CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-083

CHEMISTRY REVIEW(S)

NDA 22-083

Exelon® Patch (rivastigmine) transdermal delivery system

Novartis

HFD-120

Sherita D. McLamore, Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Appears This Way
On Original

Table of Contents

b(4)

Chemistry Review Data Sheet

1. NDA: 22-083

2. REVIEW:#1

3. REVIEW DATE: May10, 2007

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
n/a	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	September 8, 2006
Labeling Amendment	February 21, 2007
Amendment	February 2, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceutical Corporation
Address:	One Health Plaza East Hanover, New Jersey 07936-1080
Representative:	Martina Struck, PhD
Telephone:	862-778-3271

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Exelon® Patch
b) Non-Proprietary Name (USAN): Rivastigmine
c) Code Name/# (ONDC only): n/a
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of Alzheimer's disease and Parkinson's disease dementia

11. DOSAGE FORM: Transdermal Patch

12. STRENGTH/POTENCY: 9mg/5cm^2, 18mg/10cm^2, _____ b(4)

13. ROUTE OF ADMINISTRATION: Transdermal

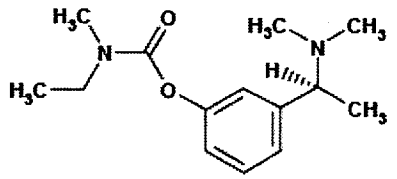
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Names: (S)-3-[1-(Dimethylamino)ethyl] phenyl ethylmethylcarbamate
Molecular Weights: 250.34
Molecular Formula: $C_{14}H_{22}N_2O_2$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[ ]				]	N/A		

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – [redacted] DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b(4)

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	10/11/06	Sherita McLamore, Ph.D.
Pharm/Tox	Pending	Pending	David Hawver, Ph.D.
Biopharm	Pending	Pending	Veeneta Tandon, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	Acceptable	Sherita McLamore, Ph.D.
DMETS	Pending	Pending	
EA	Categorical Exclusion 21 CFR 25 31(b) *Acceptable*	5/1/07	Sherita McLamore, Ph.D.
Microbiology	Pending	Pending	

The Chemistry Review for NDA 22-083

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 22-083 is approvable. The approval from a CMC standpoint is contingent on an acceptable an adequate response to the CMC deficiencies outlined in this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

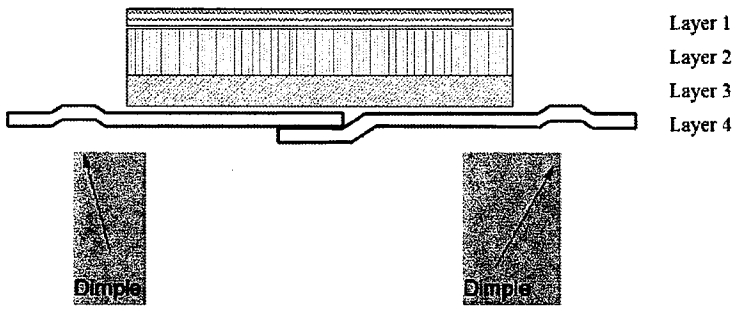
N/A

II. Summary of Chemistry Assessments

Rivastigmine has been identified as the active pharmaceutical ingredient in this application. Rivastigmine is t [redacted] rivastigmine hydrogen tartrate, which is the active in the approved product Exelon® capsules and oral solution (NDAs 20-023 and 21-025, respectively). While the hydrogen tartrate exists as crystalline solid, [redacted] is a clear, slightly brown colored viscous liquid. The drug substance is being manufactured and controlled by Novartis Pharma AG of Switzerland. The applicant includes all relevant information pertaining to the drug substances including the manufactures, acceptance criteria, certificates of analyses, methods of manufacture and 60 months of stability data for the drug substance.

b(4)

The drug product, Exelon® Transdermal Delivery Patch, is being developed as a once a day treatment for the dementia of the Alzheimer's disease and for the treatment of dementia in patients with Parkinson's disease. The patch is the first non-oral drug treatment for dementia of the Alzheimer's disease. The patch is a thin, 3-layer, matrix-type, transdermal system with a protective liner.



