. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

ii. The text under "NOTE" in this section should be boxed.

k. DOSAGE AND ADMINISTRATION

i. Add the following text as the first paragraph:

Methadone Hydrochloride Tablets USP (Dispersible) are intended for dispersion in a liquid prior to oral administration of the prescribed dose.

ii. For Maintenance Treatment, eighth sentence -

... first 3 months. After demonstrating satisfactory adherence to the program regulations for at least 3 months, the patient may be permitted to reduce to 3 times weekly the occasions when he must ingest the drug under observation. He shall receive ...

l. HOW SUPPLIED

i. We encourage the use of the NDC number in this section.

ii. Your packaging and labeling order states that the tablet is "imprinted" while the HOW SUPPLIED section says the tablet is "embossed". Please comment and/or revise.

iii. Capitalize the "M" in your corporate name.

iv. Please state that your tablet is "dispersible".

v. "quadrisected" (spelling).

Please revise your container labels and insert 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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Methadone HCl Tablets

NDA Number: 17-058

NDA Drug Name: Methadone Hydrochloride Tablets

NDA Firm: Roxane Labs (formerly held by Eli Lilly and Co)

Date of Approval of NDA Insert and supplement #: 3/19/87 (S-009)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides and approved labels for ROXANE's approved product 74-081

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? Letter has (Dispersible) after established name and strength	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book? O Book has tablet, dispersible; oral	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			

	Yes	No	N.A.
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	

Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) SEE FTR AND NOTE TO CHEMIST AND REVIEW UNDER "HOW SUPPLIED"		X*	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

See comment 2(k)(ii) in the review concerning whether the tablet is "embossed" or "imprinted". Tablet punch indicates the tablet is embossed - see batch records dtd 1/14/98

FOR THE RECORD:

1. This review was based on the labeling of Lilly's insert labeling permitted 3/19/87 (NDA 17-058/S-009) with a revision date of 9/25/86. This is the latest approved labeling though since that time Roxane bought the ANDA and hence now the Orange Book has Roxane as the holder of this NDA (17-058)

2. The packaging and labeling order submitted May 12, 1997 states that the tablet is imprinted while the HOW SUPPLIED section says "embossed". The rest of the tablet description is accurate. I have made a comment to the firm and to the chemist.

3. The inactives are correctly listed in the DESCRIPTION section (p 70 v 1.1).

4. Eon is the sole manufacturer (p 139 v 1.2)

5. Both the RLD and this ANDA have quadrisected tablets.

6. Both the RLD and the ANDA have the 100s container size.

7. The container is made of HDPE and comes with a screw cap (p 236 v 1.3).

8. This review was done with the red jackets.

Date of Review: 12-4-97 Date of Submission: May 12, 1997

Primary Reviewer: Adolph Vezza Date: 12/17/97

Team Leader: Charlie Hoppes Date: 12/17/97

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cc:

ANDA: 75-082
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/12/4/97|X:\NEW\FIRMSAM\EON\LTRS&REV\75082NA1.L
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75082

CORRESPONDENCE

Eon Labs
A Health Care Company

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

February 5, 1998

ORIG AMENDMENT

N/F A

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, MD 20857

Reference: ANDA 75-082 - AMENDMENT
METHADONE HYDROCHLORIDE TABLETS USP, 40 MG

Container 100s

Satisfactory, however as a result of the FDA Modernization Act of 1997, please note the following:

1. **Delete the"Warning : May be habit forming." statement.**

2. **Replace the " Caution: Federal law...." satement with the Rx only symbol.**

3. **Revised container labels with the above changes may be submitted in your first annual report provided the changes are described in full.**

We aknowledge your comments and will revise the container labels to reflect your comments. We will submit the revised container labels in our first annual report.

Insert

1. **DESCRIPTION**

   Revise the chemical name to be the same as the second USP 23 name.

2. **PRECAUTIONS - Drug Interactions**

   Delete the sentence "Desipramine - Blood levels of desipramine have increased with concurrent methadone therapy." This sentence does not appear in the approved labeling of the reference listed drug.

RECEIVED

FEB 0 6 1998

OFFICE OF GENERIC DRUGS

3. **See comments under "Container".**

The inserts have been revised and are being submitted in final print (***Attachment 1***).

To facilitate review of this submission, a side by side comparison of the current insert and the last submission with all differences annotated and explained is being included (***Attachment 2***) . 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.235.

Sincerely,
Eon Labs Manufacturing Inc.

Amal Shaker
Regulatory Affairs Associate

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

January 12, 1998

Rabindra N. Patnaik, Ph. D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

ORIG AMENDMENT
AB

Reference: Methadone Hydrochloride Tablets, USP, 40 MG (Dispersible Tablet)
ANDA 75-082

Dear Dr. Patnaik;

We refer to your letter of December 24, 1997 regarding our ANDA 75-082 for Methadone Hydrochloride Tablets, USP, 40 MG (Dispersible Tablet).

> **"...Please submit comparative dissolution testing data using the USP 23 for our informational review."**

Please note that this drug product is a dispersible tablet and that the USP 23 test criteria for Methadone dispersible tablets calls for disintegration and not dissolution testing. The specification for disintegration is NMT .ninutes. We are providing a Disintegration Time Comparison Report for your review ***(Attachment 1)***. This report was previously submitted on May 12, 1997 as an addendum to the original Abbreviated New Drug Application at the time of filing.

