CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

16-862

Trade Name: Darvon-N

Generic Name: (propoxyphene napsylate)

Sponsor: Eli Lilly and Company

Approval Date: September 09, 1971

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Not Approvable Letter(s)	**X**
Final Printed Labeling	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
EA/FONSI	
Pharmacology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

APPROVAL LETTER

NDA 16-862

AF 9-577

SEP 09 1971

Eli Lilly and Company
The Lilly Research Laboratories
Attention: J. G. Armstrong, M.D.
Indianapolis, Indiana 46206

Gentlemen:

This acknowledges the receipt on July 19, 1971 of your communication dated July 16, 1971, enclosing printed labeling pursuant to your new drug application for Darvon-N Tablets 50 mg. and 100 mg., NDA 16-862.

The application was filed on July 19, 1971.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit two market packages of the drug when available.

Sincerely yours,

Henry E. Simmons, M.D., M.P.H.
Director
Bureau of Drugs

Enclosures: Records and Reports Requirement (Reg. 130.13)
Conditions of Approval of NDA

cc: CIN-DO
BD-1 BD-100
BD-120 BD-242
BD-22
BD-120 WEMetzbower:mb 9/3/71
BD-120 Tocus/Ochota/Scoville/Shultz

Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

NOT APPROVABLE LETTER(S)

1/29/70

NDA 16-862

AF 9-577

The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46206

Attention: J. G. Armstrong, M. D.

Gentlemen:

Reference is made to your new drug application dated May 19, 1969 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (propoxyphene napsylate), 50 mg and 100 mg tablets.

We also acknowledge receipt of your additional communication dated October 9, 1969.

We have completed our review and find that the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

The application is inadequate under section 505(b)(1) and (6) of the Act in the absence of data which show that the drug is safe and effective in use under the conditions prescribed, recommended or suggested.

[redacted]

Biologic availability of this drug is based on data submitted to your new drug application for [redacted]

As you have been notified, it has been concluded that these data do not demonstrate satisfactory biologic availability when compared [redacted] ide).

Accordingly, the bio-availability data for this application is regarded as inadequate.

Final comment with respect to the proposed draft labeling is withheld until satisfactory biologic availability studies are completed. However, we point out at this time that under "Actions" the statement '[redacted] deviates from the April 8, 1969 Federal Register statement (copy enclosed) to a degree that is not acceptable.

We note that the container labels recommend as the usual adult dose "One or two tablets 3 or 4 times a day". As stated in the Federal Register of April 8, 1969, there is a lack of substantial evidence of effectiveness of [redacted]ose of propoxyphene hydrochloride. We regard the one tablet dosage of the 50 mg Doloxene Tablet in this category and this recommended dosage should be deleted from the labels.

We note that you intend to use the proprietary name [redacted] (as well as [redacted]) for the distribution of propoxyphene napsylate in other countries. Since "Darvon" is the proprietary name in the approved new drug application for propoxyphene hydrochloride, [redacted]

We will comment specifically on those portions of the labeling that refer to other forms of this drug when we write you regarding the new drug applications presently under consideration for those forms.

This file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, the law provides you an opportunity to obtain a hearing, if requested within 30 days from the date of issuance of this letter, on the question of whether the application, as you have presented it, is approvable. This may be obtained by a written request for filing over protest, as authorized by section 130.5(d) of the regulations. Notice of opportunity for a hearing will be published in the FEDERAL REGISTER.

Sincerely yours,

John Jennings, M. D.
Acting Director
Bureau of Medicine

Enclosure:
Federal Register Statement,
April 8, 1969

cc: Trip NDA - Cn-DO

(See Attachment for distribution and endorsements)

NDA 16-862 **Distribution & Endorsements**

cc:
Orig NDA
Dup NDA
Trip NDA - Cn-DO
MD 100
MD 120
MD 300
MD 14
MD 1
MD 456

MD 120/WmDworkin:ahe
1-27-70

WmDworkin
1-27-70

R/D endorsed by: WmDworkin 1-16-70
JMMoser 1-16-70
FEAnderson 1-16-70
WmD'Aguanno 1-16-70
MLGibson 1/16/70
WmJGyarfas 1/19/70
JJennings 1/24/70
M L Gibson 1/28/70
WJGyarfas
1/28/70

