

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21829**

**CHEMISTRY REVIEW(S)**

**Neupro**  
**(rotigotine transdermal system)**  
**NDA 21-829**

**Division Director Review #2**  
**Chemistry, Manufacturing, and Controls**

**Applicant:** Schwarz BioSciences, Inc.  
P.O. Box 110167  
Research Triangle Park, NC 27709

**Indication:** Treatment of the symptoms of early-stage idiopathic Parkinson's disease.

**Presentation:** Neupro® is a transdermal delivery system available in 3 strengths: 4.5 mg delivering 2 mg/24 hours from a 10 cm<sup>2</sup> patch; 9 mg delivering 4 mg/24 hours from a 20 cm<sup>2</sup> patch, and 13.5 mg delivering 6 mg/24 hours from a 30 cm<sup>2</sup> patch. Neupro and the strength are printed on each transdermal system. Each transdermal system is packaged in a separate pouch. Each strength is available in cartons of 7, 30, — transdermal systems.

**EER Status:** Acceptable - 18-APR-2007

**Consults:** EA — Acceptable — 10-JAN-2005  
Biopharmaceutics - Acceptable — 30-JAN-2007

**Original Submission:** 29-SEP-2004

**Action Letter Comment:**

Recommend that the following comment be added to the action letter:

( / / / / /

**Drug Substance:**

The drug substance, Rotigotine, is a small, synthetic, new molecular entity (NME) with an empirical formula of C<sub>19</sub>H<sub>25</sub>NOS and a molecular weight of 315.48 g/mol. Known chemically as (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-8-naphthalenol, Rotigotine is a chiral compound with an S-configuration at carbon atom, C-6, of the 1-naphthol.

The — retest period is deemed acceptable based on provided stability data.

**Conclusion:** Drug substance is acceptable.

**Drug Product:**

The transdermal system consists of three layers; the backing film, adhesive matrix layer containing active and a protective foil. The other inactive ingredients present are povidone, sodium bisulfite, ascorbyl palmitate and *dl*- $\alpha$ -tocopherol dispersed in a silicone adhesive.

The drug product specification includes tests for

/ / / / / / / /

Adequate stability data were provided to support the proposed expiration dating of 24 months at room temperature, 20° - 25°C (68° - 77°F); excursions permitted between 15° - 30°C (59° - 86°F), for the drug product packaged in the original pouch.

**Conclusion:** Drug product is satisfactory.

**Additional Items:**

The major CMC approvability issue from 28-FEB-2006 was that the applicant should develop a test and appropriate acceptance criterion to address the safety of a potentially genotoxic impurity that is formed as per the suggested degradation pathway. The applicant adequately addressed this issue.

Additionally, the clinical studies showed a significant frequency of patches' ends lifting off/falling off the skin during the 24 hour treatment period. For the time being, this issue is being addressed through the labeling recommendation that a bandage may be used to avoid this problem. However, to improve the quality of the product, we recommend that the applicant re-evaluate the adhesive properties of the patches and tighten the adhesion acceptance criterion accordingly.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.  
Director  
DPA I/ONDQA

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/s/

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Blair Fraser  
4/27/2007 11:00:03 AM  
CHEMIST

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** April 18, 2007

**FROM:** David J. Claffey, Ph.D., ONDQA

**SUBJECT:** **Office of Compliance Recommendation**  
NDA 21-829, Neupro (rotigotine transdermal system)

An overall acceptable recommendation was made by the Office of Compliance on 18 APR 2007 regarding the manufacturing sites provided for in NDA 21-829. This was not available at time of completion of the most recent CMC review (#3). The EER summary report is attached to this review.

All outstanding CMC-related approvability issues have been resolved. An approval recommendation from a CMC perspective is recommended.

# Attachment

## ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application : NDA 21829/000      Sponsor: SCHWARZ BIOSCIENCES  
Org Code : 120      110167  
Priority : 15      RESEARCH TRIANGLE PARK, NC 27709

Stamp Date : 29-SEP-2004      Brand Name : NEUPRO (ROTIGOTINE)  
FDOPA Date : 09-MAY-2007      BATCH) 2/4/6/8 MG/24HRS  
Action Goal :      Estab. Name:  
District Goal: 10-MAR-2007      Generic Name: ROTIGOTINE PATCH  
Dosage Form: (TRANSDERMAL SYSTEM)  
Strength : 2, 4, 6 & 8 MG

FDA Contacts:      S. GOLDIE      Project Manager      301-796-2055  
                  D. CLAFFEY      Review Chemist      301-796-1343  
                  M. HESTMAN      Team Leader      301-796-1678

Overall Recommendation:      ACCEPTABLE on 18-APR-2007 by S. ADAMS (RFD-322) 301-827-9051  
                                  ACCEPTABLE on 08-SEP-2005 by S. ADAMS (RFD-322) 301-827-9051

Establishment :      CFN :      FBI :  
                                  /      /      /

DMP No:      AADA:

Responsibilities:      /      /      /

Profile :      CSN      OAI Status:      NONE  
Last Milestone:      OC RECOMMENDATION  
Milestone Date:      16-APR-07  
Decision :      ACCEPTABLE  
Reason :      DISTRICT RECOMMENDATION

Establishment :      CFN : 9613661      FBI : 3003387535  
                                  LOHMANN THERAPIE-SYSTEME AG  
                                  LOHMANNSTRASSE 2  
                                  ANDERNACH, . GM

DMP No:      AADA:

Responsibilities:      FINISHED DOSAGE MANUFACTURER  
                                  FINISHED DOSAGE PACKAGER

Profile :      TDP      OAI Status:      NONE  
Last Milestone:      OC RECOMMENDATION  
Milestone Date:      18-APR-07  
Decision :      ACCEPTABLE  
Reason :      DISTRICT RECOMMENDATION

Establishment :      CFN : 9610732      FBI : 3002808160  
                                  SCHWARZ PHARMA  
                                  SRANON INDUSTRIAL ESTATE  
                                  COUNTY CLARE, . EI

DMP No:      AADA:

18-APR-2007

FDA CDER HES

Page 2 of 1

ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Profile : CTX OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 18-APR-07  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

---

Establishment : CFN : 1819171 FEI : 1819171  
SCHWARZ PHARMA MANUFACTURING  
1101 C AVE W  
SEYMOUR, IN 472743342

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-MAR-07  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

---

Establishment : CFN : FEI : 3002948883  
SCHWARZ PHARMA PRODUKTIONS GMBH  
GALILEISTRASSE 6  
ZNICKAU, GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 28-MAR-07  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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Establishment : CPN : FBI : 3002943189  
SCHWARZ PHARMA PRODUKTIONS GMBH  
ALFRED NOBEL STRASSE 10  
MUNSTER, GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile : CTX OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 23-MAR-07  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

