CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

12-827/S032&S033

Trade Name: Robinul & Robinul Forte Tablets

Generic Name: (glycopyrrolate)

Sponsor: A.H. Robins Company

Approval Date: November 7, 1983

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

12-827/S032 & 33

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 12-827/S032&33

APPROVAL LETTER

NOV _ 7 1983

NDA 12-827/S-032
/S-033

A.H. Robins Company
Attention: William S. White
1211 Sherwood Avenue
Richmond, Virginia 23220

Dear Mr. White:

Please refer to your supplemental new drug applications of December 2, 1982 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Robinul and Robinul Forte (glycopyrrolate) Tablets.

We also acknowledge receipt of your additional communications dated August 1, 1983.

The supplemental applications provide for new formulations for the 1 mg and 2 mg tablets and the USP dissolution test.

We have completed the review of these supplemental applications and they are approved. Our letter of December 17, 1975 detailed the conditions relating to the approval of these applications.

Sincerely yours,

11/1/83

Stewart J. Ehrreich, Ph.D.
Deputy Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
National Center for Drugs and Biologics

cc: RIC-DO
Original NDA 12-827/S-033
HFN-110
HFN-110/CSO
HFN-616
HFN-110/RWolters/10/28/83
sh/11/2/83/2431c
R/D init: SEhrreich/10/31/83
APPROVAL

11/4/83

16.1

NOV _ 7 1983

NDA 12-827/S-032
/S-033

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Deputy Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
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cc: RIC-DO
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R/D init: SEhrreich/10/31/83
APPROVAL

11/4/83

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 12-827/S032&33

APPROVABLE LETTER

MAY 13 1983

NDA 12-827/S-032/S-033

A.H. Robins Company
Attention: William S. White
1211 Sherwood Avenue
Richmond, Virginia 23220

Dear Mr. White:

Please refer to your supplemental new drug applications of December 2, 1982 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Robinul and Robinul Forte (glycopyrrolate) Tablets.

We also acknowledge receipt of your additional communications dated December 16, 1982.

The supplemental applications provide for new formulations for the 1 mg and 2 mg tablets and the USP dissolution test.

We have completed the review of these supplemental applications. Before we are able to reach a final conclusion, however, the following information is necessary:

Before the in-vivo bioavailability requirement can be waived, you must submit a dissolution study using the USP XX, 3rd supplement procedure, comparing [redacted] tablets of the old and new formulations. Submit the individual results along with the statistical analysis. b(4)

Further action on these supplemental applications will await our receipt and review of your response to this request.

Sincerely yours,

5/14/83

Stewart J. Ehrreich, Ph.D.
Deputy Director
Division of Cardio-Renal Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

cc: BLT-DO
Original NDA
HFN-110
HFN-110/CSO
HFN-110/RJWolters
sh/5/3/83;5/4/83/5806B

5/14/83

REVIEW WAITING

r/d: JFLangston/4/27/83

5/16/83

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 12-827/S032&33

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFN-110

2. NDA NUMBER: 12-827

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
A.H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220

NOV 7 1983

4. DATE NDA APPROVED

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY

6. NAME OF DRUG
Robinul
Robinul Forte

7. NONPROPRIETARY NAME
Glycopyrrolate

8. SUPPLEMENT

NUMBER	DATE
S-032	12-2-82
S-033	12-2-82

9. PURPOSE OF SUPPLEMENT
New formulations for the 1 mg and 2 mg tablets and the new USP dissolution specifications and procedure. The amendment included comparative dissolution data.

10. AMENDMENT DATE(s)
8-1-83

11. OTHER DATE *(Report, etc.)*

12. PHARMACOLOGICAL CATEGORY
Anticholinergic

13. AF NUMBER
6-375

16. RELATED IND/NDA/MF(s)

14. DOSAGE FORM
Tablet

15. HOW DISPENSED
☒ Rx ☐ OTC

17. POTENCY(ies)
1 mg and 2 mg

18. DRUG REGUIRES
☐ NDA ☐ ANDA

19. CHEMICAL NAME
USP XX

20. RECORDS AND REPORTS

CURRENT	REVIEWED
☒ YES ☐ NO	☒ YES ☐ NO

21. CHEMICAL FORMULA

22. REMARKS
Data comparing ~~X~~ tablets of the old and new formulations was submitted. For Robinul the dissolution data demonstrates that approximately ~~X~~% more glycopyrrolate is release from the tablet formulated with the new components and between ~~X~~ and ~~X~~ % is released from Robinul Forte. The data clearly demonstrates that the new formulation will release glycopyrrolate faster.

b(4)

b(4)

b(4)

23. CONCLUSIONS
Approve supplement.

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
R.J. Wolters	RJ Wolters 11/4/83	10-28-83

DISTRIBUTION ☒ ORIGINAL JACKET ☐ DUPLICATE JACKET ☐ REVIEWER

FORM FDH 2266 (11/73) HFN-110 PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFN-110

2. NDA NUMBER: 12-827

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
A.H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220

MAY 13 1983

4. AF NUMBER: 6-375

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-032	12-2-82
S-033	12-2-82

6. NAME OF DRUG
Robinul
Robinul Forte

7. NONPROPRIETARY NAME
Glycopyrrolate

8. SUPPLEMENT(S) PROVIDES FOR:
New formulations for the 1 mg and 2 mg tablets and the new USP dissolution specification and procedure. The amendments included the Uniformity of dosage unit for weight variation specification at the in-process stage as per the USP 3rd supplement.