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

MEDICAL REVIEW

July 30, 1969

MEDICAL OFFICER REVIEW OF NDA 16-862

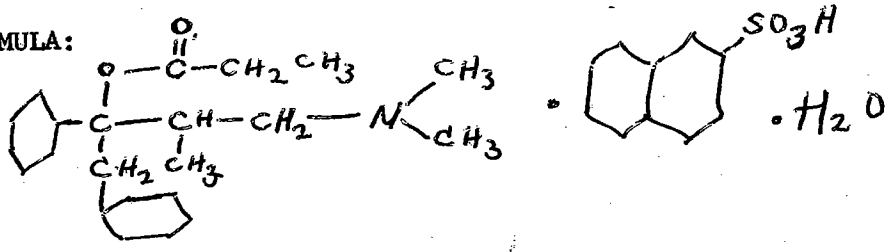
SPONSOR: Eli Lilly and Company

PRODUCT: Tablets #1882, 1883
Doloxene

GENERIC NAME: Propoxyphene napsylate
Tablets are available by prescription only and in 50 mg and 100 mg strengths.

I. CATEGORY: All-purpose analgesic

II. STRUCTURAL FORMULA:



III. DOSE RECOMMENDED: 100 mg 3 or 4 times daily.

IV. RELATED DRUGS: All presently marketed forms of Propoxyphene HCl. This product is intended as a substitute for Darvon. The present recommended dose of 100 mg of Propoxyphene napsylate is comparable on an equi-molar basis to 65 mg of Darvon. The labeling and package insert for this product is intended to be identical to that of "Darvon" with the exception of the recommended dose and the name —— to be substituted for "Darvon".

V. PHARMACOLOGY: See appropriate reviewer's comments.

VI. MANUFACTURING CONTROLS: See appropriate reviewer's comments.

VII. CLINICAL STUDIES: The firm refers us to NDA 16-827, ——, and 16-829 for data relative to the same product, (not to be approved) Propoxyphene napsylate, which is administered in Pulvule form. The data in these NDAs consists of a comparable blood level study, in which the Pulvule form of Propoxyphene napsylate was compared

to the Pulvule form of Propoxyphene HCl (Darvon) and the firm claims that the blood levels ~~are~~ of propoxyphene are similar or equal to those of Darvon. The sponsor further claims that since the blood levels of propoxyphene in Propoxyphene napsylate are equal to those of Darvon, it follows that Propoxyphene napsylate will be as effective as Darvon, and since the NAS/NRC review has stated that Darvon is an effective analgesic, when given in a dose of 65 mg 2 or 3 times a day, it follows that ~~this~~ the 100 mg dose of product Propoxyphene napsylate is equal to Darvon in effectiveness. All claims allowed in the present labeling of Darvon should apply to Propoxyphene napsylate.

The clinical studies in this present NDA consist of blood level studies using tablets of Propoxyphene napsylate and the Pulvules of Propoxyphene napsylate. The firm proposes that if the blood levels of the tablets are equal or comparable to that of the Pulvules in well-designed cross-over clinical studies, then the tablets of Propoxyphene napsylate should be allowed the same claims as the Pulvules.

COMMENT: In this reviewer's opinion, it would be more accurate to compare the blood levels of the tablets of Propoxyphene napsylate with the blood levels of the of Propoxyphene HCl (Darvon). In addition, it would save time because at the moment, approval of the tablet formulation depends entirely upon the approval of the Pulvule Propoxyphene napsylate formulation. However, the firm may have better reasons for doing it this way.

STUDY #5A, PHASE I, STUDY #1:

Investigators: H.F. Fraser, M.D., and J. Frank Nash, Ph.D. of Eli Lilly and Company. Number of subjects: 10, male employees of Eli Lilly; cross-over design and single-blind in that the chemists who analyzed the blood specimens did not know which form of Propoxyphene napsylate the subjects had been given. Two doses of Propoxyphene napsylate (100 mg and 200 mg) in suspension, tablet and Pulvule dosage forms were given to the same subjects in a cross-over technique. Following ingestion of the medication,

50 cc. of blood (venous) were obtained at o, 1, 2, 3, 4, 5 and 6 hour intervals and the Propoxyphene content was determined. It can be seen that these were single dose comparative studies.