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/s/

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David Claffey  
4/18/2007 03:12:15 PM  
CHEMIST

Ramesh Sood  
4/18/2007 04:57:00 PM  
CHEMIST

**NDA 21-829**

**Neupro (rotigotine transdermal system)**

**Schwarz BioSciences, Inc.**

**David J. Claffey, Ph.D**

**Office of New Drug Quality Assessment**



# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>7</b>
<b>I. Recommendations.....</b>	<b>7</b>
A. Recommendation and Conclusion on Approvability .....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
<b>II. Summary of Chemistry Assessments.....</b>	<b>7</b>
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
<b>III. Administrative.....</b>	<b>12</b>
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block .....	12
<b>Chemistry Assessment.....</b>	<b>5</b>
<b>I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....</b>	<b>12</b>
S DRUG SUBSTANCE [Name, Manufacturer].....	12
P DRUG PRODUCT .....	12
A APPENDICES .....	18
R REGIONAL INFORMATION.....	18
<b>II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....</b>	<b>18</b>
A. Labeling & Package Insert .....	18
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	18
<b>III. List Of Deficiencies To Be Communicated.....</b>	<b>18</b>



# Chemistry Review Data Sheet

1. NDA 21-829
2. REVIEW #3
3. REVIEW DATE: 13 APR 2007
4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA Submission (RTF)	29-SEP-2004
Resubmission	19-JAN-2005
Amendment BZ	23-JUN-2005
Amendment BC	09-AUG-2005
Amendment BC	29-SEP-2005
Amendment BC	05-JAN-2006
Amendment BL	30-JAN-2006
Resubmission (N-0019)	28 AUG 2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment BC	4 April 2007

7. NAME & ADDRESS OF APPLICANT:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Name: Schwarz BioSciences, Inc.  
Address: P.O. Box 110167  
Research Triangle Park, NC 27709  
Representative: Betsy Waldheim  
Telephone: (919) 767-2560

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Neupro
- b) Non-Proprietary Name (USAN): rotigotine
- c) Code Name/# (ONDC only): SPM 962
- d)
- e) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b) (1)

10. PHARMACOL. CATEGORY: Anti-Parkinson's

11. DOSAGE FORM: Patch / Transdermal System

12. STRENGTH/POTENCY: 2, 4, 6, — mg

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

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

(-)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino-1-naphthol  
 C<sub>19</sub>H<sub>25</sub>NOS      Formula Weight 315.47

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			4	Adequate	--	
	III			3	Adequate	1/23/2003	
	III			3	Adequate	9/29/2004	
	III			4	Adequate	--	
	III			3	Adequate	9/29/2004	
	III			4	Adequate	--	
	III			1	Adequate	12/20/2005	
	III			4	Adequate	--	
	III			4	Adequate	--	
	III			4	Adequate	--	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 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")

<sup>2</sup> 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
IND	47,852	Rotigotine patch for Parkinson's disease

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending	--	Lois Freed
Biopharmaceutics	Acceptable	30 JAN 2007	Veneeta Tandon
ODS/DSRCS	Comments forwarded to Division	11OCT 2006	Jeanine Best
ODS/DMETS	Pending	--	--
EA	Claim of categorical exclusion accepted	10 January 2005	Florian Zielinsky

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:



# The Chemistry Review for NDA 21-829

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

We recommend that this application be approved from a CMC perspective upon receipt of an acceptable recommendation from the Office of Compliance. The overall recommendation from the Office of Compliance is pending.

The CMC approvability issues detailed in the previous action letter were adequately addressed by the Applicant and were evaluated in the previous CMC review (#2). An information request containing no approvability issues was sent to the Applicant on 29 MAR 2007. This review contains this reviewers evaluation of the Applicants responses (BC, 4 APR 2007) to this IR.

Recommend that the following comment be added to the action letter:

• / / / /

Note that the acceptability of the — acceptance criterion for the — degradant in the drug product will be determined by the pharm/tox reviewer.

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

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

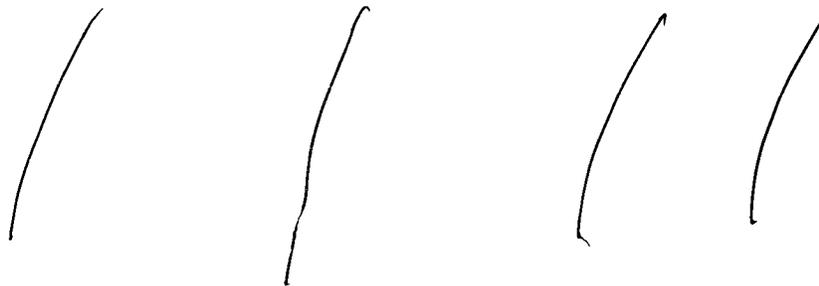
##### Drug Substance:

Rotigotine, a new molecular entity, is a white to off-white non-hygroscopic powder with a melting point range of — Rotigotine is a chiral compound with one stereogenic element. The stereogenic carbon atom, C-6 of the 1-naphthol system, has the absolute S-configuration. — are not relevant to the product formulation.

The drug substance is manufactured by \_\_\_\_\_ The starting material of the synthesis is \_\_\_\_\_ The drug substance synthesis consists of \_\_\_\_\_



Chemistry Assessment Section



The original proposal for drug substance specifications were adequate with the exception of the proposed acceptance criterion for [redacted]. This limit was revised to NLT [redacted] on the Agency's recommendation.

Stability of the drug substance was monitored for 24 months at 25°C/60%RH and [redacted] at 40°C/75%RH. All related substances remained within their specified limits. At [redacted] at 40°C/75%RH, one batch was OOS [redacted]. The batches produced by [redacted] showed no increase in impurities at 40°C/75%RH. These data support the proposed 2 year expiry period.

Drug Product:

Neupro (rotigotine transdermal system) is a three-layer adhesive patch and is available in [redacted] strength. The first layer, the backing film, is a flexible, beige to light brown colored material, [redacted]. The second layer is the drug matrix. The drug matrix consists of [redacted] povidone and rotigotine with sodium bisulfite, ascorbyl palmitate and dl-α-tocopherol [redacted] dispersed in [redacted] silicone adhesive. The third layer is a protective foil that consists of a [redacted] film that is coated on one side with a fluoro-polymer. The fluoro-polymer contacts the drug/adhesive matrix. The patch is applied to the skin (thighs, abdomen or upper arms) once daily (in a different location). The patches are packaged in a peel-off pouch made of [redacted]. Supportive data on a [redacted] was provided in the application, however the Applicant does not propose marketing this packaging configuration.

The drug substance content of the patch exceeds the delivered dose. The composition of the drug/adhesive matrix is identical for all strengths, only the patch area differs.

