

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**75-434**

**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

December 6, 1999

Robert L. West, M.S., R.Ph  
Director  
Division of Labeling and Program Support  
Office of Generic Drug  
Center for Drug Evaluation and Research  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**NDA ORIG AMENDMENT**

N/AF

**-MINOR AMENDMENT- LABELING**

**Re: Naltrexone Hydrochloride Tablets, 50 mg  
ANDA 75-434**

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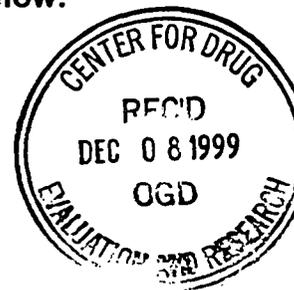
Dear Mr. West

In reference to your letter dated April 2, 1999 for labeling deficiencies for Naltrexone Hydrochloride Tablets, 50 mg, ANDA 75-539, we have made the necessary corrections indicated and we are submitting final printed insert, and side-by-side comparison.

**Labeling Deficiencies**

**Insert**

- 1. Due to recent and significant changes in the labeling of the reference listed drug (ReVia®; Dupont; Approved March 5, 1999; Revised March 1997) please revise your insert labeling to be in accord with the attached innovator insert labeling, changes in the approval letter and the changes below.**
- 2. PRECAUTION**  
**Impairment of Fertility - Naltrexone hydrochloride ...**
- 3. DOSAGE AND ADMINISTRATION**



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R. L. West

December 6, 1999

Page 1 of 2

**When referring to a dose of naltrexone please use "naloxone hydrochloride".**

**Please revise your 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.**

Response:

The insert has been revised according to your comments, and final printed insert are provided (**ATTACHMENT 1**).

To facilitate review of this submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), a side-by-side comparison of the proposed labeling as compared to the labeling in the previous submission is provided (**ATTACHMENT 2**). In addition, an annotated reference table summarizing the differences highlighted on the side-by-side comparison is provided.

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. 404.

Sincerely,  
Eon Labs Manufacturing, Inc.

  
Blessy Johns  
Regulatory Affairs Associate

November 12, 1999

Florence S. Fang, Ph.D  
Director  
Division of Chemistry II  
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**

N/RM

**-MAJOR AMENDMENT-**

**Re: Naltrexone Hydrochloride Tablets, 50 mg  
ANDA 75-434**

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Dear Dr. Fang:

We refer to your letter of April 2, 1999 commenting on our Abbreviated New Drug Application for Naltrexone Hydrochloride Tablets, 50 mg. The following are our responses to the major deficiencies noted in the letter.

**A. Chemistry Deficiencies**

1.

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las ..... o.

NOV 13 1999

Florence S. Fang, Ph.D.

Page 1 of 2

NW  
11-16-99

2.

In addition to addressing the deficiencies noted above, we are also submitting a change to the desiccant component used to package the finished product. The desiccant manufacturer, United Desiccant has changed their name to Sud-Chemie. A letter from the manufacturer to that effect is provided, **ATTACHMENT 4**.

We intend to submit final printed labeling in a separate amendment in the immediate future.

We hope our responses satisfactorily address your comments and that approval of application can move forward. If you need additional information, do not hesitate to call me at (718) 276-8607 x330.

Sincerely,  
Eon Labs a Health Care Company



Sadie M. Ciganek  
Vice President Regulatory Affairs

April 23, 1999

Florence S. Fang, Ph.D  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20857

MAJOR AMENDMENT  
FPL  
Ac

**Reference: MAJOR AMENDMENT  
Naltrexone Hydrochloride Tablets, 50 mg  
ANDA 75-434**

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Dear Dr. Fang:

We refer to your letter of April 2, 1999 commenting on our Abbreviated New Drug Application submitted on August 6, 1998 for Naltrexone Hydrochloride Tablets, 50 mg. The following are our responses to the major deficiencies noted in the letter.

**A. Chemistry Deficiencies**

**1. Regarding containers/closures:**

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Co.

**Response:**

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ε  
ε

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Dr. Fang

April 23, 1999

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Page 1 of 13

APR 27 1999

**GENERIC DRUGS**

Page(s)

6

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

4/23/99

**Response:**

The stability report formats have been revised according to your comment and are submitted for your review, ***Attachment 12***.