If additional information is required, please contact me at (718) 276-8600, extension 235.

Sincerely,
Eon Labs Manufacturing, Inc.

Amal Shaker
Regulatory Affairs Associate

RECEIVED
JAN 14 1998
GENERIC DRUGS

1/12/98
FA noted
① CTA Chemistry Reviewer
for review ② Then To
Labeling for review

Eon Labs
The Pharmacy Drug Company

EON LABS MANUFACTURING, INC
227-15 North Conduit Avenue
Laurelton, NY 11413
Telephone (718) 276-8600

FACSIMILE TRANSMITTAL SHEET

DATE: January 12, 1998 TIME: 9:08 AM

TOTAL NUMBER OF PAGES (INCLUDING COVER SHEET):_____

TO: Dr. F Holcombe, Jr. COMPANY: FDA Document Control Room

FROM: Amal Shaker

OUR FAX NUMBER: 1-718-276-8635 (Regulatory Affairs)

If busy: 1-718-949-3120

FA

MESSAGE:

Re: Facsimile Amendment for : ANDA 75-082 Methadone Hydrochloride Tablets, USP , 40 mg (Dispersible)

Attached is a copy of our responses to your letter dated December 24,1997. Please note that a copy of the final printed labeling is sent in Attachment # 3.
This letter is being sent overnight with the actual final printed labeling.

If you have any questions please do not hesitate to call me at (7180276-8607 ext.235.

Sincerely

Amal Shaker
Regulatory Affairs Associate.

ANDA 75-082

DEC 24 1997

1.1
AFTER
7.12.97
MEMO

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-082 APPLICANT: Eon Labs

DRUG PRODUCT: Methadone Hydrochloride Tablets USP, 40 mg (Dispersible Tablet)

The deficiencies presented below represent [redacted] FACSIMILE deficiencies.

A. Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Since the drug product is a USP 23 item, the unmodified analytical methods and procedures in USP 23 are official. In the event of a dispute, only the results obtained by the methods and procedures described USP 23 will be considered conclusive.

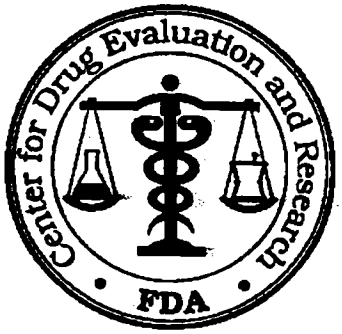
Sincerely yours,

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

FACSIMILE AMENDMENT

DEC 24 1997

ANDA: 75-082



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 Lab Manufac, Inc PHONE 718-276-8607
ATTN: Sadie Ciganek FAX 718-276-8635

FROM: Timothy W. Ames, PROJECT MANAGER (301-827-5849)

Dear ~~Sir/Madam~~: Sadie,

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 2/25/97, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Methadone Hydrochloride Tablets USP 40mg (Dispersible).

Reference is also made to your amendment(s) dated May 12, 1997.

Attached are 6 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. 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.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\faxtrak\faxcov.fax

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

May 12, 1997

NDA ORIG AMENDMENT

N/C

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, MD 20857

Reference: ANDA 75-082- AMENDMENT
METHADONE HYDROCHLORIDE TABLETS, USP, 40 MG

Dear Mr. Phillips;

We refer to your letter of May 1, 1997 **refusing to file** our ANDA 75-082 submitted February 25, 1997, and the telephone conversation of May 6, 1997, for Methadone Hydrochloride Tablets, USP, 40 mg. In accordance with the provisions outlined in the letter, we are amending our submission with the enclosed information which includes the following:

- 12 tablets disintegration time data (***attachment 1***)
- Packaging and labeling forms (***attachment 2***)
- The revised debarment certification and list of convictions (***attachment 3***)

If additional information is required, please contact me at (718) 276-8600, extension: 423

Sincerely,
Eon Labs Manufacturing, Inc.

Zohra E. Lomri
Regulatory Affairs Associate

RECEIVED
MAY 13 1997
GENERIC DRUGS

ANDA 75-082

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

MAY 1 1997

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated February, 25, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methadone Hydrochloride Tablets USP, 40 mg (Dispersable).

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:

In addition, please include packaging and labeling forms with your master production batch record.

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

Please do not use qualifying language in your debarment certification and list of convictions (i.e., to the best of my knowledge and infomation). Please provide a revised debarment certification and convictions list that eliminates this language.

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:

Cecelia Parise

Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips 5/1/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-082

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

JUN 2 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 May 1, 1997, and your amendment dated May 12, 1997.

NAME OF DRUG: Methadone Hydrochloride Tablets USP, 40 mg (Dispersible)

DATE OF APPLICATION: February 25, 1997

DATE OF RECEIPT: February 28, 1997

DATE ACCEPTABLE FOR FILING: May 13, 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) 827-5849

Sincerely yours,

Jerry Phillips 5/27/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation andResearch

cc:
ANDA 75-082
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsement: HFD-615/PRickman, Chief, DGT date 5/27/97
HFD-615/CParise,CSO 5/27 date
HFD-647/Branch 6 _____date
WP File x:\new\firmsam\eon\ltrs&rev\75-082.ack
F/T/njg/5/16/97
ANDA Acknowledgement Letter!