<u>Dose</u>	<u>Patch area</u>	<u>Drug content of the patch</u>
2 mg	10 cm <sup>2</sup>	4.50 mg
4 mg	20 cm <sup>2</sup>	9.00 mg
6 mg	30 cm <sup>2</sup>	13.5 mg

The drug product is manufactured by LTS Lohmann Therapie-Systeme AG of Andernach, Germany. Drug product matrix is made by [redacted]







Chemistry Assessment Section

It should be noted that the proposed \_\_\_\_\_ limit was based on the highest nominal 'labeled' strength of \_\_\_\_\_ day, rather than the total drug content of the highest strength patch \_\_\_\_\_. The pharm/tox reviewer was alerted to this fact and has yet to determine the acceptability of this approach. Note that the proposed method of calculation results in \_\_\_\_\_ day exposure, whereas should all the degradant be absorbed, the maximum exposure is expected to be \_\_\_\_\_ day.

A matrix design was applied to the drug product stability protocol as each strength is manufactured by the same process and differs only in patch area. The data in the initial review cycle did not support the proposed 24-month expiry period, as a maximum of just \_\_\_\_\_ data in \_\_\_\_\_ lots was available. Supportive data was provided for \_\_\_\_\_ other lots packed in the proposed \_\_\_\_\_ configuration, however the results of the \_\_\_\_\_ tests for these lots were consistently outside the specified limit at the 24 month time point. This test \_\_\_\_\_

\_\_\_\_\_ These \_\_\_\_\_ lots were produced with a different backing film and/or a different \_\_\_\_\_ process to that proposed for the marketed product and the Applicant expected that these changes would resolve any such stability issues. However given that the \_\_\_\_\_

\_\_\_\_\_ this reviewer determined that real-time stability data would be required in the full scale production lots to justify the proposed 24 month expiry period. This point was related to the applicant in the initial AE letter. In this submission full 24 months stability data were provided on \_\_\_\_\_ lots of each strength which were produced by the final commercial manufacturing process. All results remained within specified limits including those for the \_\_\_\_\_. It does appear that the recent modifications to the manufacturing process (improved \_\_\_\_\_) have gone a long way in resolving this issue. It should be noted that a \_\_\_\_\_ did occur in the lots produced with the improved process at around the \_\_\_\_\_ time point. Although the results did remain within specified limits this validates this reviewers concern over this issue. This issue should be seriously considered if the Applicant considers post-marketing changes to the formulation, packaging or manufacturing process.

In the initial submission it was noted that a relatively large number of cases of partially detached patches were found in the clinical studies. As the \_\_\_\_\_ that was carried out at release and in stability studies did not reveal any such problem, a recommendation was made to the applicant that that a \_\_\_\_\_ test be developed that will be more predictive of the actual adhesion performance of the drug product in the patient population. The applicant responded in the resubmission (review #2) with the proposal to add an additional test (\_\_\_\_\_ test) to the drug product specifications. This test will complement the \_\_\_\_\_ test as it will help control the \_\_\_\_\_. Details of the test and its evaluation are contained within this review document. It was also suggested that the applicant determine whether a relationship exists between the extent of patch detachment found in the clinical studies and \_\_\_\_\_



## Chemistry Assessment Section

It should be noted that the clinical reviewers were not overly concerned that this issue would greatly affect the safety/efficacy of this product, however the performance of this product depends on its ability to adhere to the skin and it is possible that the occurrence of patch detachment may be more frequent once the product is marketed and not used in such a controlled setting as the clinical studies would have been conducted. A recommendation was added to the labeling that bandage tape be used to secure the edges of the patch should it begin to lift; although this is a far from ideal solution this will go some way towards reducing the affects of this issue. The Applicant was asked in this review cycle if they determined the acceptability of patches which have \_\_\_\_\_; at the extremes of the proposed range. The Applicant responded (BC 4 APR 2007) stating that they had not done so. Although not an approvability issue, a recommendation will be made in the action letter that \_\_\_\_\_

Additionally, in order to ensure more consistent product quality in the future, the Applicant was asked to reevaluate the \_\_\_\_\_ y acceptance criteria for \_\_\_\_\_ o that they are more in line with the batches used in the clinical studies. This property is in this Reviewers opinion a critical attribute as it will likely affect the adhesion of the patch and possibly its mechanical properties and rate of drug delivery of the patch. In the 4 APR 2007 amendment the Applicant provided \_\_\_\_\_ data for batches of \_\_\_\_\_ used in the clinical studies and agreed to narrow the previous, rather broad, acceptance criteria.

Product labeling is generally acceptable – the applicant was asked to include a warning that the product contains sulfites on the \_\_\_\_\_ product labeling according to 21 CFR 201.22 (a) and (b). They agreed to do so in the resubmission.

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

Neupro patch is applied to the skin of the patient once daily for treatment of the symptoms of early-stage idiopathic Parkinson's disease. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time everyday, at a time convenient to the patient. Application to the same site on the skin more frequently than once every 14 days should be avoided. A single daily dose should be initiated at 2 mg/24 hours and then increased in weekly increments of 2 mg/24 hours to an effective dose of 6 mg/24 hours \_\_\_\_\_ within 3 or 4 weeks.

**C. Basis for Approvability or Not-Approval Recommendation**



Chemistry Assessment Section

The Applicant adequately addressed the major approvability issues that were found in the initial submission. These included several issues involving the acceptance criteria for impurities in the drug product specification including the addition of a new specification for a suspect mutagen. The stability data support the proposed 24-month expiry period, and it appears that the modifications to the packaging configuration and the manufacturing process have adequately resolved the issues that resulted in \_\_\_\_\_

\_\_\_\_\_. The issue relating to the partial patch detachment observed in clinical studies was addressed in the labeling, with the recommendation to use bandage tape to secure the edges should they begin to lift. It is anticipated that the applicant will take our recommendation to revisit the acceptance criteria for \_\_\_\_\_ so that the patients will be more assured of more consistent \_\_\_\_\_ performance. An acceptable recommendation has not yet been received from the Office of Compliance.

**III. Administrative**

**A. Reviewer's Signature**

Electronic signature in DFS

**B. Endorsement Block**

Chemist Name/Date: David J. Claffey, Ph.D.

Branch Chief: Ramesh Sood, Ph.D.

Project Manager: Teresa Wheelous

**C. CC Block**

Chemist Name / Date: David J. Claffey, Ph.D. / 02/27/2006

Branch Chief: Ramesh Sood, Ph.D.

