

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-434

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-434

DRUG PRODUCT: Naltrexone HCl, USP

FIRM: Eon Labs Manufacturing, Inc.

DOSAGE FORM: Tablet; Oral

227-15 North Conduit Avenue

STRENGTH: 50 mg

Laurelton, N.Y. 11413

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP certification is provided (p. 184).

An acceptable EER was issued on 9/1/99.

Facilities included:

Manufacturing, processing, packaging, labeling and testing:

Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, New York 11413

Manufacturer of the drug substance:

Analytical testing on initial release finished product as well as stability samples:

BIO STUDY

Comparative dissolution profiles and *In-Vivo* bioavailability studies were performed and found satisfactory per C. Y. Kim (11/6/98).

VALIDATION

The method validation by the NY district laboratories was completed on April 1999 and found acceptable. A compendial monograph for Naltrexone HCl Tablets was established after submission of the application (Supplement 9 to USP 23, p. 4582).

DRUG SUBSTANCE

The drug substance is compendial.

.-Satisfactory per M. Piñeiro-Sánchez, 10/13/99.

Naltrexone HCl (p. 80, 95-98).

Test	Specifications	
	Manufacturer and Firm	USP
Appearance	white/slightly of white powder	N/A

IN-PROCESS CONTROLS

The firm submitted the following in-process controls (Blank Batch Record, p. 211):

Test	Specification
Blend Uniformity	
tablet	
after coating	

CONTROLS FOR THE FINISHED DRUG PRODUCT

The following are the specifications for Naltrexone HCl Tablets (p. 442-443):

Test	Specifications
Peak in the chromatogram of the	1.05 to 1.15

NOTE: The firm established a limit of _____ for each unknown. Although we recommend that this limit be established at NMT _____ has been previously approved (see below) and therefore is acceptable. In addition USP recommends a value _____ or all other impurities.

STABILITY

Post-approval commitments are in accordance with FDA Stability Guidelines (p. 512-513). Three month accelerated (40°C/75% RH) and room temperature (25-30°C/ambient humidity) stability data is provided for the C/C proposed for marketing (100 cc round, white, vottle with 38 mm white plastic CR cap). A Summary of the container/closure system is provided (p. 334-337). Three-month stability data for the bulk sample stored at normal plant environmental conditions (ambient temperature & relative humidity) in the warehouse area, is provided (p. 516-545). All of the stability data obtained conform to specifications.

Test	Specifications

Expiration date: 24 months based on accelerated stability data.

LABELING

Professional labeling - Pending review.

STERILIZATION VALIDATION (IF APPLICABLE)

N/A

SIZE OF BIO/STABILITY BATCHES

Exhibit batch: Lot #971001, 115,000 tablets.

PROPOSED PRODUCTION BATCH

The commercial batch size of 500,000 tablets is within the 10X scale-up rule.

CHEMIST: Mayra L. Piñeiro-Sánchez, Ph.D. ^{MP3}_{2/24/00} DATE: December 16, 1999

SUPERVISOR: Glen Jon Smith  DATE: 2/24/00

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

ANDA Number: 75-434 Date of Submission: August 6, 1998

Applicant's Name: Eon Labs Manufacturing, Inc.

Established Name: Naltrexone Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. CONTAINER 30s and 100s

Add the statement "Protect from light."

2. INSERT

- a. DESCRIPTION

- i. First paragraph, last sentence - "naltrexone" (lower case "n").
- ii. Last paragraph - Each tablet for oral administration contains ... In addition, each tablet contains the following inactive ingredients:

- b. CLINICAL PHARMACOLOGY

- i. Delete "hydrochloride" throughout this section except where indicated below.
 - A). Pharmacodynamic Actions, fourth paragraph, first sentence.
 - B). Clinical Trials
 - 1). Alcoholism, second sentence.
 - 2). Treatment of Alcoholism, first paragraph, first sentence, second occurrence.

3). Treatment of Narcotic Dependence

a). First paragraph

i). First sentence.

ii). Fourth sentence.

b). Last paragraph, first sentence

ii. Pharmacodynamic Actions - Upper case "A".

iii. Pharmacokinetics, penultimate sentence -
Delete the "(" before "6-β-naltrexol".

iv. Metabolism, first sentence - Delete the blank
space between "is" and "3.5".

v. Clinical Trials

A). Upper case "T".

B). Alcoholism - The following text at the
end of the first paragraph and the
beginning of the second paragraph has
been deleted in error. Please correct.

... and secondary psychiatric diagnoses
were excluded from these studies.

In one of these studies, 104 alcohol-
dependent patients were randomized to
receive either naltrexone hydrochloride
50 mg once daily or placebo. In this
study naltrexone proved superior to
placebo in measures of ...

C). "Treatment of Narcotic Addiction",
"Individualization of Dosage",
"Treatment of Alcoholism" and "Treatment
of Narcotic Dependence" are all sub
subsections (of the "Clinical Trials"
subsection) and should all be
differentiated accordingly.

D). Individualization of Dosage - Upper Case
"D".

