

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21829**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

21-829

NAME OF APPLICANT / NDA HOLDER

SCHWARZ BIOSCIENCES, INC.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

NEUPRO

ACTIVE INGREDIENT(S)

ROTIGOTINE

STRENGTH(S)

2MG/24HR

4MG/24HR

6MG/24HR

DOSAGE FORM

FILM, EXTENDED RELEASE; TRANSDERMAL

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

4,885,308

b. Issue Date of Patent

12/5/1989

c. Expiration Date of Patent

12/5/2006

d. Name of Patent Owner

ADERIS PHARMACEUTICALS, INC.

Address (of Patent Owner)

2028 DABNEY ROAD  
SUITE E-17

City/State

RICHMOND/VIRGINIA

ZIP Code

23230-3311

FAX Number (if available)

N/A

Telephone Number

(804) 358-9468

E-Mail Address (if available)

N/A

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

N/A

Address (of agent or representative named in 1.e.)

N/A

City/State

N/A

ZIP Code

N/A

FAX Number (if available)

N/A

Telephone Number

N/A

E-Mail Address (if available)

N/A

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

*Appears This Way  
On Original*

*Appears This Way  
On Original*

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.  
N/A

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent) SEE ATTACHED PAGES Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) SEE ATTACHED PAGES

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

*Margaret M. K. Richardson*

*14 September 2004*

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

MARGARET MARY KOZIK RICHARDSON, ESQ.  
ASSOCIATE DIRECTOR, CONTRACTS MANAGEMENT  
SCHWARZ BIOSCIENCES, INC.

Address

P.O. BOX 110167

City/State

RESEARCH TRIANGLE PARK/NORTH CAROLINA

ZIP Code

27709

Telephone Number

(919)767-2555

FAX Number (if available)

(919) 767-2570

E-Mail Address (if available)

margaret.richardson@schwarzbiosciences.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 21829

SUPPL #

HFD # 120

Trade Name Neupro

Generic Name rotigotine

Applicant Name Schwarz Biosciences, Inc.

Approval Date, If Known May 9, 2007

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>



Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

Name of person completing form: Teresa Wheelous  
Title: Sr. Regulatory Management Officer  
Date: May 8, 2007

Name of Office/Division Director signing form: Dr. Russell Katz  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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/

-----  
Russell Katz  
5/17/2007 08:34:07 AM

Debarment Certification

Rotigotine

NDA 021-829

### DEBARMENT CERTIFICATION

NDA 021-829

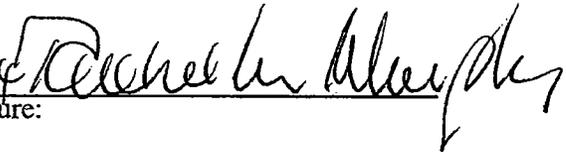
neupro™ (rotigotine transdermal system)

SCHWARZ BIOSCIENCES, INC. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Name: Rachel M. Murphy

Title: Director, Clinical Quality

Department: Clinical Quality

31 Aug 04   
Date/Signature:



The list of all investigators for the above titled submission has been compared with the 22 Oct 2003 Food and Drug Administration Debarment List and the 03 Jun 2004 Disqualified, Restricted, and Given Assurances lists.

Name: Peter Odenthal

Title: Therapeutic Representative

Department: Clinical Quality

31 Aug 04   
Date/Signature:  
FOR PETER ODENTHAL

# NDA ACTION PACKAGE CHECKLIST

## Volume 1

APPLICATION IDENTIFICATION			
NDA 21-829	NEUPRO		
Drug: Rotigotine Transdermal 2 MG/24 hr., 4MG/24 hr., 6MG/24 hr Patches		Applicant: Schwarz Biosciences, Inc.	
RPM: CDR Teresa Wheelous		HFD-120	Phone # 301-796-1161
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)		NME	
• Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates			
		5/9/07 Approval 2/28/06 Approvable	
❖ Special programs (indicate all that apply)			
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
• User Fee (19-JAN-2005 SCHWARZ BIOSCIENCES, 4916 N021829 672,000)		<input checked="" type="checkbox"/> Paid UF ID number <u>4916</u>	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)			
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)			
• OC clearance for approval			

<b>A</b> Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
<b>B</b> Patent	
<ul style="list-style-type: none"> <li>Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> <li></li> <li></li> </ul>	(X) Verified
<b>C</b> Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> <li>Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	No
<ul style="list-style-type: none"> <li>Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	( ) Yes, Application # _____ (x) No
<b>D</b> Administrative Reviews (Project Manager, ADRA)	PM - 5/2/07 & 2/6/06
<b>E</b> Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	(x) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	2/28/06 AE
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
<b>F</b> Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	(x) Yes ( ) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	( ) None (x) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
<b>G</b> Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> <li>Most recent applicant-proposed labeling</li> <li>Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	DMETS 2/22/06 & 4/20/07 DSRCS 2/14/06 Labeling Meetings - 5/2/07 & 5/08/07
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	Mirapex & Requip
<b>H</b> Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> <li>Applicant proposed</li> <li>Reviews</li> </ul>	
<b>I</b> Post-marketing commitments	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> <li>Documentation of discussions and/or agreements relating to post-marketing</li> </ul>	

commitments	
Outgoing correspondence (i.e., letters, E-mails, faxes)	
<b>K</b> Memoranda and Telecons	
<b>L</b> Minutes of Meetings (IND 47,852)	
• EOP2 meeting	6/14/01
• Pre-NDA meeting	12/17/03
• Pre-Approval Safety Conference (indicate date; approvals only)	4/27/07
• Other	1/18/06 (Safety)
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
<b>Summary Application Review</b>	
<b>M</b> Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Division Director (draft) Medical Team Leader – 02/21/06
<b>Clinical Information</b>	
<b>N</b> Clinical review(s) <i>(indicate date for each review)</i>	5/11/07 – Efficacy Review 2/28/06 – Efficacy Review  4/16/07 – Safety Review 2/16/06 – Safety Team Leader 2/16/06 – Safety Reviewer
Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	See above
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet <i>(NME approvals only)</i>	
<b>O</b> Statistical review(s) <i>(indicate date for each review)</i>	10/19/05

## VOLUME 2

<b>P</b> Clinical Pharmacology review(s) (indicate date for each review)	1/30/07 & 2/23/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
<b>Q</b> Clinical Inspection Review Summary (DSI)	
• Clinical studies	6/21/06, 11/01/05
<b>CMC Information</b>	
<b>R</b> CMC review(s) (indicate date for each review)	4/27/07 Director 4/17/07 Reviewer 4-03-07 Reviewer 2/28/06 – Supervisor 2/28/06 - Reviewer
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	CMC 2/28/06 pg.104
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
<b>S</b> Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Supervisor 03/01/06 - 3/01/06 - Reviewer
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	2/03/06

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # **21-829**  
Trade Name: Neupro  
Generic Name: rotigotine  
Strengths: 2 mg/24, 4 mg/24, 6/24 mg, a      hour transdermal patches  
Applicant: Schwarz Biosciences, Inc.