Project Manager: Teresa Wheelous

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       Deliberative Process

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/s/

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David Claffey  
4/17/2007 05:11:31 PM  
CHEMIST

Ramesh Sood  
4/17/2007 05:17:56 PM  
CHEMIST

**NDA 21-829**

**Neupro (rotigotine transdermal system)**

**Schwarz BioSciences, Inc.**

**David J. Claffey, Ph.D**

**Office of New Drug Quality Assessment**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>7</b>
<b>I. Recommendations.....</b>	<b>7</b>
A. Recommendation and Conclusion on Approvability .....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
<b>II. Summary of Chemistry Assessments.....</b>	<b>7</b>
A. Description of the Drug Product(s) and Drug Substance(s) .....	7
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
<b>III. Administrative.....</b>	<b>11</b>
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block .....	12
<b>Chemistry Assessment.....</b>	<b>12</b>
<b>I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....</b>	<b>12</b>
S DRUG SUBSTANCE [Name, Manufacturer].....	12
P DRUG PRODUCT .....	12
A APPENDICES .....	30
R REGIONAL INFORMATION.....	30
<b>II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....</b>	<b>30</b>
A. Labeling & Package Insert .....	30
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	33
<b>III. List Of Deficiencies To Be Communicated.....</b>	<b>33</b>



# Chemistry Review Data Sheet

1. NDA 21-829
2. REVIEW #2
3. REVIEW DATE: 28 MAR 2007
4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA Submission (RTF)	29-SEP-2004
Resubmission	19-JAN-2005
Amendment BZ	23-JUN-2005
Amendment BC	09-AUG-2005
Amendment BC	29-SEP-2005
Amendment BC	05-JAN-2006
Amendment BL	30-JAN-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission (N-0019)	28 AUG 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Schwarz BioSciences, Inc.



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Address: P.O. Box 110167  
Research Triangle Park, NC 27709

Representative: Betsy Waldheim

Telephone: (919) 767-2560

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: neupro
- b) Non-Proprietary Name (USAN): rotigotine
- c) Code Name/# (ONDC only): SPM 962
- d)
- e) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b) (1)

10. PHARMACOL. CATEGORY: Anti-Parkinson's

11. DOSAGE FORM: Patch / Transdermal System

12. STRENGTH/POTENCY: 2, 4, 6, — mg

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

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

(-)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol  
 C<sub>19</sub>H<sub>25</sub>NOS      Formula Weight 315.47

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
7	III			4	Adequate	--	
	III			3	Adequate	1/23/2003	
	III			3	Adequate	9/29/2004	
	III			4	Adequate	--	
	III			3	Adequate	9/29/2004	
	III			4	Adequate	--	
	III			1	Adequate	12/20/2005	
	III			4	Adequate	--	
	III			4	Adequate	--	
	III			4	Adequate	--	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 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")

<sup>2</sup> 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
IND	47,852	Rotigotine patch for Parkinson's disease

### 18. STATUS:

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

**ONDC:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
EES	Pending		
Pharm/Tox	Pending	--	Paul Roney
Biopharmaceutics	Acceptable	30 JAN 2007	Veneeta Tandon
ODS/DSRCS	Pending	14 February 2006	Jeanine Best
ODS/DMETS	Pending	--	--
EA	Claim of categorical exclusion accepted	10 January 2005	Florian Zielinsky

**19. ORDER OF REVIEW (OGD Only)**

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:



# The Chemistry Review for NDA 21-829

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend that this application is approvable from a CMC perspective on receipt of an acceptable recommendation from the Office of Compliance.

The CMC approvability issues detailed in the previous action letter have been adequately addressed by the Applicant in this submission. Although an information request was sent to the Applicant on 29 MAR 2007, it contained no approvability issues. Note that the acceptability of the \_\_\_\_\_ acceptance criterion for the \_\_\_\_\_ degradant in the drug product will be determined by the pharm/tox reviewer.

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

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

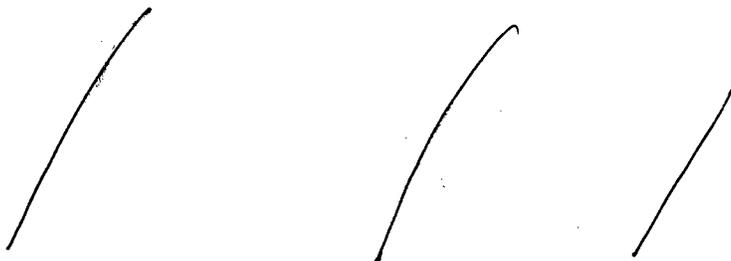
##### Drug Substance:

Rotigotine, a new molecular entity, is a white to off-white non-hygroscopic powder with a melting point range of \_\_\_\_ Rotigotine is a chiral compound with one-stereogenic element. The stereogenic carbon atom, C-6 of the 1-naphthol system, has the absolute S-configuration. \_\_\_\_ are not relevant to the product formulation.

The drug substance is manufactured by \_\_\_\_\_  
material of the synthesis is \_\_\_\_\_

The starting

The drug substance synthesis consists of \_\_\_\_\_





# CHEMISTRY REVIEW TEMPLATE



## Chemistry Assessment Section

The original proposal for drug substance specifications were adequate with the exception of the proposed acceptance criterion for \_\_\_\_\_ . This limit was revised to NLT \_\_\_\_\_ on the Agency's recommendation.

Stability of the drug substance was monitored for 24 months at 25°C/60%RH and \_\_\_\_\_ at 40°C/75%RH. All related substances remained within their specified limits. At \_\_\_\_\_ at 40°C/75%RH, one batch was OOS \_\_\_\_\_ . The batches produced by \_\_\_\_\_ showed no increase in impurities at 40°C/75%RH. These data support the proposed 2 year expiry period.

### Drug Product:

Neupro (rotigotine transdermal system) is a three-layer adhesive patch and is available in \_\_\_\_\_ strength. The first layer, the backing film, is a flexible, beige to light brown colored material, \_\_\_\_\_ . The second layer is the drug matrix. The drug matrix consists of \_\_\_\_\_ povidone and rotigotine with sodium bisulfite, ascorbyl palmitate and *dl*- $\alpha$ -tocopherol \_\_\_\_\_ dispersed in a \_\_\_\_\_ silicone adhesive. The third layer is a protective foil that consists of \_\_\_\_\_ film that is coated on one side with a fluoro-polymer. The fluoro-polymer contacts the drug/adhesive matrix. The patch is applied to the skin (thighs, abdomen or upper arms) once daily (in a different location). The patches are packaged in a peel-off pouch made of \_\_\_\_\_ . Supportive data on a \_\_\_\_\_ was provided in the application, however the Applicant does not propose marketing this packaging configuration.

The drug substance content of the patch exceeds the delivered dose. The composition of the drug/adhesive matrix is identical for all strengths, only the patch area differs.