**Comment:**

- b. A matrix system is proposed in your post approval stability commitment (p. 512). Please clarify.

**Response:**

The post approval stability commitment report has been revised to delete the "matrix system" statement that does not apply in the case of a single strength product such as Naltrexone Hydrochloride Tablets, 50 mg. The revised document is submitted for your review, ***Attachment 13***.

**Comment:**

- B. In addition to responding to the deficiencies presented above, please not and acknowledge the following comments in your response:

**We have submitted your analytical methods for validation by our district laboratory.**

**Response:**

We acknowledge that our analytical method must be tested by the district laboratory, before approval of our application.

**Labeling Deficiencies:**

**Comment:**

**1. CONTAINER            30s and 100s**

**Add the statement "Protect form light."**

**Response:**

We acknowledge your comment and have revised our container labels accordingly. Final printed labels and side-by-side comparison of our previously submitted labels are provided, ***Attachment 14***.

**2. INSERT**

**Comments:**

**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 measurers 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 sections).

**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.
- ii. Reported Adverse Events, last sentence - (see CLINICAL PHARMACOLOGY, Clinical Trials, Individualization of Dosage).
- iii. Narcotic Addition, 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 where indicated below.
- 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, Naltrexone Challenge Test, Intravenous challenge - "naltrexone hydrochloride" rather than "naltrexone"

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 form light"

**Response:**

Final Printed insert and a side by side comparison of the current insert and the last submission with all differences annotated and explained, **Attachment 15**.

Please note that we do not include NDC numbers on our insert. This is due to the fact that the same insert is used by our private customer label distributors and therefore, it would be inappropriate to include NDC numbers.

If there are any comments or questions regarding this submission, please contact me at (718) 276-8607, extension 393.

Sincerely,  
Eon Labs Manufacturing, Inc.



Zohra E. Lomri  
Sr. Regulatory Affairs Associate

November 6, 1998

ORIG AMENDMENT

N/AB

Ms. Lizzie Sanchez  
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, Maryland 20855

**RE: Bioequivalence - Telephone Amendment — ANDA 75-434  
Naltrexone Hydrochloride Tablets, 50 mg**

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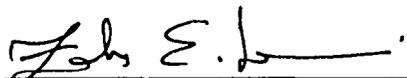
Dear Ms. Sanchez:

Reference is made to your telephone conversation of October 28, 1998 with Ms. Patricia Kaufold commenting on Eon's original Abbreviated New Drug Application for Naltrexone Hydrochloride Tablets, 50 mg. We have included the requested data as follows:

- 69 days frozen stability data, **Appendix 1.**
- explanation as to why the concentration for the frozen samples are lower than the fresh samples (page 3065), **Appendix 2.**

We hope this response satisfactorily addresses your comments. If you need further clarification or additional information regarding this Telephone Amendment, please do not hesitate to contact me at (718) 276-8607, extension 393.

Sincerely,  
Eon Labs Manufacturing, Inc.



Zohra E. Lomri  
Sr. Regulatory Affairs Associate

RECEIVED

NOV 13 1998

GENERIC DRUGS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75434

APPLICANT: Eon Labs Manufacturing Inc.

DRUG PRODUCT: Naltrexone Hydrochloride Tablets, 50 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 ml of water at 37°C using USP 23 Apparatus II (paddles) at 50 rpm. The test should meet the following specifications:

Not less than \_\_\_\_\_ of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

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,



Dale P. Conner, Pharm. D.  
Director

Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75434

APPLICANT: Eon Labs Manufacturing Inc.