Layer 1 = Backing film
Layer 2 = Drug product (acrylic) matrix
Layer 3 = Adhesive (silicone) matrix
Layer 4 = (Protective) release liner [redacted]

b(4)

There are —— batch sizes and strengths. The patches are qualitatively indistinguishable as they are all cut from the same intermediate laminate. The patch sizes and strengths are: 9 mg/5 cm^2, 18 mg/10 cm^2, —————— b(4)
While the patches are available in 9, 18. ———— only about 50% of the drug is delivered during the 24 hour in-use period. *In vivo* release rates per 24 hours for the ——strengths are 4.6, 9.5, ———— respectively. The initial dose is one 5 cm^2 Exelon® TDS Patch once daily. Maintenance is one 10 cm^2 Exelon® TDS Patch once daily.

Patches	rivastigmine base dose load	rivastigmine base *in vivo* release rates per 24 h
Exelon Patch 5	9 mg	4.6 mg
Exelon Patch 10	18 mg	9.5 mg
[		] b(4)

The applicant indicates that the drug product is manufactured by LTS Lohmann Therapies of Germany. The drug product will be stability tested by Novartis Pharmaceuticals of Switzerland. The drug product is packaged in individual sachets in 30 —— count cartons. The applicant includes a complete description of each of the packaging component including manufacturers, certificates of analyses, drawings, diagrams and specifications for each of the packaging components.

As indicated in the stability section of this review, the applicant includes up to 36 months of long term stability for ——production batches each of the 9 mg, 18 mg and —— drug product. The applicant tests the following attributes on stability: appearance, release rate, assay (drug substance and tocopherol), related substances, microbiological limit test, adhesion strength and peel force. The stability protocol was based on a bracketing and matrixing protocol in which the 27 mg patches were bracketed by the highest and lowest strengths. Because all strengths were package in the same material and were cut from the same master laminate, the bracket was appropriate. The applicant provided up to 36 months of data for the drug product stored under long term conditions. The applicant has requested a —month shelf life for the drug product; however, at this time biopharm is in the process of resolving the dissolution acceptance criteria. Accordingly, no recommendation will be made on the expiry at this time. b(4)

B. Description of How the Drug Product is Intended to be Used

The drug product is being developed for treatment of Alzheimer disease. The hydrogen tartrate salt of the drug substance is currently approved for use in two immediate release oral formulations (capsules and oral solution); however, this dosage form allows for once-a-day administration and will prove to be useful in patients that are reluctant to be compliant.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-083 is Approvable from a Chemistry standpoint due to chemistry,

manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review. All sites were submitted to the Office of Compliance in October of 2006 and found acceptable based on OC recommendation at the same time. None of the sites required inspection and the overall recommendation of acceptable was issued on October 11, 2006.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
SMcLamore/Date
RSood

C. CC Block
Orig. NDA 22-083

83 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
6/22/2007 03:32:11 PM
CHEMIST

Ramesh Sood
6/22/2007 03:42:12 PM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-083
Applicant:	Novartis Pharmaceuticals Corporation
Stamp Date:	08-Sep-2006
PDUFA Date:	08-Jul-2006
Trademark:	Exelon® Patch
Established Name:	Rivastigmine Transdermal System
Dosage Form:	Patch
Route of Administration:	Transdermal
Indication:	**Mild to moderate Alzheimer's disease and mild to moderate dementia related to Parkinson's disease**
PAL:	Martha R. Heimann, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

Novartis currently markets rivastigmine, as the tartrate salt, in two immediate release dosage forms, i.e., Exelon® Capsules (NDA 20-823) and Exelon® Oral Solution (NDA 21-025) which are administered twice daily. In the current submission, the applicant proposes a new dosage form, a matrix type transdermal patch containing rivastigmine base. —— strengths are proposed, 9 mg/5 cm^2, 18 mg/10 cm^2 ——————— ——————. Approximately 50% of the active content is delivered over a 24 hour period, allowing for once daily administration. Clinical efficacy and safety evaluations of Exelon Patch are based on three phase II studies, one clinical pharmacology study, and one phase III study with long-term extension. b(4)