<u>Dose</u>	<u>Patch area</u>	<u>Drug content of the patch</u>
2 mg	10 cm <sup>2</sup>	4.50 mg
4 mg	20 cm <sup>2</sup>	9.00 mg
6 mg	30 cm <sup>2</sup>	13.5 mg

The drug product is manufactured by LTS Lohmann Therapie-Systeme AG of Andernach, Germany. Drug product matrix is made by \_\_\_\_\_

The drug product specification includes tests for \_\_\_\_\_

Release results of the validation batches \_\_\_\_\_ (batches of each strength) are adequate. All samples complied with acceptance criteria.

## Chemistry Assessment Section

Two degradation products, \_\_\_\_\_ and are thus qualified. \_\_\_\_\_ is considered an unqualified degradation product. The proposed limits for this and 'other single' impurities of the 4.5 and 9 mg / 24 hour patches are based on the ICH Q3B qualification threshold (< 10 mg maximum daily dose). Initially the Applicant proposed \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

This approach was not appropriate

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

These recommendations were made to the applicant in the initial approvable action letter. In this resubmission the Applicant agreed to revise the acceptance criteria for \_\_\_\_\_ to \_\_\_\_\_ and the unknowns to \_\_\_\_\_ for all the strengths. This approach is acceptable.

In addition, the proposed \_\_\_\_\_ degradation pathway of rotigotine to the known degradants \_\_\_\_\_ includes the concomitant production of \_\_\_\_\_, a suspect mutagen. In the initial submission the Applicant did not address what levels of this compound were present in the drug product at release or through the shelf life, nor was a specified limit proposed. This information was requested in the initial AE action letter. In this submission the Applicant proposed a limit of \_\_\_\_\_ for this degradant. \_\_\_\_\_ analytical methods for its detection were developed and validated, and its levels were quantified in several batches of drug substance and drug product. All the more recent lots had levels within the proposed limits. There appeared to be much scatter in the results with no obvious trends. It should be noted that the proposed \_\_\_\_\_ limit was based on the highest nominal 'labeled' strength of \_\_\_\_\_ day, rather than the total drug content of the highest strength patch. *The pharm/tox reviewer was alerted to this fact and has yet to determine the acceptability of this approach. Note that the proposed method of calculation results in \_\_\_\_\_ day exposure, whereas should all the degradant be absorbed, the maximum exposure is expected to be \_\_\_\_\_ /day.*

A matrix design was applied to the drug product stability protocol as each strength is manufactured by the same process and differs only in patch area. The data in the initial review cycle did not support the proposed 24-month expiry period, as a maximum of just \_\_\_\_\_ data in \_\_\_\_\_ lots was available. Supportive data was provided for \_\_\_\_\_ other lots packed in the proposed \_\_\_\_\_ packaging

Chemistry Assessment Section

configuration, however the results of the [redacted] tests for these lots were consistently outside the specified limit at the 24 month time point. This test [redacted] These [redacted] lots were produced with a [redacted] process to that proposed for the marketed product and the Applicant expected that these changes would resolve any such stability issues. However given that the [redacted]

[redacted] this reviewer determined that real-time stability data would be required in the full scale production lots to justify the proposed 24 month expiry period. This point was related to the applicant in the initial AE letter. In this submission full 24 months stability data were provided on [redacted] lots of each strength which were produced by the final commercial manufacturing process. All results remained within specified limits including those for the [redacted] It does appear that the recent modifications to the manufacturing process (improved [redacted], have gone a long way in resolving this issue. It should be noted that [redacted] did occur in the lots produced with the improved process at around the [redacted] time point. Although the results did remain within specified limits this validates this reviewers concern over this issue. This issue should be seriously considered if the Applicant considers post-marketing changes to the formulation, packaging or manufacturing process.

In the initial submission it was noted that a relatively large number of cases of partially detached patches were found in the clinical studies. As the [redacted] that was carried out at release and in stability studies did not reveal any such problem, a recommendation was made to the applicant that that a [redacted] test be developed that will be more predictive of the actual adhesion performance of the drug product in the patient population. The applicant responded in this submission with the proposal to add an additional test ([redacted] test) to the drug product specifications. This test will complement the [redacted] test as it will help control the [redacted] It was also suggested that the applicant determine whether a relationship exists between the extent of patch detachment found in the clinical studies and th [redacted]



It should be noted that the clinical reviewers were not overly concerned that this issue would greatly affect the safety/efficacy of this product, however the performance of this product depends on its ability to adhere to the skin and it is possible that the occurrence of patch detachment may be more frequent once the product is marketed and not used in such a controlled setting as the clinical studies would have been conducted. A recommendation was added to the labeling that bandage tape be used to secure the edges of the patch should it begin to lift; although this is a far from ideal solution this will go some way towards reducing the affects of this issue. The Applicant was asked in this review cycle if they determined the acceptability of patches which have [redacted] at the extremes of the proposed range.

Chemistry Assessment Section

Product labeling is generally acceptable – the applicant was asked to include a warning that the product contains sulfites on the \_\_\_\_\_ product labeling according to 21 CFR 201.22 (a) and (b). They agreed to do so in this submission.

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

Neupro patch is applied to the skin of the patient once daily for treatment of the symptoms of early-stage idiopathic Parkinson’s disease. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time everyday, at a time convenient to the patient. Application to the same site on the skin more frequently than once every 14 days should be avoided. A single daily dose should be initiated at 2 mg/24 hours and then increased in weekly increments of 2 mg/24 hours to an effective dose of 6 mg/24 hours \_\_\_\_\_ within 3 or 4 weeks.

**C. Basis for Approvability or Not-Approval Recommendation**

The Applicant adequately addressed the major approvability issues that were found in the initial submission. These included several issues involving the acceptance criteria for impurities in the drug product specification including the addition of a new specification for a suspect mutagen. The stability data support the proposed 24-month expiry period, and it appears that the modifications to the packaging configuration and the manufacturing process have adequately resolved the issues that resulted in \_\_\_\_\_

\_\_\_\_\_ The issue relating to the partial patch detachment observed in clinical studies was addressed in the labeling, with the recommendation to use bandage tape to secure the edges should they begin to lift. It is hoped that the applicant will take our recommendation to develop a method that \_\_\_\_\_

\_\_\_\_\_ so that any post-marketing changes in this property will be more confidently predicted. An acceptable recommendation has not yet been received from the Office of Compliance.