Date of Application: September 24, 2004 incomplete submission, resubmitted January 19, 2005,  
November 9, 2006 resubmission to the 2/28/06 approvable letter  
Date of Receipt: January 28, 2005; November 9, 2006  
Date of Filing Meeting: 12/20/04, 2/25/05, 11/17/06  
Filing Date: March 28, 2005  
Action Goal Date (optional): May 9, 2007  
User Fee Goal Date: **February 28, 2006** (clock extended by three months due to Sept. 13, 2005  
submission)  
11/9/06 Complete Response Received – Due Date **5/9/07**

Indication requested: treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease

Type of Original NDA: (b)(1)   X   (b)(2)             
OR  
Type of Supplement: (b)(1)            (b)(2)           

**NOTE:**

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*
- NDA is a (b)(1) application                      OR                           NDA is a (b)(2) application

Therapeutic Classification: S   X   P             
Resubmission after withdrawal?      NO                      Resubmission after refuse to file? YES  
Chemical Classification: (1,2,3 etc.)      1       
Other (orphan, OTC, etc.)           

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid   X   Exempt (orphan, government)             
Waived (e.g., small business, public health)           

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

*product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO  
If yes, explain:
  
- Does another drug have orphan drug exclusivity for the same indication? NO
  
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A  
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
  
- Is the application affected by the Application Integrity Policy (AIP)? NO  
If yes, explain.
  
- If yes, has OC/DMPQ been notified of the submission? NO
  
- Does the submission contain an accurate comprehensive index? YES
  
- Was form 356h included with an authorized signature? YES  
**If foreign applicant, both the applicant and the U.S. agent must sign.**
  
- Submission complete as required under 21 CFR 314.50? YES  
If no, explain:
  
  
- If an electronic NDA, does it follow the Guidance? YES  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?  
eCTD – containing all parts of the NDA  
  
Additional comments:
  
- If in Common Technical Document format, does it follow the guidance? YES
  
- Is it an electronic CTD? YES  
**If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Administrative & prescribing Info, Summary, Quality, Safety, Clinical study reports, i.e. -Complete eCTD submission (certifications have been submitted in paper).

Additional comments:

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? NO  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? - missing FDA form 3455 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 47,852
- End-of-Phase 2 Meeting(s)? Date(s) \_\_6/14/01\_\_  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_1/17/03\_\_  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? YES

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

N/A

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?

N/A

- Has DOTCDP been notified of the OTC switch application?

N/A

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

N/A

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment?  
 If no, did applicant submit a complete environmental assessment?  
 If EA submitted, consulted to Florian Zielinski (HFD-357)?  
 NO
- |  |     |     |
|--|-----|-----|
|  | YES | NO  |
|  |     | YES |
- Establishment Evaluation Request (EER) submitted to DMPQ?
  - If a parenteral product, consulted to Microbiology Team (HFD-805)?

YES

NO

YES

YES

N/A

ATTACHMENT

MEMO OF FILING MEETING

**BACKGROUND:**

This application, originally dated September 24, 2004, was not filed, for reasons described in an Agency letter dated November 24, 2004. The resubmission to this application is dated January 19, 2005, and was received on January 28, 2005. There was a major amendment submitted with on September 13, 2005, causing the review clock to be extended by three months. Therefore, the new user fee date is February 28, 2006. The sponsor completely responded to the approvable letter, dated Feb. 28, in a November 7, 2006 submission, which was received on November 9, 2006.

On Dec. 14, 2005 the Committee for Medicinal Products for Human Use in the European Medicines Agency adopted a positive opinion recommending to grant a marketing authorization for Neupro. The approved indication is for the treatment of the signs and symptoms of early stage idiopathic Parkinson's disease as monotherapy.

**MEETING DATE:** February 25, 2005  
**APPLICATION:** NDA21-829 Rotigotine Transdermal for Parkinson's disease  
**TYPE OF MEETING:** RTF (filing)  
**MEETING CHAIR:** Dr. Russell Katz

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Dr. Russell Katz – Division Director  
Dr. John Feeney – Group Leader  
Dr. Leonard Kapcala – Medical Reviewer, Efficacy  
Dr. Marc Stone – Medical Reviewer, Safety  
Dr. Lois Freed – Pharmacology /Toxicology Supervisor  
Dr. Paul Roney – Pharmacology /Toxicology Reviewer  
Dr. Sally Yasuda - Clinical Pharmacology & Biopharmaceutics (acting) Team Leader  
Dr. Ronald Kavanagh – Clinical Pharmacology & Biopharmaceutics Reviewer  
Dr. Ohidul Siddiqui – Biometrics Reviewer  
Dr. Kun Jin – Biometrics Team Leader  
Dr. Martha Heimann – CMC Team Leader  
Dr. Thomas Broadbent – CMC Reviewer  
Carolanne Courier – DSI Reviewer

**ASSIGNED REVIEWERS:**

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Kapcala
Secondary Medical:	Marc Stone and Gerald Boehm
Statistical:	Ohidul Siddiqui
Pharmacology:	Paul Roney
Statistical Pharmacology:	
Chemistry:	Thomas Broadbent / Martha Heimann
Environmental Assessment (if needed):	
Biopharmaceutical:	Ronald Kavanagh
Microbiology, sterility:	

DSI: Carolanne Currier  
 Regulatory Project Management: Teresa Wheelous

Per reviewers, are all parts in English or English translation? YES  
 If no, explain:

CLINICAL		FILE <input checked="" type="checkbox"/>		
• Clinical site inspection needed:			YES	
• Advisory Committee Meeting needed?			NO	
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?			N/A	NO
CLINICAL MICROBIOLOGY	NA <input checked="" type="checkbox"/>	FILE _____		REFUSE TO FILE _____
STATISTICS		FILE <input checked="" type="checkbox"/>		REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>		REFUSE TO FILE _____
• Biopharm. inspection needed:				NO
PHARMACOLOGY	NA _____	FILE <input checked="" type="checkbox"/>		REFUSE TO FILE _____
• GLP inspection needed:			YES	NO
CHEMISTRY		FILE <input checked="" type="checkbox"/>		REFUSE TO FILE _____
• Establishment(s) ready for inspection?			YES	NO
• Microbiology			YES	NO

ELECTRONIC SUBMISSION:  
 Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- \_\_\_\_\_ The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- \_\_\_\_\_ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

---

Regulatory Project Manager, HFD-

### Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO  
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO  
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

*NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

N/A

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).

N/A

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).

N/A

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). N/A
10. Are there certifications for each of the patents listed for the listed drug(s)? N/A
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

\_\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

N/A

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?