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
December 16, 1982

10. PHARMACOLOGICAL CATEGORY
Anticholinergic

11. HOW DISPENSED
☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S)
1 mg and 2 mg

14. POTENCY *(ies)*

15. CHEMICAL NAME AND STRUCTURE
USP XX

16. RECORDS AND REPORTS
CURRENT ☒ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS The main changes were the addition of more [redacted] and addition of [redacted] b(4) The total weigh did not change.
Satbility-The protocol provides for testing of test batches at [redacted], [redacted] weeks; RT, [redacted] weeks, [redacted] and [redacted] years; [redacted] °C, [redacted] and [redacted] weeks; [redacted] and [redacted] weeks; [redacted] (HDPE and blister) [redacted] and [redacted] weeks. Production batches [redacted] and [redacted] years, dissolution [redacted] weeks, [redacted] and [redacted] years. Data were submitted at RT in [redacted] glass bottles [redacted] years and HDPE and [redacted] weeks, [redacted] weeks, [redacted] % RH; [redacted] °C and RT for [redacted] years. The three year expiration date is acceptable based on the above data and the data on the old formulation which demonstrated the stability of glycopyrrolate for up to [redacted] years. b(4)

18. CONCLUSIONS AND RECOMMENDATIONS
Request a dissolution study comparing the old and new formulations.

cc:BLT-DO
Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/RJWolters
sh/5/3/83/5806B
REVIEW WAITING r/d: JFLangston/4/27/83

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
R.J. Wolters	5/9/83	4-27-83

DISTRIBUTION ☒ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

HFN-110/CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 12-827/S032&33

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

APR 22 1983

Glycopyrrolate tab.
2mg
NDA 12827/S-033
Reviewer:
Mei-Ying Huang, Ph.D

A.H. Robins
Richmond, Virginia
Submission Date:
December 2, 1982
Wang #5363e

REVIEW OF A REQUEST FOR WAIVER OF IN VIVO BIOAVAILABILITY (1 WAIVER)

BACKGROUND

The firm submitted the current supplement to NDA 12827 for Robinul Forte tablets providing for a reformulation designed to enhance the dissolution characteristics of the product. This reformulation is necessitated by the recent inclusion of a dissolution specification in the official USP monograph for Glycopyrrolate tablets. Since the reformulated product has improved dissolution characteristics that exceed the specifications established by USP, the firm requests a waiver of in-vivo bioavailability study.

DISCUSSION

1. Formulation:

a. Old formulation (see NDA 12-827/S-025, vol. 15.1):

Glycopyrrolate 2 mg

b(4)

b. New formulation:

Glycopyrrolate 2 mg

b(4)

DISSOLUTION:

The dissolution tests were conducted according to the USP XX dissolution procedure using the Basket Method. Tests were performed using simulated b(4) [redacted] Dissolution data are present in Table I. The proposed USP method is USP method I in 0.5 l water. The firm did not document the dissolution data using water as a medium. The firm should submit dissolution data of both old and new formulations using 0.5 l water as medium.

CONCLUSION:

The Division of Biopharmaceutics has received a request for a waiver for a bioavailability requirement (Submission Date: December 2, 1982). According to "Approved Prescription Drug Products with Therapeutic Equivalence Evaluations," Glycopyrrolate was chategorized under code AA i.e. products not presenting bioequivalence problems, in conventional dosage forms. (Products coded as AA are standard formulations of those active ingredients that are not regarded as presenting either actual or potential bioequivalence problems. In addition, the drug products of the active ingredient are manufactured in dosage forms not presenting bioequivalence problems, such as plain tablets, capsules, solutions, elixirs, syrup, and tinctures). The Division of Biopharmaceutics is not aware of any in vivo bio-study performed by generic company. Accordingly, a waiver should be granted, however, because of lack of proper dissolution data, the Division of Biopharmaceutics cannot waive in vivo bioavailability now. The firm is to submit dissolution results using water as medium. The above recommendation should be forwarded to the firm.