**III. Administrative**

**A. Reviewer’s Signature**

Electronic signature in DFS

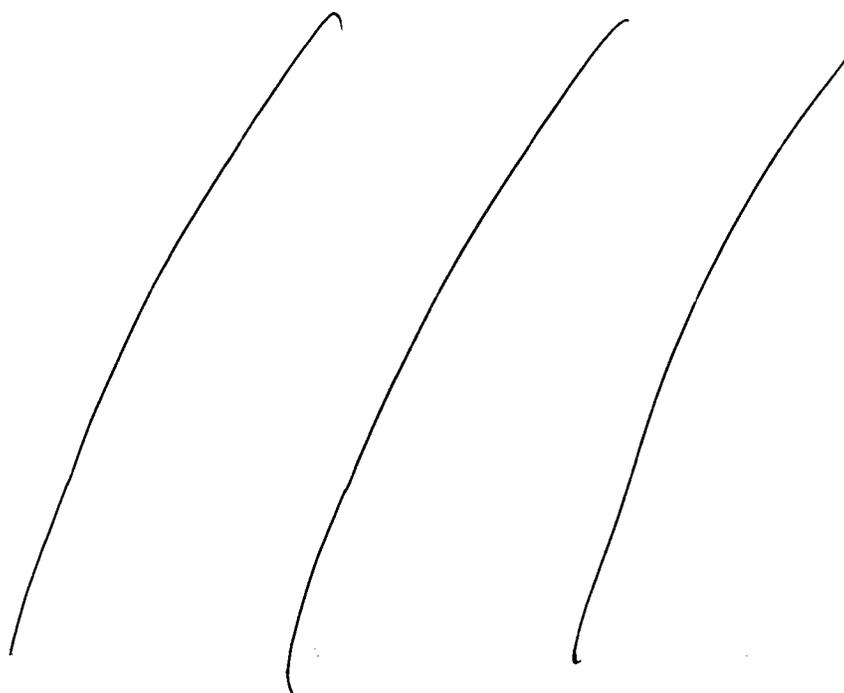
**B. Endorsement Block**

Chemistry Assessment Section

Chemist Name/Date: David J. Claffey, Ph.D.  
Branch Chief: Ramesh Sood, Ph.D.  
Project Manager: Teresa Wheelous

**C. CC Block**

Chemist Name / Date: David J. Claffey, Ph.D. / 02/27/2006  
Branch Chief: Ramesh Sood, Ph.D.  
Project Manager: Teresa Wheelous



22 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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

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David Claffey  
3/29/2007 05:08:26 PM  
CHEMIST

Ramesh Sood  
4/3/2007 01:47:40 PM  
CHEMIST

## MEMORANDUM

**To:** NDA 21-829  
**From:** Ramesh Sood, Branch Chief, ONDQA  
**Through:** Chi-wan Chen, Deputy Director, ONDQA  
**Date:** 28-Feb-2006  
**Subject:** Approvable recommendation for NDA 21-829

---

**Introduction:** Neupro (rotigotine transdermal system), indicated for parkinson's disease, contains 4.5, 9.0, 13.5 mg of active and is designed to deliver 2, 4, 6 mg of active in 24 hour period. The transdermal system should be applied at approximately the same time everyday, at a time convenient to the patient. The product will be packaged and marketed in pouches. The product is labeled to be stored at room temperature in the original pouch.

**Drug Substance:** Rotigotine is a new molecular entity. Rotigotine is a chiral nonracemic compound with one stereogenic element. It is (S). The stereogenic carbon atom, C-6 of the 1-naphthol system, has the absolute S-configuration. The acceptance criterion for [redacted] is set at NLT [redacted] are not relevant to the product formulation. The drug substance is manufactured by [redacted] using a synthetic path. The absence of potential genotoxic impurities [redacted] has been shown in the validation batches. The quality of the drug substance will be controlled through well-controlled and validated manufacturing process and drug substance specification. The retest period is deemed acceptable based on provided stability data. There are no pending issues related to drug substance.

**Drug Product:** The transdermal system consists of three layers; the backing film, adhesive matrix layer containing active and a protective foil. The other inactive ingredients present are povidone, sodium bisulfite, ascorbyl palmitate and dl- $\alpha$ -tocopherol dispersed in [redacted] silicone adhesive. The drug product is manufactured by LTS Lohmann Therapie-Systeme AG of Andernach, Germany. The drug product specification includes tests for [redacted]

**Recommended action:** The overall expected action for this NDA is approvable. An approvable action is also recommended from CMC view point. The major CMC approvability issue is that the applicant should develop a test and appropriate acceptance criterion to address the safety of potentially genotoxic [redacted] impurity that is formed as per the suggested degradation pathway.

The following additional CMC comments that are not necessarily approvability issues should be provided to the applicant for resolution in the next cycle. The provided stability data for drug product does not support the requested 24-month expiration date. Although a [redacted]

expiration date can be assigned to the product based on the available data, additional stability data at the time of resubmission should be requested to justify the requested expiration date. The sponsor should also be asked to tighten impurity acceptance criteria for \_\_\_\_\_ and unspecified impurities.

The clinical studies have shown a significant frequency of patches ends lifting off/falling off the skin to various extents during the 24 hour treatment period. Although the product meets the provided \_\_\_\_\_ test acceptance criterion, this test may not be adequate to predict the adhesion of patches during the actual use. The applicant should be encouraged to develop some more relevant test to evaluate the adhesion properties of patches. The applicant should also provide data to show that skin adhesion property of the patches do not change during the shelf life.

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Ramesh Sood  
2/28/2006 08:49:03 AM  
CHEMIST

For your concurrence

Chi Wan Chen  
2/28/2006 09:28:28 AM  
CHEMIST



**NDA 21-829**

**Neupro (rotigotine transdermal system)**

**Schwarz BioSciences, Inc.**

**Thomas A. Broadbent, Ph.D.**

**and**

**David J. Claffey, Ph.D**

**Office of New Drug Quality Assessment**



# Table of Contents

Chemistry Review Data Sheet.....	4
The Executive Summary.....	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product and Drug Substance.....	8
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment.....	11
3.2.S DRUG SUBSTANCE [rotigotine, —].....	11
3.2.S.1 General Information [rotigotine, —].....	11
3.2.S.1.1 Nomenclature [rotigotine, —].....	11
3.2.S.1.2 Structure [rotigotine, —].....	11
3.2.S.1.3 General Properties [rotigotine, —].....	11
3.2.S.2 Manufacture [rotigotine, —].....	13
3.2.S.2.1 Manufacturers [rotigotine, —].....	13
3.2.S.2.2 Description of Manufacturing Process and Process Controls [rotigotine, —].....	13
3.2.S.2.3 Control of Materials.....	18
3.2.S.2.4 Controls of Critical Steps and Intermediates [rotigotine, —].....	22
3.2.S.2.5 Process Validation and/or Evaluation [rotigotine, —].....	26
3.2.S.2.6 Manufacturing Process Development [rotigotine, —].....	27
3.2.S.3 Characterization [rotigotine, —].....	29
3.2.S.3.1 Elucidation of Structure and other Characteristics [rotigotine, —].....	29
3.2.S.3.2 Impurities [rotigotine, —].....	30
3.2.S.4 Control of Drug Substance [rotigotine, —].....	35
3.2.S.4.1 Specification [rotigotine, —].....	35
3.2.S.4.2 Analytical Procedures [rotigotine, —].....	36
3.2.S.4.3 Validation of Analytical Procedures [rotigotine, —].....	38
3.2.S.4.4 Batch Analyses [rotigotine, —].....	39
3.2.S.4.5 Justification of Specification [rotigotine, —].....	42
3.2.S.5 Reference Standards or Materials [rotigotine, —].....	43
3.2.S.6 Container Closure System [rotigotine, —].....	44
3.2.S.7 Stability [rotigotine, —].....	44
3.2.S.7.1 Stability Summary and Conclusions [rotigotine, —].....	44
3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment [rotigotine, —].....	47
3.2.S.7.3 Stability Data [rotigotine, —].....	48