RESULTS: The hourly concentration of Propoxyphene in the plasma showed no significant difference between the suspension, tablet, or Pulvule formulation of Propoxyphene napsylate in these 10 subjects.

LABELING REVIEW: In this particular case, the labeling for the package insert should be in accord with the Federal Register statement of April 8, 1969 for Propoxyphene HCl.

PACKAGE INSERT: Page 1. Under "Actions", the Federal Register statement asserts it to be approximately 1/2 to 2/3 as effective on a milligram basis as codeine; the firm states in this package insert This deviates from, and is not in accord with the Federal Register statement and it should be changed.

Page 2. Acceptable.

Page 3. Acceptable.

Page 4. Acceptable.

Page 5. Acceptable.

Page 6. Under "How Supplied". The composition of tablets oes not follow the recommendations of the Federal Register statement. If a

[ ]

COMMENTS AND EVALUATION:
This is another formulation of Propoxyphene napsylate submitted in tablet form. The firm submits data from cross-over blood level studies purporting to show that the blood levels of this tablet formulation are equal to those in Propoxyphene napsylate Pulvule formulation. These blood level studies are acceptable provided our Bureau of Medicine statisticians accept the studies per se. And also provided the NDA 16-827 which is for the Pulvule formulation of Propoxyphene napsylate is approved.

The labeling submitted in rough draft form with NDA is generally in accord with that of the Federal Register statement of April 8, 1969. However, the two disagree in the "actions" paragraph and the present statement by the firm ' _____ is not acceptable and should be revised to agree with the present Register statement.

The composition of tablets labeled " _____ should not be approved because excessive doses of the other ingredients would result when physicians prescribed 100 mg of "Doloxene".

James M. Moser, Jr.

James M. Moser, Jr., M. D.
Division of Neuropharmacological Drugs

cc:
Dup NDA
Trip NDA
MD-100
MD-120
MD-300

MD-120/JMMoser/ahe 8-7-69

December 10, 1969

MEDICAL OFFICER REVIEW OF NDA 16-862

Addendum

A memorandum dated 12/1/69 has been received from our Statistics Analysis Branch. In essence it states that the experimental design and sample sizes of the bio-availability studies for NDA 16-827 are not acceptable. Therefore NDA 16-827 is not approvable because satisfactory biologic availability of propoxyphene napsylate pulvule 100 has not been demonstrated. Data is not adequate to show that this preparation is equal to Darvon in providing relief of pain. The results of the blood level studies comparing present NDA to NDA 16-827 are not acceptable as satisfactory regarding biologic availability of Tablets Doloxene #1882, 1883.

Labeling Comments: [ ]

Conclusion: The application is incomplete and approval is not recommended.

James M. Moser, Jr.

James M. Moser, Jr., M.D.
Division of Neuropharmacological Drugs

cc:
Dup NDA
Trip NDA (CIN-DO)
MD-100
MD-120 MCS 12/16/69
MD-300
MD-120/JMMoser:js
12/10/69

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

CHEMISTRY REVIEW(S)

orig

Chemist: WILLIAM E. METZGOWER

DATE: May 12, 1971

addendum to
CHEMIST REVIEW OF NDA 16-827

Sponsor: Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46206

NDA 16-829
NDA 16-861
NDA 16-862
NDA 16-863
NDA 16-864

AF

Proprietary Name: Propoxyphene napsylate

Non-Proprietary Name:

Dosage Form: Pulvules 50 mg. and 100 mg.

Chemical Name:

Family or Related Drugs:

Related NDA, IND, MF'S: NDA 16-827, ---, 16-829, 16-861, 16-862, 16-863, 16-864

Structural Formula:

Original Submission Dated: November 15, 1968

Amendment (s) Dated:

(Amendment (s) continued on page 2 or 3)

Rema

NDA 16-862

September 8, 1970

RESUBMISSION OF CHEMIST REVIEW OF NDA 16-862

SPONSOR: Eli Lilly & Company
Indianapolis, Indiana 46206

AF# 9-577

PROPRIETARY NAME: Tablets No. 1882, 1883

NON-PROPRIETARY NAME: Propoxyphene Napsylate

DOSAGE FORM: Tablets 50 mg. and 100 mg.