N/A

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 47852

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

N/A

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

/s/

-----  
Teresa Wheelous  
5/2/2007 01:34:08 PM  
CSO

## Wheelous, Teresa A

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Tuesday, May 08, 2007 12:01 PM  
**To:** Wheelous, Teresa A  
**Subject:** Adhesion Specification acceptance

**Attachments:** NDA\_021829\_letter.pdf; NDA\_021829\_356h.pdf; emfalert.txt



NDA\_021829\_letter.pdf (107 KB) NDA\_021829\_356h.pdf (352 KB) emfalert.txt (2 KB)

Teresa, Letter and 356h forma attached for the Adhesion specification acceptance. Official life cyle will follow.

Regards,

David

---

SCHWARZ BIOSCIENCES, Inc.

Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA

Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA

Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail info@schwarzpharma.com

**Wheelous, Teresa A**

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Tuesday, May 08, 2007 11:59 AM  
**To:** Wheelous, Teresa A  
**Subject:** Neupro - Revised Phase IV commitments

**Attachments:** NDA\_021829\_letter.pdf; NDA\_021829\_356h.pdf; emfalert.txt



NDA\_021829\_letterNDA\_021829\_356h emfalert.txt (2 KB)  
.pdf (266 KB)... .pdf (352 KB)

Teresa, Letter and 356h form attached for the Phase

IV commitments.  
Official life cycle to follow.

Regards,

David

---

SCHWARZ BIOSCIENCES, Inc.

Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA

Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA

Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail info@schwarzpharma.com

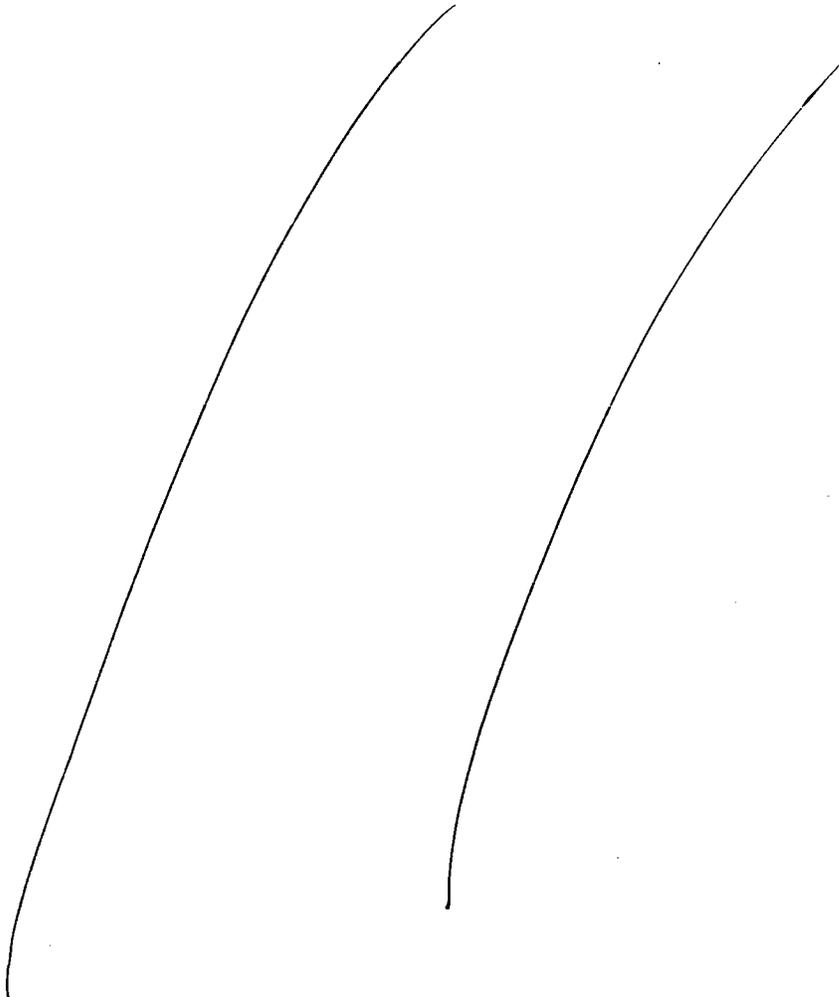
**Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Monday, May 07, 2007 5:38 PM  
**To:** 'David Dobrowski'  
**Subject:** Phase 4 Commitments

David,  
We have had an opportunity to review the proposed [have 4 commitments; and we have the following phase 4 commitments revisions along with some information requests (specifically, please complete the highlighted dates that have not been completed)

These commitments are listed below.



a  
c

A

1 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

**Wheelous, Teresa A**

---

**From:** WHEELOUST [teresa.wheelous@fda.hhs.gov]  
**Sent:** Friday, April 27, 2007 11:01 AM  
**To:** Toscano, Amy; Boehm, Gerard A; Wheelous, Teresa A  
**Subject:** Scanned document from WHEELOUST

**Attachments:** Neupro Safety Meeting Slides ScanDoc.pdf



Neupro Safety  
Meeting Slides S...

This is a copy of the slides from this morning's Neupro safety meeting

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Monday, April 23, 2007 3:01 PM  
**To:** 'David Dobrowski'  
**Subject:** FW: NDA 21829 Neupro - Patient Information Comments from DSRCS

**Attachments:** PPI DRSCS Comments to Sponsor 101306.doc

David,

I sent the following email to Betsy in October, please provide the date of the submission that addresses the comments provided in the attachment. Also, let me know if Schwarz agrees with the recommendation to package the Patient Info leaflet with the unit of use cartons.

Thank you,  
Teresa

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, October 13, 2006 9:54 AM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21829 Neupro - Patient Information Comments from DSRCS

Betsy,

The attached, is a copy of the Patient Information label comment for NDA 21829 Rotigotine:



PPI DRSCS  
Comments to Sponsor

We have the following comment:

Although voluntary, we recommend that you package the Patient Information leaflet containing instructions for use with the unit-of-use Neupro cartons for patient receipt. See a copy of the recommended Patient Information leaflet attached.

Regards,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*  
New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Monday, April 23, 2007 1:59 PM  
**To:** 'David Dobrowski'  
**Subject:** FW: NDA 21829 Neupro - Patient Information Comments from DSRCS

**Attachments:** PPI DRSCS Comments to Sponsor 101306.doc

David,

Do you know if the response to the attached email was ever submitted? If so, what is the submission date? Also, does Schwartz agree to the recommendation regarding the Patient Information leaflet (see email below).

Thanks,  
Teresa

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, October 13, 2006 9:54 AM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21829 Neupro - Patient Information Comments from DSRCS

Betsy,

The attached, is a copy of the Patient Information label comment for NDA 21829 Rotigotine:



PPI DRSCS  
Comments to Sponsor

We have the following comment:

Although voluntary, we recommend that you package the Patient Information leaflet containing instructions for use with the unit-of-use Neupro cartons for patient receipt. See a copy of the recommended Patient Information leaflet attached.