Critical issues for review

Drug Substance

Rivastigmine drug substance used in the manufacture of the Exelon Patch is prepared by ——————— The current NDA provides CMC information for the ——————— and characterization. Per pre-NDA agreement, the firm is cross-referencing NDA 20-823 for all information pertaining to the tartrate salt. The salt will comply with all requirements for rivastigmine tartrate (——————— b(4)

Rivastigmine base is described in the submission as a viscous (approximately —— mPa.s) clear, colourless to yellow to very slightly brown liquid. As the bulk drug is not a solid there are no issues related to solid state characterization. As the —— rivastigmine in liquid form is extremely sensitive to oxidation, light and high temperature and it is hygroscopic. The bulk drug substance is stated to be stable for extended periods when stored at -20°C or 5°C under inert atmosphere (argon or nitrogen) in amber glass containers. The drug substance is also stable for shorter periods (up to 6 months) at 30°C if protected from air and light. b(4)

Critical Issues

The most critical issue is carry-over of impurities from rivastigmine tartrate and the stability of rivastigmine base. Related substances that are observed in the base may require toxicological evaluation for the current route of administration even if they have previously been allowed in the oral formulations.

Drug Product

The Exelon Patch (rivastigmine transdermal system) is a circular patch for transdermal administration —— strengths are proposed, 9 mg/5 cm^3, 18 mg/10 cm^3, —— —— which release approximately 4.6 mg, 9.5 mg, —— rivastigmine, respectively per 24 hours. The patch is intended to be worn for one day and then replaced by a new patch. It comprises a four layer laminate containing the backing layer, drug matrix (acrylic), adhesive matrix (silicone and overlapping release liner with dimples. The compositions of the individual strengths are quantitatively proportional. b(4)

Critical Issues

Drug loading: The active acrylic matrix contains — rivastigmine. In early patch formulations, the high drug concentration resulted in oozing during storage and poor adhesion. Additionally, since approximately half of the drug is delivered over 24 hours, the effects of the change in active concentration on adhesion and peel force should be assessed. b(4)

Chemical stability: As noted above for the drug substance, rivastigmine base is somewhat susceptible to oxidation, light and high temperatures. The proposed commercial formulation includes an antioxidant, —— (Vitamin E). Justification for the antioxidant level should include evidence that there is a sufficient level over the proposed product shelf life.

Manufacturing: Critical steps in the manufacturing process are —— b(4)

—— Due to the instability of the drug substance it is suggested that the reviewer verify that packaging and storage conditions for in-process material provide adequate protection.

Drug Product Specification: The applicant proposes separate in-vitro release acceptance criteria for batch release and shelf life. The acceptability of this should be determined as it relates to in vivo bioavailability.

Other Issues

Labeling: Rivastigmine is USAN. The product labeling is acceptable with respect to established name, potency (mg/patch) and active content per patch and amount of drug released per 24 hours.

Comments for 74-Day Letter

There are no CMC comments for the 74-Day Letter.

Review, Comments and Recommendation:

NDA 22-083 provides for a line extension of an approved product. Consequently, there are relatively few critical issues related to the bulk drug substance. Similarly, matrix type transdermal systems involve well-developed technology. Assignment of the NDA to a reviewer familiar with transdermal systems is recommended.

Recommended reviewer: Sherita McLamore

Administrative: All manufacturing facilities have been entered into EES.
A claim for categorical exclusion was submitted in the NDA.

Martha R Heimann, Ph.D. _____
Pharmaceutical Assessment Lead Date

Ramesh Sood, Ph.D. _____
Branch Chief Date

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martha Heimann
10/10/2006 03:07:59 PM
CHEMIST

Ramesh Sood
10/10/2006 03:32:05 PM
CHEMIST

Appears This Way
On Original