<b>3.2.P DRUG PRODUCT [neupro, transdermal system]</b> .....	50
<b>3.2.P.1 Description and Composition of the Drug Product [neupro, transdermal system]</b> .....	50
<b>3.2.P.2 Pharmaceutical Development [neupro, transdermal system]</b> .....	51
3.2.P.2.1 Components of the Drug Product [neupro, transdermal system].....	51
3.2.P.2.2 Drug Product [neupro, transdermal system].....	53
3.2.P.2.3 Manufacturing Process Development [neupro, transdermal system] .....	54
3.2.P.2.4 Container Closure System [neupro, transdermal system] .....	56
3.2.P.2.5 Microbiological Attributes [neupro, transdermal system] .....	57
3.2.P.2.6 Compatibility[neupro, transdermal system] .....	57
<b>3.2.P.3 Manufacture [neupro, transdermal system]</b> .....	57
3.2.P.3.1 Manufacturers [neupro, transdermal system] .....	57
3.2.P.3.2 Batch Formula [neupro, transdermal system].....	58
3.2.P.3.3 Description of Manufacturing Process and Process Controls .....	59
3.2.P.3.4 Controls of Critical Steps and Intermediates [neupro, transdermal system] .....	64
3.2.P.3.5 Process Validation and/or Evaluation [neupro, transdermal system] .....	65
<b>3.2.P.4 Control of Excipients [neupro, transdermal system]</b> .....	66
3.2.P.4.1 Specifications [neupro, transdermal system] .....	66
3.2.P.4.2 Analytical Procedures neupro, transdermal system].....	67
3.2.P.4.3 Validation of Analytical Procedures [neupro, transdermal system] .....	68
3.2.P.4.4 Justification of Specifications [neupro, transdermal system].....	69
3.2.P.4.5 Excipients of Human or Animal Origin [neupro, transdermal system].....	69
3.2.P.4.6 Novel Excipients [neupro, transdermal system] .....	69
<b>3.2.P.5 Control of Drug Product [neupro, transdermal system]</b> .....	70
3.2.P.5.1 Specifications [neupro, transdermal system] .....	70
3.2.P.5.2 Analytical Procedures [neupro, transdermal system] .....	72
3.2.P.5.3 Validation of Analytical Procedures [neupro, transdermal system] .....	75
3.2.P.5.4 Batch Analyses [neupro, transdermal system] .....	76
3.2.P.5.5 Characterization of Impurities [neupro, transdermal system] .....	80
3.2.P.5.6 Justification of Specifications [neupro, transdermal system].....	81
<b>3.2.P.6 Reference Standards or Materials [neupro, transdermal system]</b> .....	82
<b>3.2.P.7 Container Closure System [neupro, transdermal system]</b> .....	82
<b>3.2.P.8 Stability [neupro, transdermal system]</b> .....	85
3.2.P.8.1 Stability Summary and Conclusion [neupro, transdermal system] .....	85
3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment .....	88
3.2.P.8.3 Stability Data [neupro, transdermal system].....	89
<b>3.2.A APPENDICES</b> .....	98
A.2 Adventitious Agents .....	98
A.3 Excipients .....	98
<b>3.2.R REGIONAL INFORMATION</b> .....	98
R.1 Executed Production Records.....	98
R.2 Methods Validation Package .....	98
R.3 Environmental Assessment.....	98
R.4 Establishment Evaluation .....	99
R.5 Labeling .....	103



# Chemistry Review Data Sheet

1. NDA 21-829
2. REVIEW #: 1
3. REVIEW DATE: 27-FEB-2006
4. REVIEWER: Thomas A. Broadbent, Ph.D. and David J. Claffey, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA Submission (RTF)	29-SEP-2004
Resubmission	19-JAN-2005
Amendment BZ	23-JUN-2005
Amendment BC	09-AUG-2005
Amendment BC	29-SEP-2005
Amendment BC	05-JAN-2006
Amendment BL	30-JAN-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Schwarz BioSciences, Inc.  
Address: P.O. Box 110167  
Research Triangle Park, NC 27709  
Representative: Betsy Waldheim  
Telephone: (919) 767-2560



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: neupro  
b) Non-Proprietary Name (USAN): rotigotine  
c) Code Name/#: SPM 962  
d) Chem. Type/Submission Priority:  
• Chem. Type: 1  
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b) (1)

10. PHARMACOL. CATEGORY: Anti-Parkinson's

11. DOSAGE FORM: Patch

12. STRENGTH/POTENCY: 2, 4, 6, — mg

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED:  Rx  OTC

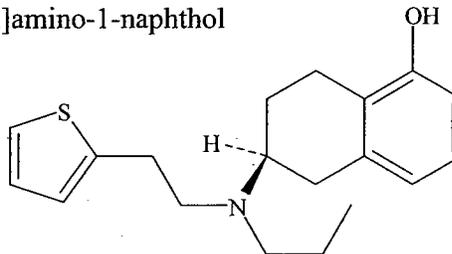
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SPOTS product – Form Completed

Not a SPOTS product

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

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C<sub>19</sub>H<sub>25</sub>NOS      Formula Weight 315.47





# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	Insufficient information (Carcinogenicity)	19 January 2005	Roswitha Kelly
EES	Acceptable	08 September 2005	S. Adams
Pharm/Tox	Pending	--	Paul Roney
Biopharmaceutics	Pending	--	Ron Kavanagh
Methods Validation	Submission of MV to DPA is not recommended	--	Tom Broadbent
ODS/DSRCS	Changes recommended to PI	14 February 2006	Jeanine Best
ODS/DMETS	Pending	--	--
EA	Claim of categorical exclusion accepted	10 January 2005	Florian Zielinsky



# The Chemistry Review for NDA 21-617

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is approvable from a CMC perspective, pending resolution of the issues relating to the acceptance criteria for drug product degradants and the other issues listed on p 115 of this review.

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

No phase 4 commitments are requested for CMC.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

##### Drug Substance:

Rotigotine is a new molecular entity. It is a white to off-white powder with a melting point range of [redacted]. It is not hygroscopic. Rotigotine is a chiral nonracemic compound with one stereogenic element. It is [redacted]. The stereogenic carbon atom, C-6 of the 1-naphthol system, has the absolute S-configuration. [redacted] are not relevant to the product formulation.