Mei-Ying Huang 4/21/83

Mei-Ying Huang, Ph.D
Pharmacokinetics Branch

RD INITIALED BY VISWANATHAN
FT INITIALED BY PURICH Edward D. Purich

HUANG/kak/3/28/83:FT:4/18/83:cs

cc: NDA 12827/S-033 orig., HFN-110, HFN-525 (HUANG), Chron File, Drug File, Review File.

1 Page(s) Withheld

1 Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 12-827
S032
S037

NDA 12-827

SEP 13 1983

A.H. Robins Company
Attention: William S. White
1211 Sherwood Avenue
Richmond, Virginia 23220

Dear: Mr. White

We acknowledge receipt of your resubmitted supplemental application for the following:

Name of Drug: Robinul Tablets

NDA Number: 12-827

Supplement Number: S 032, S 033

Date of Resubmitted Supplement: August 1, 1983

Date of Receipt: August 4, 1983

All communications concerning this NDA should be addressed as follows:

National Center for Drugs and Biologics
Division of Cardio-Renal Drug Products, HFN-110
Attention: DOCUMENT CONTROL ROOM #16B-30
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Natalia A. Morgenstern 9/12/83
Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
National Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO ABrown
HFN-110/~~JCarter~~/9-6-83
dmu//9-12-83/1181c
R/D init. ~~ABrown~~ J. Carter

RESUBMITTED SUPPLEMENT ACKNOWLEDGEMENT

Acarter 9/12/83

William S. White
Drug Registration Specialist

A. H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220
Telephone (804) 257-2502

ORIGINAL

NDA SUPPL AMENDMENT

A-H-ROBINS

Division of Cardio-Renal Drug
Products
HFN 110, Room 16B-30
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 1, 1983

Re: NDA 12-827,S-033
Robinul Forte Tablets

Gentlemen:

This is an amendment to supplement S-033 to our New Drug Application for Robinul Forte (glycopyrrolate) Tablets. This supplement provides for a reformulation designed to enhance the dissolution characteristics of the product.

Reference is also made to your letter of May 13, 1983, requesting additional information before approving our supplement. As requested, attached are the results of a dissolution study using the procedure in Addendum a to Supplement 3, USP XX, comparing X tablets of the old and new formulations. Individual results along with the statistical results are included. This information should permit a waiver of any in vivo bioavailability requirement. b(4)

This information is concurrently being submitted to supplement S-032 for Robinul Tablets.

Sincerely,

William S. White

slw

RECEIVED
AUG 04 1983
HFD-110
BUREAU OF DRUGS

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 12-827
8032
8033

William S. White
Drug Registration Specialist

ORIGINAL

A. H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220
Telephone (804) 257-2502

A-H-ROBINS

NDA SUPPLEMENT

Division of Cardio-Renal Drug Products
HFN 110, Room 16B-30
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 1, 1983

Re: NDA 12-827,S-032
Robinul Tablets

Gentlemen:

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Reference is also made to your letter of May 13, 1983, requesting additional information before approving our supplement. As requested, attached are the results of a dissolution study using the procedure in Addendum a to Supplement 3, USP XX, comparing X tablets of the old and new formulations. Individual results along with the statistical results are included. This information should permit a waiver of any in vivo bioavailability requirement. b(4)

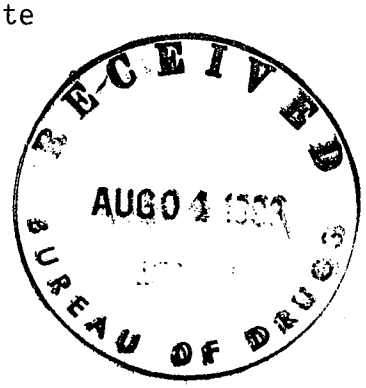
This information is concurrently being submitted to supplement S-033 for Robinul Forte Tablets.

Sincerely,

William S. White

William S. White

slw



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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative 12827
5032
5033

William S. White
Drug Registration Specialist

A. H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220
Telephone (804) 257-2502

ORIGINAL

NDA NO. 12-827 REF. NO. S-033

NDA SUPPL FOR CF

A-H-ROBINS

Division of Cardio-Renal Drug
Products
HFD 110, Room 16B-30
National Center for Drugs and
Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 2, 1982

Re: NDA 12-827
(Robinul Forte Tablets)

Gentlemen:

This manufacturing supplement to our apporved New Drug Application for Robinul Forte Tablets provides for a reformulation designed to enhance the dissolution characteristics of the product. This reformulation is necessitated by the recent inclusion of a dissolution specification in the official USP monograph for Glycopyrrolate Tablets.

The reformulation permits our product to be in compliance with the new dissolution specification, as indicated by the enclosed dissolution data, and at the same time to retain its present appearance.