RELATED NDA, IND MF's:

ORIGINAL SUBMISSION DATED: May 19, 1969

AMEND. DATED: July 24, 1970 Reply to Dr. Jenning's not-approvable letter dated January 28, 1970. Bio-availability study submitted to NDA 16-827 cross-referenced to this NDA; labeling; control information.

REMARKS: The one problem associated with manufacturing controls was answered in this letter which stated that the tradename would only be used with propoxyphene napsylate and the tradename Darvon would only be used with propoxyphene hydrochloride.

CONCLUSIONS: The Application is complete under Section 505(b)(4) of the Act with regards to manufacturing controls for the products, Tablets No. 1882, 1883, Propoxyphene Napsylate 50 mg. and 100 mg.

1. Labeling

Labels were submitted for the following:

A. 500 tablets No. 1882 container 50 mg.
B. 100 tablets No. 1882 container
C. ID 100 Tablets No. 1882 Idanti-Dose outer carton
D. Identi-Dose 50 mg. Propoxyphene napsylate
E. Container for 500 Tablets No. 1883 100 mg.
F. Container for 100 tablets No. 1883
G. Carton for ID 100 Tablets No. 1883
H. Identi-Dose 100 mg. Propoxyphene napsylate
I. Export Labels - multilith printing 50 mg. and 100 mg. dosage forms.
J. Package Insert

Labels "A through H" fail to bear a lot or control number.

Labels "D and H" fail to bear the name and address of the manufacturer, distributor or packer of the drug.

Export labels appear to be satisfactory.

Package insert, although a "shot gun" type of labeling, also appears to be satisfactory.

2. Stability Data:

[ ]

All data submitted was satisfactory.

William E. Metzbower

cc:
BD-100
BD-120
WEMetzbower/nlp 1/27/71

prs 2-9-71

January 22, 1970

CHEMIST REVIEW OF NDA 16-862

SPONSOR: Eli Lilly & Company
Indianapolis, Indiana

AF 9-577

PROPRIETARY NAME: ——— Tablets - Tablets No. 1882, 1883

NON-PROPRIETARY NAME: Propoxyphene napsylate

DOSAGE FORM: tablets 50 mg and 100 mg

RELATED NDA's, IND's, MF's: NDA 16-861, 16-863, 16-864, 16-827, ——— , 16-829,

ORIGINAL SUBMISSION DATED: May 19, 1969

REMARKS: The method validation study for NDA 16-862 which was sent to the Dallas District laboratory and the Division of Pharmaceutical Sciences (DPS) for confirmation has been evaluated.
had some problems with the assay of the propoxyphene napsylate in the finished dosage form. The original and reported results were low; however, they reassayed the following day and the results were within the specified limits. They surmised that the

On the basis of the results obtained the Division of Pharmaceutical Sciences considers the methods to be suitable for control and regulatory analysis.

William E. Metzbower
Div. of Neuropharmacological Drugs

cc:
Cn-DO
Dup NDA
MD 100, MD 120, MD 300
MD 120/WEMetzbower:ahe
R/D init FEAnderson 2-6-70
Typed 2-11-70

M L Gibson 2/12/70

FEA 2-10-70

CONCLUSION:

Notice remains incomplete under Section 505(b)(4) of the Act as detailed in chemist review dated November 7, 1969.

Results for the method validation study have been received and the methods submitted are considered to be suitable for control and regulatory analysis.

November 7, 1969

CHEMIST REVIEW OF NDA 16-862

Submission of October 9, 1969

Sponsor: Eli Lilly and Company
P. O. Box 618
Indianapolis, Indiana 46206

Attention: J. G. Armstrong, M.D.

Proprietary Name: Tablets No. 1882, 1883 Doloxene [R] Propoxyphene napsylate

Dosage Form: Tablets 50 mg and 100 mg.