E). Treatment of Narcotic Dependence, first paragraph, penultimate sentence - Delete the extra blank spaces between "and" and "150 mg".

c. INDICATIONS AND USAGE

Delete "hydrochloride" throughout this section.

d. CONTRAINDICATIONS

Delete "hydrochloride" throughout this section.

e. WARNINGS

i. Delete "hydrochloride" throughout this section except where indicated below.

A). First paragraph after black box, first sentence, second occurrence.

B). Second paragraph after black box.

ii. Third paragraph after black box, first sentence - "cases" rather than "case".

iii. Last sentence - ... (See **PRECAUTIONS, Information for Patients** section).

f. PRECAUTIONS

i. Delete "hydrochloride" throughout this section except where indicated below.

A). Impairment of Fertility

B). Pregnancy: Category C, first paragraph, second sentence.

ii. "General", "Laboratory Tests", "Drug Interactions", "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy: Category C", "Labor and Delivery", "Nursing Mothers", and "Pediatric Use" are all subsection titles and should be of lesser prominence than the section title "PRECAUTIONS". The other titles in this section are all sub subsection titles and should be differentiated accordingly.

iii. When Reversal of Naltrexone Blockade is Required - Note the capitalization.

iv. Laboratory Tests - Upper case "T".

v. Mutagenesis - "E Coli" (*italic print*).

g. ADVERSE REACTIONS

i. Delete "hydrochloride" throughout this section except where indicated below.

Second paragraph, third occurrence.

ii. Reported Adverse Events, last sentence - (see **CLINICAL PHARMACOLOGY, Clinical Trials, Individualization of Dosage**).

iii. Narcotic Addiction, The following events occurred in less than 1% of subjects

A). Cardiovascular - "changes" (print font)

B). Musculoskeletal - ";" rather than ":".

C). Other - First sentence - delete the extra blank spaces between "narcotic" and "dependence".

h. DRUG ABUSE AND DEPENDENCE

Delete "hydrochloride".

i. OVERDOSAGE

i. Delete "hydrochloride" throughout this section except in the second sentence.

ii. Treatment of Overdosage - Last sentence - "for" rather than "of".

j. DOSAGE AND ADMINISTRATION

i. Delete "hydrochloride" throughout this section except where indicated below.

Alternative Dosing Schedules, first and third sentences.

- ii. Treatment of Narcotic Dependence, Initiate treatment with naltrexone using the following guidelines, Naloxone Challenge Test, Intravenous challenge - "naloxone hydrochloride" rather than "naloxone"
 - iii. Alternative Dosing Schedules, second paragraph (see **CLINICAL PHARMACOLOGY, Clinical Trials, Individualization of Dosage**).
- k. HOW SUPPLIED
- i. We encourage the use of the NDC number in this section.
 - ii. Relocate the "Rx only" symbol to appear immediately beneath the title of the insert.
 - iii. Dispense in tight ... (delete "a").
 - iv. Add the statement "Protect from light."

Please revise your container labels and insert labeling, as instructed above, and submit container labels and insert labeling 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
 If no, list why:

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: Revia®

NDA Number: 18-932

NDA Drug Name: Revia® (Naltrexone Hydrochloride Tablets, 50 mg)

NDA Firm: DuPont Merck

Date of Approval of NDA Insert and supplement #: 12/30/94 (S-010)

Has this been verified by the MIS system for the NDA? Yes - But in the MIS system there is no S-010 -- it is designated S-011

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		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?		X	
If not USP, has the product name been proposed in the PF?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		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: (PTR: 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)		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.			

FOR THE RECORD:

1. This review is based on the labeling for Revia (DuPont, approved 12-30-94, revised 1/95). Acknowledge and retain 3-4-96. ANDA 74-918, Barr Labs approved PI (5-8-98) was also used to assist in the review process.

2. Storage/Dispensing Recommendations:

ANDA: Store at CRT. Dispense in tight, light resistant containers as defined in the USP, with a child-resistant closure, as required. Keep tightly closed. [container]

Store at CRT. Keep tightly closed. [insert]

NDA: Store at CRT. Dispense in a tight container as defined in the USP. [container]

Protect from light. [insert]

USP: Not a USP item.

Proposed in PF as - Naltrexone Hydrochloride Tablets

I have asked the firm to add "Protect from light." to both the container and the insert. ANDA 74-918 includes this statement on both the insert and the container (though they have "Dispense in a tight container ..." - no mention of "light")

3. Both the ANDA and the RLD are scored.
4. RLD is marketed in bottles of 50s. The firm proposes to market in bottles of 30s and 100s. Both containers are HDPE with CRC caps (p 337 v 1.3).
5. Eon is the sole manufacturer (p 183 v 1.2).
6. The tablet description is accurate as listed in the HOW SUPPLIED section (p 439 v 1.3).
7. The inactives are accurately listed in the DESCRIPTION section (p 73 v 1.1).
8. Bio is pending.

Date of Review: 11-4-98 Date of Submission: 8-6-98

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

11/12/98

Team Leader: Charlie Hoppes

Date:

Charlie Hoppes

11/12/98

cc:

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