CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-025

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls MAR 22 1999

NDA #: 21-025 **CHEM.REVIEW #** 1 **REVIEW DATE:** 12-MAR-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11-AUG-98	12-AUG-98	25-AUG-98

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

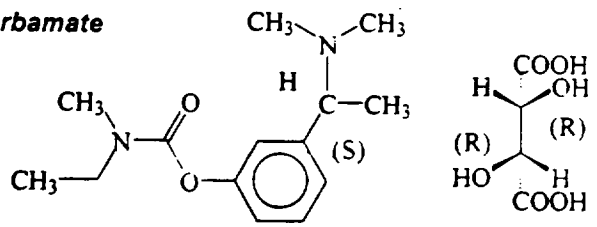
DRUG PRODUCT NAME
Proprietary: EXELON (rivastigmine tartrate) Oral Solution
Nonproprietary/USAN: Rivastigmine hydrogen tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: AChE Inhibitor

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Oral Solution
STRENGTHS: 2 mg/ mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate



$C_{14}H_{22}N_2O_2.C_4H_6O_6 = C_{18}H_{28}N_2O_6$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS #: 129101-54-8
SUPPORTING DOCUMENTS ; NDA 20-823
RELATED DOCUMENTS
REMARKS/COMMENTS: Oral solution of rivastigmine tartrate. Application lacks spectroscopic identification method for API.

. For some reason the batches with the developed substantial leaks when stored in inverted position. Additional data has been provided also for another Telecon with Ms Sheryl LeRoy on 12-MAR-99 revealed that the sponsor . The dispenser system is difficult do review since the drawings have been provided in German. The drug product is stable The proposed labeling seems a bit optimistic and should be lowered. The sponsor promised to amend the NDA to include the response to the deficiencies listed. No need to issue the IR letter now.

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 21-025 not approvable do to lack of proper analytical method to identify API in the drug product and the lack of stability data for the drug product in a new untested container/closure system. See the list of deficiencies below.

cc:
Orig. NDA 21-025
HFD-120
HFD-120/WJRzeszotarski
HFD-[redacted]
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by:MEG 3.22.99

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

filename:E:\msword\n21025r.001

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

30 pages

Application: NDA 21025/000
Stamp: 11-AUG-1998
Regulatory Due: 19-SEP-1999
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 1S
Org Code: 120

Action Goal:
District Goal: 12-APR-1999
Brand Name: EXELON(RIVASTIGMINE TARTRATE)2MG/ML ORAL
Estab. Name:
Generic Name: RIVASTIGMINE TARTRATE

Dosage Form: (SOLUTION)
Strength: 2 MG/ML

Application Comment:
FDA Contacts: R. NIGHSWANDER (HFD-120) 301-594-2850 , Project Manager
W. RZESZOTARSKI (HFD-120) 301-594-2850 , Review Chemist
M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation: ACCEPTABLE on 21-SEP-1998 by J. D. AMBROGIO (HFD-324) 301-827-0062

Establishment: 9611204
NOVARTIS PHARMA INC (SANDOZ)
LICHTSTRASSE 35
BASEL, , SZ ch-4002
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-SEP-1998				RZESZOTARS
OC RECOMMENDATION	11-SEP-1998			ACCEPTABLE	FERGUSONS

Establishment: 1911445
SANDOZ CONSUMER PHARMACEUTICALS DIV
NORTHEAST US 6 AND INTERSTATE 80
LINCOLN, NE 68517
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: LIQ OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-SEP-1998				RZESZOTARS
SUBMITTED TO DO	11-SEP-1998	10D			FERGUSONS
DO RECOMMENDATION	18-SEP-1998			ACCEPTABLE	GDICKINS
				BASED ON FILE REVIEW	
				THE LAST CGMP INSPECTION OF THIS FIRM WAS CONDUCTED 4/24/98 AND INCLUDED COVERAGE OF THE PROFILE CLASS LIQUIDS. ONLY MINOR DEFICIENCIES WERE NOTED.	
OC RECOMMENDATION	21-SEP-1998			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

AUG 18 1999

NDA #: 21-025 CHEM.REVIEW # 2 REVIEW DATE: 16-AUG-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11-AUG-98	12-AUG-98	25-AUG-98
Resubmission	18-NOV-98	19-NOV-98	20-NOV-98
BC	25-MAR-99	29-MAR-99	29-MAR-99
BC	15-JUL-99	16-JUL-99	16-JUL-99
BB	26-JUL-99	27-JUL-99	27-JUL-99

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary: EXELON (rivastigmine tartrate) Oral Solution
Nonproprietary/USAN: Rivastigmine hydrogen tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: AChE Inhibitor

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Oral Solution
STRENGTHS: 2 mg/ mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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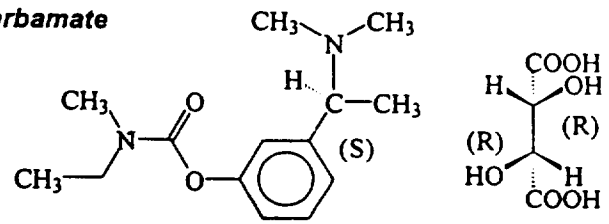
$C_{14}H_{22}N_2O_2.C_4H_6O_6 = C_{18}H_{28}N_2O_6$; Molecular Weight: 250.3 + 150.1 = 400.4;



CAS #: 129101-54-8

SUPPORTING DOCUMENTS: ——— NDA 20-823

RELATED DOCUMENTS:

REMARKS/COMMENTS: Amendments to the original submission consisting of: 1) response to 12-MAR-99 request for the translated copy of the drawing, the following documentation is provided as Attachment I: a Figure - Cylinder for metering pump 6 mg dispenser set, drawing no. E298-03.40, dated 29-Apr-97 (translation of version appearing on page 3-26 of the original NDA); 2) response to 12-MAR-99 request to enclose the following: a. Exelon Oral Solution package (bottle with cap) with dispenser as currently described in pending NDA (carton labeled Exelon Oral Solution "old"), and b. Exelon Oral Solution package with dispenser for which the sponsor will be providing an amendment to the NDA shortly (carton labeled Exelon Oral Solution "new"); 3. response to 18-NOV-98 request to provide an additional identification method (only one, HPLC method was submitted)

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 21-025 approved with the Exelon Oral Solution package (bottle with cap) with dispenser as described in the original application. The new package configuration described in the response to 12-MAR-99 request on 26-MAR-99 was never submitted as an amendment and will have to be submitted as a supplement in the future.

cc:
Orig. NDA 21-025
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by:MEG 8.18.99

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

filename:E:\msword\n21025r.002

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages
+ 2 pages

7 pages

NDA Secondary

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

MAR 13 2000

NDA #: 21-025 **CHEM.REVIEW #** 3 **REVIEW DATE:** 08-MAR-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AZ	22-OCT-99	22-OCT-99	25-OCT-99

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

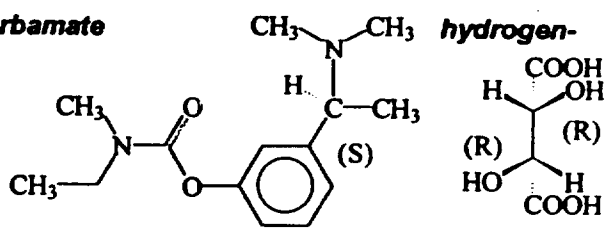
Proprietary: EXELON (rivastigmine tartrate) Oral Solution
Nonproprietary/USAN: Rivastigmine hydrogen tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: AChE Inhibitor

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Oral Solution
STRENGTHS: 2 mg/ mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate



$C_{14}H_{22}N_2O_2.C_4H_6O_6 = C_{18}H_{28}N_2O_6$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS #: 129101-54-8
SUPPORTING DOCUMENTS: ——— NDA 20-823
RELATED DOCUMENTS:
REMARKS/COMMENTS: In previous correspondence Novartis had indicated that it would be submitting a ; however, at this time the sponsor states that they will not be providing for such an amendment. Novartis will continue to use the bottle, which was described in the original NDA submission. Furthermore, Novartis agrees to adjust the storage specifications to "below 25 degrees C" ——— teleconference between Mr. R. Nighswander (HFD-120) and the sponsor on September 8, 1999. The attached labeling has been modified to reflect this. See the review notes for reviews 1 & 2.
The text of the attached draft package insert includes all of the information from the Revised Draft Labeling for EXELON Capsules (NDA 20-823), submitted October 21, 1999 in the Exelon Capsule Complete Response. That information is printed in regular font. Changes to this label, which are relevant for EXELON Oral Solution are underlined. Information, which does not pertain to EXELON Oral Solution, is crossed-out. These changes were predominantly made to the "Dosage, and Administration" and "How Supplied" sections of the package insert. The final package insert for Exelon Oral Solution will be adapted to the Exelon Capsule labeling upon approval of the Exelon Capsule NDA. For logistical reasons, Novartis intends to combine the Exelon Capsule and Oral Solution Package Inserts as a Changes Being Effected Supplement only after each of the two NDAs are approved individually with formulation specific labels.
CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 21-025 approved with the Exelon Oral Solution package (bottle with cap) with dispenser as described in the original application. EER acceptable as of 21-SEP-98 (copy enclosed).
cc:Orig. NDA 21-025
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by:MEG 3/13/00

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

filename:E1:\msword\n21025r.003

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21025/000
Stamp: 11-AUG-1998
Regulatory Due: 22-APR-2000
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 1S
Org Code: 120

Action Goal:
District Goal: 12-APR-1999
Brand Name: EXELON(RIVASTIGMINE TARTRATE)2MG/ML ORAL
Estab. Name:
Generic Name: RIVASTIGMINE TARTRATE

Dosage Form: (SOLUTION)
Strength: 2 MG/ML

Application Comment:
FDA Contacts: R. NIGHSWANDER (HFD-120) 301-594-2850 , Project Manager
W. RZESZOTARSKI (HFD-120) 301-594-2850 , Review Chemist
M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation: ACCEPTABLE on 21-SEP-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1911445
NOVARTIS CONSUMER HEALTH INC
NORTHEAST US 6 AND INTERSTATE 80
LINCOLN, NE 68517

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: LIQ
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-SEP-1998				RZESZOTARS
SUBMITTED TO DO	11-SEP-1998	10D			FERGUSONS
DO RECOMMENDATION	18-SEP-1998			ACCEPTABLE	GDICKINS
				BASED ON FILE REVIEW	
THE LAST CGMP INSPECTION OF THIS FIRM WAS CONDUCTED 4/24/98 AND INCLUDED COVERAGE OF THE PROFILE CLASS LIQUIDS. ONLY MINOR DEFICIENCIES WERE NOTED.					
OC RECOMMENDATION	21-SEP-1998			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 9611204
NOVARTIS PHARMA INC (SANDOZ)
CH-4002
BASEL, , SZ

DMF No:
AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-SEP-1998				RZESZOTARS
OC RECOMMENDATION	11-SEP-1998			ACCEPTABLE	FERGUSONS