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Sincerely yours,

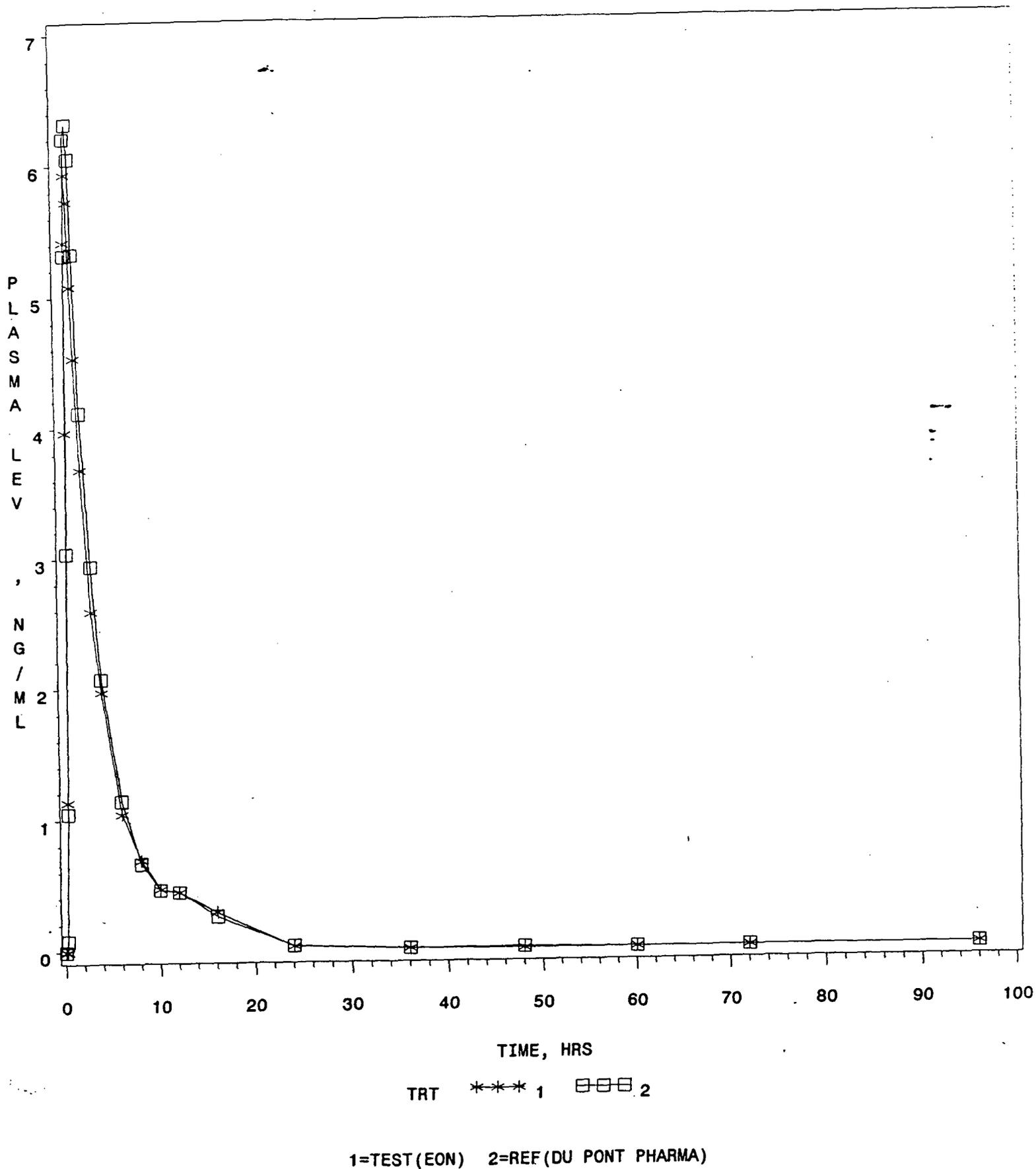


Dale P. Conner, Pharm. D.  
Director

Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

# FIG 1 PLASMA NALTREXONE LEVELS

NALTREXONE TABLETS, 50 MG, ANDA #75-434  
UNDER FASTING CONDITIONS  
DOSE=1 X 50 MG

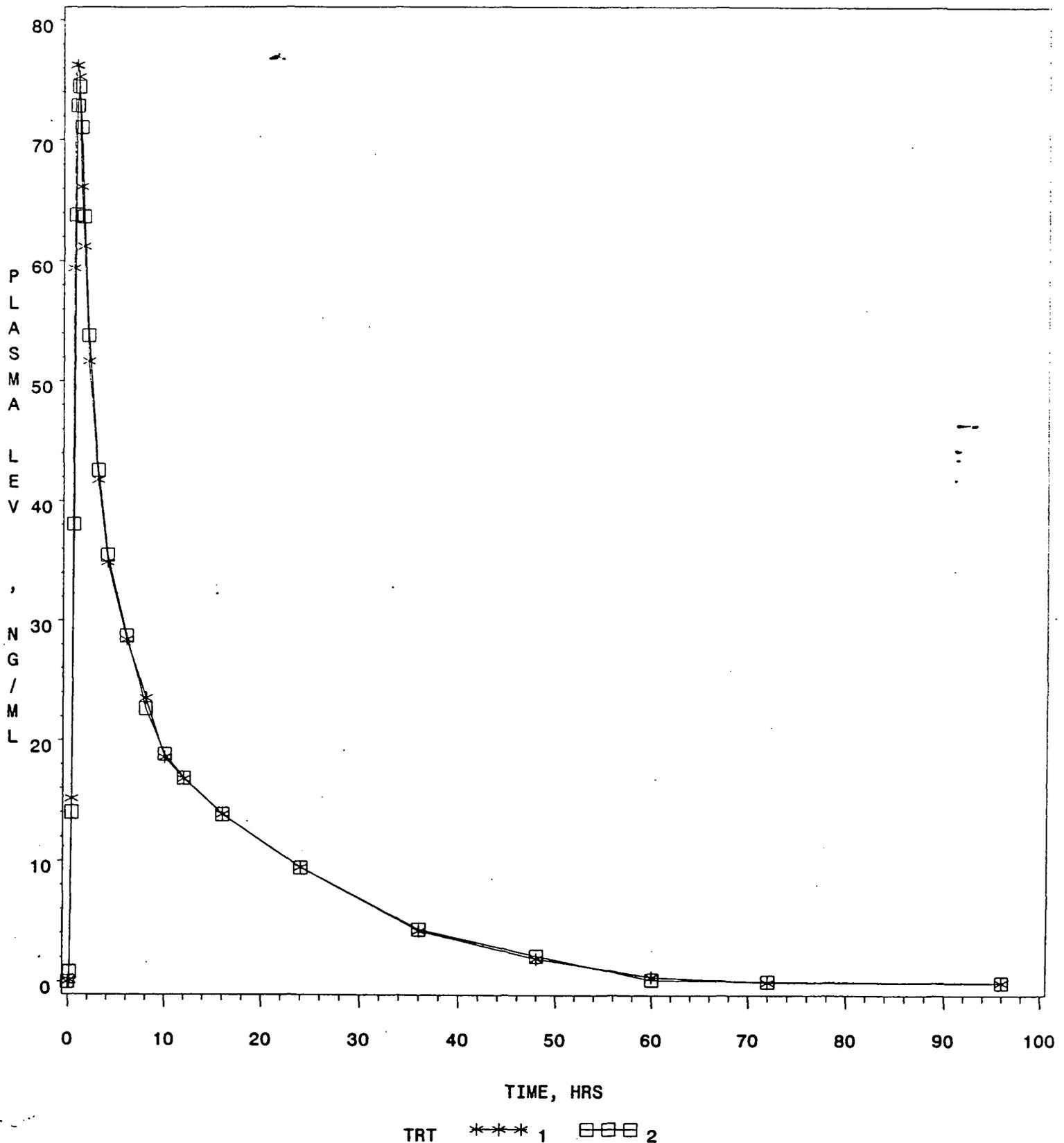


# FIG 1 PLASMA NALTREXOL LEVELS

NALTREXOL TABLETS, 50 MG, ANDA #75-434

UNDER FASTING CONDITIONS

DOSE=1 X 50 MG



1=TEST(EON) 2=REF(DU PONT PHARMA)

August 6, 1998

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

505(j)(2)(a) OK  
8/25/98  
Gregory J. Davis

RE: **Original ANDA**  
**Naltrexone Hydrochloride Tablets, 50 mg**

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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 Naltrexone Hydrochloride Tablets, 50 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 record.
- Volume 3 Container/closure, finished product control, methods validation, stability data, control numbers, samples, and environmental impact statement.
- Volume 4 through 16 Biostudy summary and test results. Also included are diskettes of raw data.

A full table of contents 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 will also be submitted to the District Field Office.

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D. Sporn

August 6, 1998

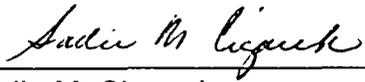
**RECEIVED** Page 1 of 2

AUG 11 1998

**GENERIC DRUGS**

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  
Sadie M. Ciganek  
Vice President Regulatory Affairs