Chemical Name: a-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate (ester) 2-naphthalene sulfonate (salt) hydrate

Related NDA, IND, MF'S: NDA 10-996, 10-997, 16-844, 16-827, 16-829, 16-861, 16-863, 16-864, —

Structural Formula:

Original Submission Dated: May 19, 1969

Amendment (s) Da

[ ]

Remarks: These

Conclusions: This application remains incomplete under Section 505(b)(4) of the Act with regards to manufacturing controls for the products, Tablets No. 1882 — and Tablets No. 1883 — 50 mg and 100 mg. Propoxyphene napsylate.

We have the following comment. We note that the applicant proposes to — propoxyphene napsylate, the active ingredient of — under the name of — or Darvon. Since Darvon is the registered name for Propoxyphen hydrochloride an inconsistency is apparent. This inconsistency needs correction.

FEA
11-26-69
MDL 12/1/69

cc: Orig., Dup., Trip. NDA, MD-100, MD-120, MD-300, MD-120/WEMetzbower/dm
11/20/69,R/D initialed by FEAnderson 11/7/69

William E. Metzbower

William E. Metzbower, chemist
Division of Neuropharmacological Drugs

Submission of October 9, 1969

1. Draft copies of the labels for the 50 mg and 100 mg dosage forms were submitted which contained an expiration date and a control number.

2. [redacted]

Comment:

In the original chemist review, dated July 15, 1969, a comment was made concerning the export label. Briefly, Eli Lilly proposed using the names [redacted] or Darvon on the bulk export label for propoxyphene napsylate. This inconsistency needs correction. Darvon is the registered name for propoxyphene hydrochloride.

July 15, 1969

CHEMIST REVIEW OF NDA 16-862

Original

SPONSOR: Eli Lilly and Company
Attention: J.G. Armstrong, M.D.
P.O. Box 618
Indianapolis, Indiana 46206

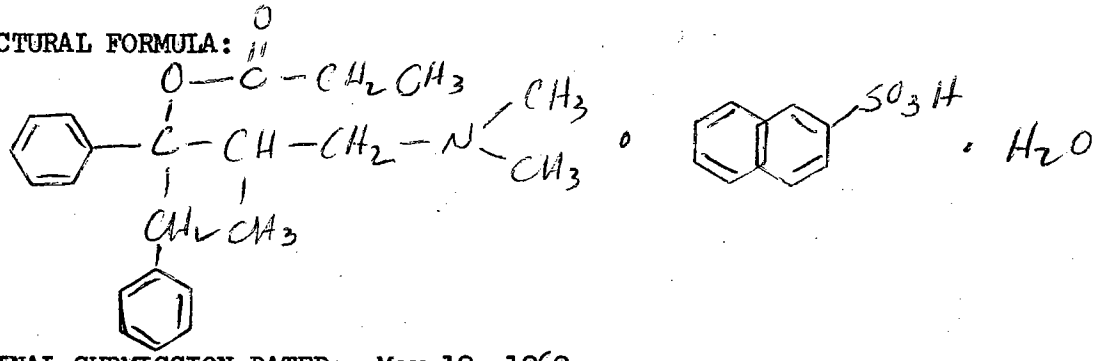
PROPRIETARY NAME: Tablets No. 1882, 1883 ——— Propoxyphene napsylate

DOSAGE FORM: Tablets 50 mg and 100 mg

CHEMICAL NAME: α-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate (ester) 2-naphthalene sulfonate (salt) hydrate

RELATED NDA, IND, MF'S: NDA 10-997, 10-996, 12-032, 16-844, 16-827 ——— 16-829, 16-861, 16-863, 16-864,

STRUCTURAL FORMULA:



ORIGINAL SUBMISSION DATED: May 19, 1969

William E. Metzbower

William E. Metzbower, Chemist
Division of Neuropharmacological Drugs

cc:
Dup NDA
Trip NDA
MD-100
MD-120
MD-300

MD-120/WEMetzbower/bjb
7/18/69

R/D initialed by FEAnderson, Ph.D. 7/17/69
mfb 8/7/69

WITHHOLD 15 PAGE(S)

chemistry Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

PHARMACOLOGY REVIEW

October 23, 1969

PHARMACOLOGIST REVIEW OF NDA 16-862, 16-863, 16-864

Original Summary

Sponsor: Eli Lilly and Company
Indianapolis, Indiana

(AF 9-577)

Drug: Tablets Doloxene (propoxyphene napsylate)

NDA	16-862		16-863	16-864	
Tablet #	1882	1883	1884	1885	1886

[redacted]

Category: Analgesic

Related NDAs: (numbers respectively equivalent to above dosages and combinations).