Regards,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*  
New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)

## Wheelous, Teresa A

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Wednesday, April 04, 2007 11:41 AM  
**To:** Wheelous, Teresa A  
**Cc:** Goldie, Scott  
**Subject:** NDA 21-829 CMC Response

**Attachments:** FDA-CMC-Answers-04022007\_1.zip; emfalert.txt



FDA-CMC-Answers- emfalert.txt (2 KB)  
04022007\_1.zip...

Hello Teresa,

Attached is our response to the CMC Information Request Letter dated 4/2/07. The file is a zip file which contains 14 small PDF files. The zip file can be opened using winzip. The answers are provided in the file named "FDA-CMC-answers-04-02-2007". The other files are the supporting CTD documents.

The official eCTD lifecycle submission to NDA 21-829 will be filed to FDA tomorrow as submission sequence 0027.

If you are unable to open the zip file or have any other questions, please give me a call or email. I may be able to send you the files unzipped.

Best Regards,

David  
919-767-3227

---

SCHWARZ BIOSCIENCES, Inc.  
Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA  
Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA  
Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail info@schwarzpharma.com

## Wheelous, Teresa A

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Int:** Tuesday, March 20, 2007 10:18 AM  
**To:** Wheelous, Teresa A  
**Subject:** Re: NDA 21-829 Safety Information Request

**Attachments:** 20Mar07\_0569\_GC.pdf; emfalert.txt



20Mar07\_0569\_GC.emfalert.txt (2 KB)  
pdf (563 KB)

Good Morning Teresa,

Please see the attached additional information on the safety report 001#1#2007-00095. This information has been sent to IND 47,852 has a general correspondence letter.

Please give me a call or email if there are any other questions on this issue.

Best Regards,

David  
919-767-3227

>> "Wheelous, Teresa A" <teresa.wheelous@fda.hhs.gov> 03/16/07 10:22 AM >>>

\* PGP Decrypted Message

\* PGP Bad Signature, Signed by a unverified key

David,

The safety reviewer for NDA 21-829 Rotigotine, has the following info request:

We request additional information about the spontaneous post marketing report of QT prolongation, syncope and death that you submitted on 2/16/07 (Mfg. Report number: 001#1#2007-00095).

The report states that the patient experienced QT prolongation but the report also states that no ECG was performed. Please clarify this apparent discrepancy.

If there was an ECG which demonstrated prolonged QT interval, please provide the results and if possible a copy of the ECG.

Please provide more information about the circumstances surrounding the patient's death.

Please provide any available information about the patient's medical history with emphasis on the patient's cardiac history and all concomitant medications.

If a post mortem examination was performed, please provide the results.

Thanks,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*

\* FDA HHS GOV Secure Server (proxy) <Teresa.Wheelous@fda.hhs.gov>  
\* Issuer: FDA HHS GOV - Unverified

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SCHWARZ BIOSCIENCES, Inc.  
Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA  
Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA  
Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail [info@schwarzpharma.com](mailto:info@schwarzpharma.com)

**Wheelous, Teresa A**

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Int:** Friday, March 16, 2007 11:37 AM  
**To:** Wheelous, Teresa A  
**Subject:** Re: NDA 21-829 Safety Information Request

**Attachments:** emfalert.txt



emfalert.txt (2 KB)

Hi Teresa,

We are actively querying for the additional information. At this point we understand that the treating doctor inquired as to whether rotigotine is associated with QT prolongation but did not report an actual QT prolongation by ECG. We were not provided an ECG and are verifying that an ECG was not performed.

We are requesting any available additional information on medical history, con. meds., ECG, and autopsy from the treating physician.

Best Regards,

David  
^19-767-3227

>>> "Wheelous, Teresa A" <teresa.wheelous@fda.hhs.gov> 03/16/07 10:22 AM >>>

\* PGP Decrypted Message

\* PGP Bad Signature, Signed by a unverified key

David,

The safety reviewer for NDA 21-829 Rotigotine, has the following info request:

We request additional information about the spontaneous post marketing report of QT prolongation, syncope and death that you submitted on 2/16/07 (Mfg. Report number: 001#1#2007-00095).

The report states that the patient experienced QT prolongation but the report also states that no ECG was performed. Please clarify this apparent discrepancy.

If there was an ECG which demonstrated prolonged QT interval, please provide the results and if possible a copy of the ECG.

Please provide more information about the circumstances surrounding the patient's death.

Please provide any available information about the patient's medical history with emphasis on the patient's cardiac history and all concomitant medications.

If a post mortem examination was performed, please provide the results.

Thanks,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*

\* FDA HHS GOV Secure Server (proxy) <Teresa.Wheelous@fda.hhs.gov>

\* Issuer: FDA HHS GOV - Unverified

---

SCHWARZ BIOSCIENCES, Inc.

Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA

Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA

Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail [info@schwarzpharma.com](mailto:info@schwarzpharma.com)

# MEMORANDUM

Division of Medication Errors and Technical Support  
Office of Surveillance and Epidemiology  
HFD-420; White Oak BLDG 22, Room 4447  
Center for Drug Evaluation and Research

**To:** Russell Katz, M.D.  
Director, Division of Neurology Products, HFD-120

**Through:** Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Linda Wisniewski, RN, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**Date:** February 16, 2007

**Subject:** Neupro (Rotigotine Transdermal System) 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours,  
NDA#: 21-829

**Project #:** 2006-1096

This memorandum was written in response to a request from the Division of Neurology Products (HFD-120), for a re-assessment of the proprietary name Neupro and a review of the revised labels and labeling. DMETS first evaluated Neupro in OSE Consult #'s 03-0227 and 05-0110-1, dated December 1, 2003 and February 22, 2006, respectively, and found the name Neupro acceptable at that time. Additionally, DMETS also evaluated the labels and labeling for Neupro in OSE Consult # 05-0110-1. However, DMETS recommendations are not reflected in the August 28, 2006 submission.