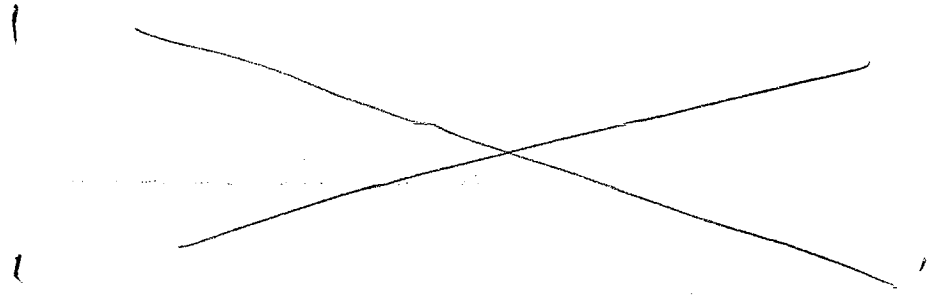
Since the reformulated product has improved dissolution characteristics that exceed the specifications established by USP, we hereby request a waiver of any in-vivo bioavailability testing that may be deemed necessary.

Enclosed, in triplicate, are the following:

NDA Part	Description
6	Full List of Articles Used as Components
7	Full Statement of Composition
8(d)	Raw Material Specifications
8(g)	Method of Preparation of Master Formula Records
8(h)	Manufacturing Instructions

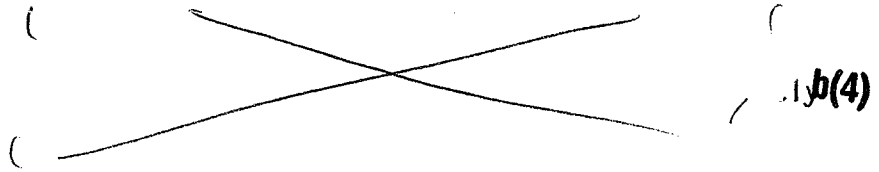
RECEIVED
DEC 9 1982
HFD-110
BUREAU OF DRUGS

NDA Part	Description
8(n)	Finished Product Specifications (Q.A. Spec. No.4 dated November, 1981) revised to incorporate the dissolution specifications required in the USP monograph for Glycopyrrolate Tablets. The other specifications and test procedures remain the same, as per the USP monograph. Note: The disintegration specification was deleted upon adoption of the dissolution specification.
8(p)	Stability Data, Dissolution Data, and Proposal of Expiration Dating Period
10	Preclinical Investigations



b(4)

Note:



b(4)

Sincerely,

William S. White
Drug Registration Specialist

rlm

Enclosures

NDA NO. 12-827 REF. NO. S-032
DA SUPPL FOR CF

William S. White
Drug Registration Specialist

A. H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220
Telephone (804) 257-2502

ORIGINAL

A·H·ROBINS

Division of Cardio-Renal Drug
Products
HFD 110, Room 16B-30
National Center for Drugs and
Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 2, 1982

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(Robinul Tablets)

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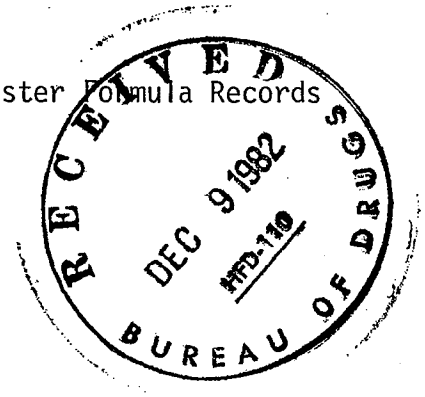

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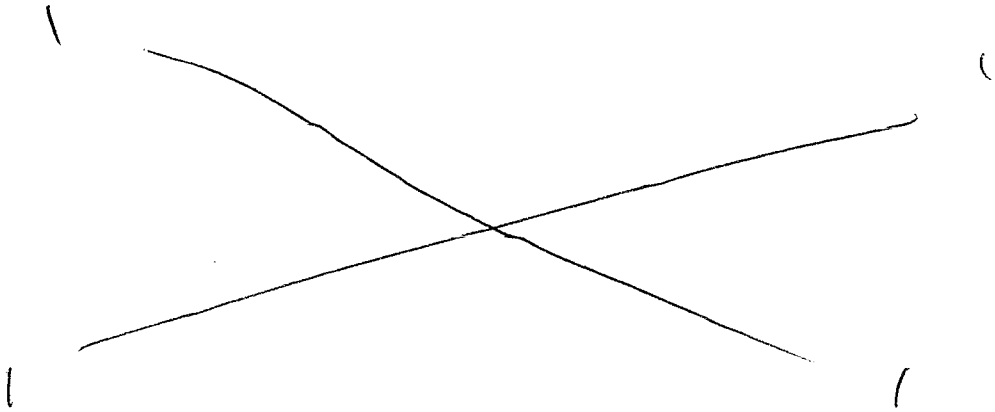

b(4)

Sincerely,

William S. White
Drug Registration Specialist

rlm

Enclosures