Pulvules [redacted] propoxyphene napsylate);
NDAs 16-827, 16-829, [redacted]; not approvable June 13, 1969 because of insufficient data to support effectiveness; resubmission pending review.

Pulvules Darvon (propoxyphene HCl);
NDAs 10-997, 10-995, 10-996; approved 1957.

Preclinical Studies: Authorized reference to information in NDAs 16-827, 16-828, 16-829; see Pharmacologist Review of April 21, 1969.

Evaluation: The preclinical data for propoxyphene napsylate and its combinations were evaluated in the above Pharmacologist Review in which it was concluded that these data are adequate to support safety for approval of the above applications for Pulvules _____. This conclusion would also apply to the present applications for Tablets Doloxene since a difference in drug availability between these two formulations would not be expected to involve a problem of safety.

Vera C. Glocklin

Vera C. Glocklin, Ph.D.
Division of Neuropharmacological Drugs

cc:
Orig NDA 16-862, 16-863, 16-864
Dup NDA 16-862, 16-863, 16-864
Trip NDA (CIN-DO) 16-862, 16-863, 16-864
MD-100 (NDA 16-862, NDA 16-863, NDA 16-864
MD-120 (NDA 16-862, NDA 16-863, NDA 16-864)
MD-300 (NDA 16-862, NDA 16-863, NDA 16-864)
MD-120/VCGlocklin:js
11/13/69
R/D initialed by Dr. D'Aguanno 10/28/69
M L Gibson 11/17/69

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

16-862

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

January 12, 1970

MEMORANDUM OF CONFERENCE

Product: 1. Bolazene NDA's (16-827, — 829, 16-861, (862) 863, 864)

Firm: Eli Lilly & Co. Indianapolis, Indiana

2. Darvocet NDA 16-844

Present: John J. Jennings, M.D., Acting Director, BM
Wm Gyarfas, M.D. , Acting Director, OND
M. L. Gibson, M.D., Director, DND/OND
J. M. Moser, Jr., M.D., DND/OND
R.E. Newberry, Staff, BM

Meeting was called to discuss the requirements needed for approval of the —— NDA's.

After some discussion it was decided that statistically valid bio availability studies would be acceptable.

Regarding NDA 16-844, Darvocet, Dr. Jennings felt that this is not the same as the —— products. More than one independent well controlled clinical trial demonstrating that this combination is effective in "painful, febrile conditions" should be required for approval of this application.

James M. Moser, Jr.

James M. Moser, Jr., M.D.
Division of Neuropharmacological Drugs

cc:

Orig. NDA 16-827, — 829, 16-861, (862), 863, 864, 16-844
Dup. NDA 16-827, 829, 16-861, 862, 863, 864, 16-844
Trip. NDA 16-827, 829, 16-861, 862, 863, 864, 16-844 (CEN-DO)
MD-100 NDA 16-827, 829, 16-861, 862, 863, 864, 16-844
MD-120 NDA 16-827, 829, 16-861, 862, 863, 864, 16-844
MD-300 NDA 16-827, 829, 16-861, 862, 863, 864, 16-844
MD-14 NDA 16-827, — 829, 16-861, 862, 863, 864, 16-844

MD-120/JMMoser/dm
1/13/70

JUN 13 1969

NDA 15 662

Eli Lilly and Company
Attention: J. G. Armstrong, M.D.
P.O. Box 618
Indianapolis, Indiana 46206

Gentlemen:

We acknowledge the receipt of your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of drug: Tablets No. 1082, 1085, [redacted] propoxyphene napsylate

Date of application: May 19, 1969

Date of receipt: May 21, 1969

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

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

Sincerely yours,

MLG

Merle L. Gibson, M.D.
Director
Division of Neuropharmacological Drugs
Office of New Drugs
Bureau of Medicine

cc
CIN-DO
Dup
Trip
MED-MD-14
OND-MD-100
DND-MD-120
jmm-6-11-69
Ack.