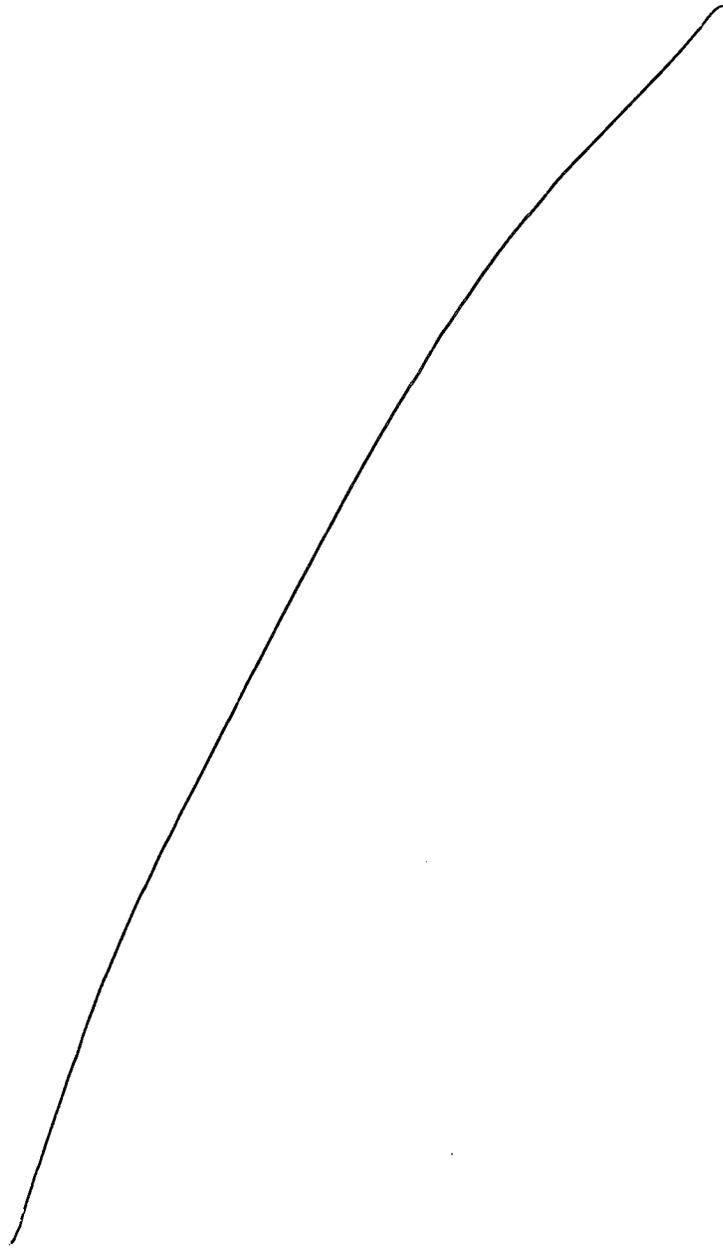
Since the previous reviews, DMETS identified four additional proprietary names with potential for confusion with Neupro. They are Neupogen, Norco, Naropin, and Nepro. However, upon analysis of these names, Neupogen, Norco, and Naropin were not considered further because they lack significant look-alike and sound-alike properties as well as having multiple differentiating product characteristics. The remaining name, Nepro was reviewed in depth and determined to not have a significant risk for error based on the following:

Nepro was identified as a name that may look and sound similar to Neupro when written or spoken. Nepro is a specialty nutritional product used to augment the nutritional status of patients in Stage 5 Kidney Disease that are receiving dialysis. Both names begin and end in the same letters (Ne and pro). However, Neupro has an additional letter 'u', which may make it look longer when written. Although both names also have two syllables (Neu-pro vs. Ne-pro), the additional letter 'u' in Neupro may not clearly differentiate these two names when spoken.



Despite the potential for look-alike and sound-alike characteristics, there are some product characteristics that may help to differentiate these two products when ordered, such as dose (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, vs. one can, XX mL/hour or XX mL/24 hours, etc), frequency of administration (daily vs. once or continuous infusion), strength (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours vs. no strength), route of administration (topical vs. oral), and dosage form (transdermal patch vs. liquid). Nepro would most likely be ordered as one can X times a day or in a number of mL (e.g. 1000 mL to be infused over a period time) whereas Neupro would most likely be ordered as

2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list trailing zeros on their dangerous abbreviations and dose designations list.



B

  1   Page(s) Withheld

       Trade Secret / Confidential

  ✓   Draft Labeling

       Deliberative Process

**Wheelous, Teresa A**

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Tuesday, February 06, 2007 11:45 AM  
**To:** Goldie, Scott  
**Cc:** Wheelous, Teresa A  
**Subject:** NDA 21-829: Stability update

**Attachments:** cover-letter-fda-stability-update-0026.pdf; emfalert.txt



cover-letter-fda-sta emfalert.txt (2 KB)  
bility-upd...

Hello Mr. Goldie,

In January you called and requested a stability update for drug substance and drug product for our rotigotine NDA 21-829.

We have completed and submitted the requested stability update to the agency. The submission was sent to FDA yesterday and should be loaded on your system soon. The submission sequence number is 0026. Attached is a copy of the cover letter for your reference. Please don't hesitate to give me a call if you have any questions regarding this submission.

Best Regards,

David Dobrowski  
Director, Regulatory Affairs  
Schwarz Biosciences  
919-767-3227

## Wheelous, Teresa A

---

**From:** Goldie, Scott  
**Sent:** Friday, January 26, 2007 1:36 PM  
**To:** Claffey, David  
**Cc:** Heimann, Martha R; Sood, Ramesh; Wheelous, Teresa A  
**Subject:** RE: Rotigotine stability request

Made the call. Can they just submit the data with the stability update in 2 weeks, or do you need it sooner?

Scott

---

**From:** Claffey, David  
**Sent:** Thursday, January 25, 2007 4:22 PM  
**To:** Goldie, Scott  
**Subject:** Rotigotine stability request

Scott:  
Can you please forward the following request to Schwarz regarding NDA 21-829 (Neupro rotigotine patch)?

Provide a full update on all most recently available drug substance and drug product stability data.

Here is the contact information:

<< OLE Object: Picture (Enhanced Metafile) >>

Thanks,

David.

---

**From:** Claffey, David  
**Sent:** Tuesday, January 23, 2007 2:24 PM  
**To:** Wheelous, Teresa A  
**Subject:**

Teresa:  
Martha will not be able to make the rotigotine meeting this afternoon....she thought that I would be able to cover it, but I am on flexiplace today (with email problems) and was not invited to the meeting. I don't have my notes for this NDA at home, but you can let the group know that I have started the review, and that the applicant appears to have adequately addressed the approvability issues on what I have reviewed thus far. I plan on getting the review finished before the end of Feb.

Thanks,  
David.