The drug substance is manufactured by [redacted] The starting material of the synthesis is [redacted] The drug substance synthesis consists of [redacted]

[redacted]

The original proposal for drug substance specifications was justified except for the limit for [redacted]. The limit for [redacted] was set at NLT [redacted] according to the reviewer's (Dr Broadbent's) recommendation.

Stability of the drug substance was monitored for 24 months at 25°C/60%RH and [redacted] 40°C/75%RH. At 24 months 25°C/60%RH, [redacted] was observed. There is only slight degradation at controlled room temperature at 24 months. All related substances remain within specifications. At [redacted] at [redacted]



# CHEMISTRY REVIEW



## Executive Summary Section

40°C/75%RH, one batch was OOS for [redacted]. The batches produced by [redacted] showed no increase in impurities at 40°C/75%RH.

The sponsor proposes a retest period of [redacted] for the drug substance. The [redacted] retest period is deemed acceptable.

### Drug Product:

Neupro (rotigotine transdermal system) is an adhesive patch available in [redacted] strengths consisting of three layers. The first layer, the backing film, is a flexible, beige to light brown colored backing film, [redacted]. The second layer is the drug matrix. The drug matrix consists of [redacted] povidone and rotigotine with sodium bisulfite, ascorbyl palmitate and *dl*- $\alpha$ -tocopherol [redacted], dispersed in a [redacted] silicone adhesive. The third layer is a protective foil that consists of a [redacted] film that is coated on one side with a fluoro-polymer. The fluoro-polymer contacts the drug/adhesive matrix. The patch is applied to the skin of the patient (thighs, abdomen or upper arms) once daily (in a different location). The patches are packaged in a [redacted] pouch made of [redacted].

The drug substance content of the patch exceeds the delivered dose. The dose is proportional to the area of the patch. The composition of the drug/adhesive matrix is identical for all strengths.

Dose	Patch area	Drug content of the patch
2 mg	10 cm <sup>2</sup>	4.50 mg
4 mg	20 cm <sup>2</sup>	9.00 mg
6 mg	30 cm <sup>2</sup>	13.5 mg

The drug product is manufactured by LTS Lohmann Therapie-Systeme AG of Andernach, Germany. Drug product matrix is made by [redacted]

The drug product specification includes tests for [redacted]

Release results of the validation batches ([redacted] batches of each strength) are adequate. All samples complied with acceptance criteria.

Two degradation products [redacted] and are thus qualified. [redacted] is considered an unqualified degradation product. The proposed limits for this and 'other single' impurities of the 4.5 and 9 mg / 24 hour patches are based on the ICH Q3B qualification threshold (< 10 mg maximum daily dose). The proposed limits for the unqualified degradation products: [redacted]

[redacted]

## Executive Summary Section

This approach is not appropriate

applicant in the action letter.

These recommendations will be made to the

In addition the proposed \_\_\_\_\_, degradation pathway of rotigotine to the known degradants \_\_\_\_\_, includes the concomitant production of \_\_\_\_\_ a suspect mutagen. The applicant did not address what levels of this compound were present in the drug product at release or through the shelf life, nor was a specified limit proposed. This information was requested in the action letter.

A matrix design was applied to the drug product stability protocol as each strength is manufactured by the same process and differs only in patch area. The data did not support the proposed 24-month expiry period, as a maximum of just \_\_\_\_\_ data in \_\_\_\_\_ lots was available in this review cycle. Supportive data was provided for three other lots packed in the proposed \_\_\_\_\_ configuration, however the results of the \_\_\_\_\_ tests for these lots were consistently outside the specified limit at the 24 month time point. This test

These three lots were produced with a \_\_\_\_\_ process to that proposed for the marketed product and the sponsor expects that these changes will alleviate any such stability issues. However given that the \_\_\_\_\_,

real-time stability data will be required in the full scale production lots to justify the proposed 24 month expiry period. This point will be related to the applicant.

It was noted that a relatively large number of cases of partially detached patches were found in the clinical studies. As the \_\_\_\_\_ that was carried out at release and in stability studies did not reveal any such problem, a recommendation was made to the applicant that that a \_\_\_\_\_ test be developed that will be more predictive of the actual adhesion performance of the drug product in the patient population. It was also suggested that the applicant determine whether a relationship exists between the extent of patch detachment found in the clinical studies \_\_\_\_\_

It should be noted that the clinical reviewers were not overly concerned at this point in time that this issue would greatly affect the safety/efficacy of this product, however the performance of this product depends on its ability to adhere to the skin and it is possible that the occurrence of patch detachment may be more frequent once the product is marketed and not used in such a controlled setting as the clinical studies would have been conducted.

Product labeling is generally acceptable – the applicant was asked to include a warning that the product contains sulfites on \_\_\_\_\_ product labeling according to 21 CFR 201.22 (a) and (b).



Executive Summary Section

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

The neupro patch is applied to the skin of the patient once daily for treatment of the symptoms of early-stage idiopathic Parkinson's disease. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time everyday, at a time convenient to the patient. Application to the same site on the skin more frequently than once every 14 days should be avoided. A single daily dose should be initiated at 2 mg/24 hours and then increased in weekly increments of 2 mg/24 hours to an effective dose of 6 mg/24 hours within 3 or 4 weeks.

**C. Basis for Approvability or Not-Approval Recommendation**

The approvability of this application depends chiefly on the applicants ability to adequately address the issue relating to the levels of the suspect mutagen in the drug product. It is expected that the applicant will address the other approvability issues relating to the drug product impurity acceptance criteria and the drug product identity test. The proposed 24-month expiry period was not supported by stability data to-date, but may be once further stability data is available. All other CMC provisions in the NDA appear justified. CMC labeling recommendations were referred to the DNDP review team. The issue relating to the partial patch detachment was addressed in the labeling, with the recommendation to use bandage tape to secure the edges should they begin to lift – it is hoped that the applicant will take our recommendation to develop a method, so that any post-marketing changes in this property will be more confidently predicted.

**III. Administrative**

**A. Reviewer's Signature**

Electronic signature in DFS

**B. Endorsement Block**

Chemist Name/Date: David J. Claffey, Ph.D.  
Branch Chief: Ramesh Sood, Ph.D.  
Project Manager: Teresa Wheelous

**C. CC Block**

Chemist Name / Date: David J. Claffey, Ph.D. / 02/27/2006  
Branch Chief: Ramesh Sood, Ph.D.  
Project Manager: Teresa Wheelous

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/s/

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David Claffey  
2/28/2006 08:37:07 AM  
CHEMIST

Ramesh Sood  
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