**Wheelous, Teresa A**

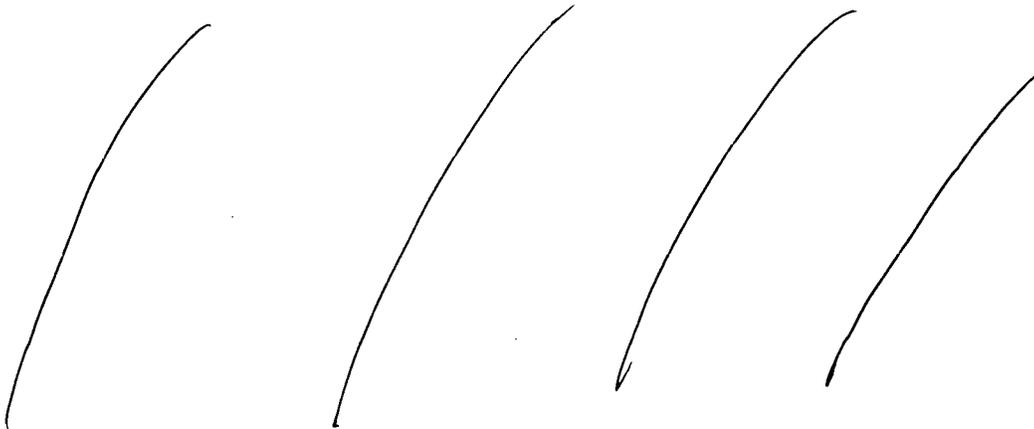
---

**From:** Wheelous, Teresa A  
**Sent:** Wednesday, January 17, 2007 9:43 AM  
**To:** 'David Dobrowski'  
**Subject:** NDA 21-829 Clin Pharm. Info Request

David,

The following are clinical pharmacology information requests for NDA 21-829 Rotigotine:

For labeling justification for



Regards,  
CDR Teresa Wheelous, R. Ph.  
Sr. Regulatory Management Officer  
FDA  
Division of Neurology  
10903 New Hampshire Avenue, Bldg. #22  
Silver Spring, MD 20993-0002  
(telephone) 301-796-1161  
(fax) 301-796-9842  
New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)

**Wheelous, Teresa A**

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Tuesday, January 09, 2007 2:03 PM  
**To:** Wheelous, Teresa A  
**Subject:** Re: Rotigotine Additional Safety Information Requests NDA 21-829

**Attachments:** FDA Safety response 01052007.doc; emfalert.txt



FDA Safety  
sponse 01052007.d



emfalert.txt (2 KB)

Hello Teresa,

Attached in the WORD file are the responses to the 7 questions from the safety reviewer (emails dated 01/05/2007).

Do we also need to send these responses officially the NDA as a life cycle submission?

Best regards,

David

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**sent:** Friday, January 05, 2007 5:39 PM  
**to:** 'David.Dobrowski@schwarzbiosciences.com'  
**Subject:** Rotigotine Additional Safety Information Requests

David,

The following are more safety information requests:

6. There are 626 laboratory values that were obtained during the "PRE" phase but 4 to 28 days after the designated baseline value. These appear to have been obtained on the date of first treatment but were still considered pretreatment values by their phase designation as well as a most recent preceding dose of rotigotine of zero (519 of the 626 values belong to subjects assigned to rotigotine). Shouldn't these values be considered the baseline values?

7. There are 52,449 laboratory values from the "POST" phase where the "most recent preceding dose" is not zero. "most recent preceding dose" can have two interpretations: 1) If the subject is no longer under treatment, the "most recent preceding dose" is zero. 2) The last dose of active drug received, even if the last dose was received days or weeks earlier. Can you verify that you were operating under the second interpretation and that the "POST" classification was not given to values obtained from subjects who were still receiving study treatment?

Thanks,

*CDR Teresa Wheelous, R. Ph.*

*Sr. Regulatory Management Officer*

*FDA*

*Division of Neurology*

*10903 New Hampshire Avenue, Bldg. #22*

*Silver Spring, MD 20993-0002*

*(telephone) 301-796-1161*

*(fax) 301-796-9842*

*New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)*

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, January 05, 2007 5:17 PM  
**To:** 'David.Dobrowski@schwarzbiosciences.com'  
**Subject:** NDA 21-829 Rotigotine Safety Dataset Information Request

David,

The following is a list of safety information requests:

1. Laboratory values in Study 503 are reported as being almost entirely obtained during the "PRE" and "POST" phases; fewer than 1% come from the maintenance ("MN") phase. Is this correct? If so, please explain the rationale for this pattern of data collection.
2. Studies 506 and 515 report extremely low but non-zero numbers of laboratory values (less than 0.1%) during the de-escalation "DE" phase. Are these values correctly labeled? If so, please explain why there are so few values.
3. Studies 535, 540 and 591 have extremely low numbers of laboratory values from the maintenance phase. Again, please explain.
4. Please explain how a de-escalation phase is included with the open label extension designs for studies 513, 515, 709 and 824.
5. Please explain the very low proportion of laboratory values (less than 2%) obtained during the titration phases of studies 513, 630, 651, 709, 825 and 826

Thank you,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*  
New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)

## Wheelous, Teresa A

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**ent:** Thursday, December 21, 2006 12:23 PM  
**To:** Wheelous, Teresa A  
**Subject:** Re: NDA 21-829 Rotigotine Safety Reviewer Question

**Attachments:** emfalert.txt



emfalert.txt (2 KB)

Hi Teresa, the MIDI will be administered by the site personnel.

David

-----Original Message-----

**From:** "Wheelous, Teresa A" <teresa.wheelous@fda.hhs.gov>  
**To:** David Dobrowski <David.Dobrowski@schwarzbiosciences.com>  
**Creation Date:** 12/21 5:41 pm  
**Subject:** NDA 21-829 Rotigotine Safety Reviewer Question

\* PGP Decrypted Message  
\* PGP Bad Signature, Signed by a unverified key  
David,

The safety reviewer for NDA 21-829 has the following question:

In your 11/16/06 submission regarding monitoring subjects in new and ongoing Rotigotine studies for compulsive behaviors, you proposed the use of a modified MIDI assessment tool. Did you intend this to be self-administered or would study site personnel administer this questionnaire?

Thanks,

Teresa

-----Original Message-----

**From:** David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Tuesday, December 19, 2006 7:44 AM  
**To:** Wheelous, Teresa A  
**Subject:** RE: NDA 21-829

Hi Teresa,

David

>>> "Wheelous, Teresa A" <teresa.wheelous@fda.hhs.gov> 12/18/06 2:24 PM  
>>>

Old Decrypted Message

> Old Signed by an unverified key: 12/18/2006 at 08:17:22 PM

David,

**From:** David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Monday, December 18, 2006 2:05 PM  
**To:** Wheelous, Teresa A  
**Subject:** NDA 21-829

Hi Teresa,

I need to let you know that \_\_\_\_\_  
\_\_\_\_\_ Please send all correspondence regarding rotigotine to me  
starting today (12/18).

Two questions on NDA 21-829; Will a letter of classification be issued for the complete  
response to the approvable letter for early PD indication? \_\_\_\_\_  
\_\_\_\_\_

Thanks and Happy Holidays!

David  
919-767-3227

\* FDA HHS GOV Secure Server (proxy) <Teresa.Wheelous@fda.hhs.gov>

\* Issuer: FDA HHS GOV - Unverified



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.  
Attention: Betsy J. Waldheim  
Head, US Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

We acknowledge receipt on November 9, 2006 of your November 7, 2006 resubmission to your new drug application for Neupro (rotigotine) transdermal system 2, 4, 6, — mg/24 hour.

We consider this a complete, class 2 response to our February 28, 2006 action letter. Therefore, the user fee goal date is **May 9, 2007**.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric studies requirement for this application.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301)796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/

-----  
Russell Katz  
12/21/2006 09:42:07 AM

**Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Tuesday, December 05, 2006 9:20 AM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21-829 Rotigotine Follow up Safety Question

Betsy,

The safety reviewer has a follow up Rotigotine request:

In a previous email the Division requested the following information:

In the Cardiac arrhythmia analysis submitted as part of the Action Letter Response on 8/28/06, Table 1d.1.1c identifies 3 rotigotine subjects with ventricular tachycardia AEs. I searched the Narrative directory and was able to find narratives for only 2 subjects with ventricular tachycardia AEs (Subject SP512OL/15303 and Subject SP709/10404). If you have submitted a narrative for the third subject with a ventricular tachycardia AE, please identify the location for that narrative. If you have not submitted a narrative, please do so.

You responded in a 12/4/06 email with the following:

This third narrative is for subject SP824/014812 (same as above). This narrative can be found in Submission Sequence 0019, Module 5352, under trial SP824, Section 12.2

After reviewing the narrative for subject SP824/014812, it seemed that the AE being described was tachycardia and not necessarily ventricular tachycardia. The identified event term in the heading for this narrative stated only tachycardia and there was no information in the body of the narrative to support that the AE being described was ventricular tachycardia.

In examining this issue further, I found in listing 3d.1 of the Cardiac arrhythmia analysis that you identified subject SP650/12003 as having a ventricular tachycardia AE. The submitted narrative for this subject provided information only about an atrial fibrillation AE.

We ask that you definitively identify the third subject with an AE of ventricular tachycardia. If subject SP824/014812 is indeed the third subject with ventricular tachycardia, please provide any available information to support this diagnosis. Please also explain why subject SP650/12003 is identified in listing 3d.1 as having an AE of ventricular tachycardia if this subject did not experience this event.

If subject SP650/12003 is the third subject with ventricular tachycardia then please provide a narrative with details of this event.

Thank you,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*  
*New email address: teresa.wheelous@fda.hhs.gov*

**Wheelous, Teresa A**

---

**From:** Betsy Waldheim [Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Monday, December 04, 2006 3:45 PM  
**To:** Wheelous, Teresa A  
**Subject:** Re: NDA 21-829 Rotigotine Safety Information Request

**Attachments:** SP666.doc; SP666\_1.doc; SP666\_2.doc; SP666\_3.doc; emfinfo.txt



SP666.doc (73 KB) SP666\_1.doc (73 KB) SP666\_2.doc (75 KB) SP666\_3.doc (73 KB) emfinfo.txt (775 B)

Teresa,

Following each of your comments below is my response. For the 4 narratives which the ECG data was missing we will submit a life-cycle submission to include this data. However in the mean time these narratives are attached to this email.

If you or the reviewer has any more questions please let me know.

Regards,  
Betsy

>>> "Wheelous, Teresa A" <teresa.wheelous@fda.hhs.gov> 12/04/06 9:55 AM >>>

\* PGP Decrypted Message

\* PGP Signed by an unverified key: 12/04/2006 at 03:48:38 PM

Betsy,

The following information is requested by the rotigotine safety reviewer:

Please provide the location of the narratives for the following subjects/adverse events.

For any of these narratives that have already been submitted please provide the exact location (submission, section, page number). For narratives that have not yet been submitted please provide a narrative for the identified event.

Subject SP515/102805 QT increased (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation). This event actually occurred when subject was in the open-label extension part of the trial (SP516). This narrative can be found in the Final Safety Update on page 4008 of 4339.

Subject SP650/0013905 Hepatic enzymes increased (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation). The narrative for this subject was included in the list of narratives in our Cardiac Arrhythmia narrative listing which can be found in Section 5353 of the Submission Sequence 00019. If you go to page 5 of 6 of the Cardiac Arrhythmia Narrative Directory you can find this subject number and it will link you to the narrative.

**Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Monday, December 04, 2006 9:56 AM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21-829 Rotigotine Safety Information Request

Betsy,

The following information is requested by the rotigotine safety reviewer:

Please provide the location of the narratives for the following subjects/adverse events.

For any of these narratives that have already been submitted please provide the exact location (submission, section, page number). For narratives that have not yet been submitted please provide a narrative for the identified event.

Subject SP515/102805 QT increased (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation).

Subject SP650/0013905 Hepatic enzymes increased (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation).

Subject SP511/000509 Bullous eruption (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation).

Subject SP824/014812 Tachycardia (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation).

Subject SP709/012207 Arrhythmia (identified in Final Safety Update listing 817.2.2 as an AE leading to discontinuation).

In the Cardiac arrhythmia analysis submitted as part of the Action Letter Response on 8/28/06, Table 1d.1.1c identifies 3 rotigotine subjects with ventricular tachycardia AEs. I searched the Narrative directory and was able to find narratives for only 2 subjects with ventricular tachycardia AEs (Subject SP512OL/15303 and Subject SP709/10404). If you have submitted a narrative for the third subject with a ventricular tachycardia AE, please identify the location for that narrative. If you have not submitted a narrative, please do so.

The narrative for subject SP666 indicated that a table of ECG results would be provided but no such table was included. Please provide a table of ECG results for this subject.

Thank you,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*

*Division of Neurology*  
*0903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*

Subject SP511/000509 Bullous eruption (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation). This AE was identified in the original Submission 0000. The narrative can be found in the original submission 0000, section 5354, under trial SP511, page 156 of 13108

Subject SP824/014812 Tachycardia (identified in Final Safety Update listing 717.2.2 as an AE leading to discontinuation). This narrative can be found in Submission Sequence 0019, Module 5352, under trial SP824, Section 12.2

Subject SP709/012207 Arrhythmia (identified in Final Safety Update listing 817.2.2 as an AE leading to discontinuation). Please note that this AE actually occurred in the open-label extension portion of the trial (SP710). This narrative can be found in the Cardiac Arrhythmia section of the response in section 5353. If you go to page 6 of 6 of the Cardiac Arrhythmia Narrative Directory you can find this subject number (Trial SP710) and it will link you to the narrative.

In the Cardiac arrhythmia analysis submitted as part of the Action Letter Response on 8/28/06, Table 1d.1.1c identifies 3 rotigotine subjects with ventricular tachycardia AEs. I searched the Narrative directory and was able to find narratives for only 2 subjects with ventricular tachycardia AEs (Subject SP512OL/15303 and Subject SP709/10404). If you have submitted a narrative for the third subject with a ventricular tachycardia AE, please identify the location for that narrative. If you have not submitted a narrative, please do so. This third narrative is for subject SP824/014812 (same as above). This narrative can be found in Submission Sequence 0019, Module 5352, under trial SP824, Section 12.2

The narrative for subject SP666 indicated that a table of ECG results would be provided but no such table was included. Please provide a table of ECG results for this subject. Narratives for 4 subjects in SP666 did not have the ECG table results attached. These complete narrative are provided in this email. We will submit a life-cycle to the NDA which will include the full narratives with ECG results.

Thank you,

*CDR Teresa Wheelous, R. Ph.*

*Sr. Regulatory Management Officer*

*FDA*

*Division of Neurology*

*10903 New Hampshire Avenue, Bldg. #22*

*Silver Spring, MD 20993-0002*

*(telephone) 301-796-1161*

*(fax) 301-796-9842*

New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)

\* FDA HHS GOV Secure Server (proxy) <[Teresa.Wheelous@fda.hhs.gov](mailto:Teresa.Wheelous@fda.hhs.gov)>

\* Issuer: FDA HHS GOV - Unverified

RECEIVED

NOV 14 2006

CDER White Oak DR1

**SCHWARZ**  
**PHARMA**

November 7, 2006

N-000-62

Russell Katz, M.D.  
Director  
Division of Neurology Products (HFD-120)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

DUPLICATE

ORIG AMENDMENT

RECEIVED

NOV 09 2006

CDER CDR

**RE: NDA 21-829 Neupro® (rotigotine transdermal system) (SPM 962)  
For the treatment of early stage Parkinson's disease  
Submission Sequence 0022**

**Amendment to Pending Application: Resubmission, Complete Response**

Dear Dr. Katz:

Reference is made to our New Drug Application 21-829 Neupro® (rotigotine transdermal system) for the treatment of early stage Parkinson's disease. Reference is also made to correspondence dated October 16, 2006 in which the Division notified Schwarz Biosciences of deficiencies in the laboratory data set filed October 02, 2006, submission sequence 0021. In addition, reference is also made to and FDA teleconference November 02, at which the Division and Schwarz agreed to the specifications of the new data set to be provided.

The purpose of this submission is to provide the requested revised data set as specified by the Division. As agreed in the November 02, 2006 teleconference with the Division, Schwarz has revised the laboratory data set according to the specifications listed below:

1. The qualitative laboratory parameters will be removed from the dataset.
2. Data from trial SP666 will be removed from the dataset.
3. Missing baseline parameters for Phase 1 trial SP503 will be included.
4. For missing baseline observations, the last value during the drug-free run-in period preceding trial medication exposure up to 7 days will be included as a baseline value in the dataset.
5. For the remaining missing baseline observations after applying the imputation rule # 4, values on the baseline day following trial medication exposure will be included as a baseline value in the dataset.
6. For the remaining missing baseline observations after applying the imputation rule # 5, the last value during the drug-free run-in period preceding trial medication exposure days occurring on day 8 or greater will be included as a baseline value in the dataset.

The data set has also been modified to add a field showing the relative date to drug exposure from which the baseline value has been obtained.

SCHWARZ BIOSCIENCES, Inc.

Mail P.O. Box 110167 · Research Triangle Park · NC 27709 · Via Courier 8010 Arco Corporate Drive · Suite 100 · Raleigh · NC 27617 · USA  
Phone +1 919 767 2555 · Toll Free +1 866 724 2467 · Fax +1 919 767 2570 · www.schwarzpharma.com

**SCHWARZ**  
**P H A R M A**

NDA 21-829  
November 7, 2006  
Page 2 of 2

This submission consists of 1 CD and is approximately 250 megabytes in size. All files were determined to be virus free using McAfee VirusScan Enterprise V 8.0.0, Virus Definitions 4889, Date 11/06/2006 and and F-Secure Anti-Virus 2006 6.12, Build 90, Virus Definition File 2006-11-07-07.

We look forward to working with the Division to facilitate the approval of Neupro<sup>®</sup> for the treatment of signs and symptoms of early-stage idiopathic Parkinson's disease. Should you have any questions regarding this submission, please contact me at (919) 767-2560 (phone) and (919) 767-3139 (fax) or in my absence David Dobrowski, Associate Director, Regulatory Affairs at (919) 767-3227.

Sincerely,



Betsy Waldheim  
Head, US Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430  
Expiration Date: April 30, 2009  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Schwarz Biosciences, Inc.

DATE OF SUBMISSION

11/07/2006

TELEPHONE NO. (Include Area Code)

919-767-2555

FACSIMILE (FAX) Number (Include Area Code)

919-767-3139

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

8010 Arco Corporate Drive      Mail:  
Suite 100                              P.O. Box 110167  
Raleigh, NC 27617                  Research Triangle Park  
North Carolina 27709

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Not applicable

RECEIVED

NOV 09 2006

CDER CDR

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 021-829

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)  
rotigotine

PROPRIETARY NAME (trade name) IF ANY  
Neupro®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

(6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol

CODE NAME (If any)

SPM 962

DOSAGE FORM:

patch

STRENGTHS:

2, 4, 6. — mg/24 hrs

ROUTE OF ADMINISTRATION:

transdermal

(PROPOSED) INDICATION(S) FOR USE:

For the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (CDA, 21 CFR 314.50)     ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)     505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug \_\_\_\_\_ Holder of Approved Application \_\_\_\_\_

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: \_\_\_\_\_

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

Resubmission of Data Sets, Complete Response

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 incl. 1 CD

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 47,852

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

**CERTIFICATION**

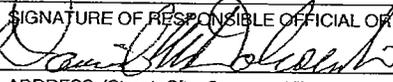
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Betsy J. Waldheim, Head, US Regulatory Affairs	DATE: 11/07/2006
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 110167, Research Triangle Park, NC 27709		Telephone Number ( 919 ) 767-2560

**Public reporting burden for this collection of information** is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448
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An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## Wheelous, Teresa A

---

**Subject:** NDA 21-829 Rotigotine internal meeting - Preparation for Telecon  
**Location:** CDER WO 4201 conf rm Bldg22

**Start:** Thu 11/2/2006 9:00 AM  
**End:** Thu 11/2/2006 9:30 AM

**Recurrence:** (none)

**Meeting Status:** Meeting organizer

**Required Attendees:** Wheelous, Teresa A; Katz, Russell G; Hughes, Alice; Feeney III, John J; Stone, Marc; Boehm, Gerard A; Siddiqui, Ohidul I; Jin, Kun

**Optional Attendees:** CDER 120 Calendar

**Resources:** CDER WO 4201 conf rm Bldg22

Internal meeting -

The meeting question is:

Does the Division concur with Schwarz' proposal to submit a new laboratory dataset with the BASEVAL values imputed according to the specifications listed below:

1. The qualitative laboratory parameters will be removed from the dataset.
2. Data from trial SP666 will be removed from the dataset.
3. Missing baseline parameters for Phase 1 trial SP503 will be included.
4. For missing baseline observations, the last value during the entire drug-free run-in period preceding trial medication exposure will be included as a baseline value in the dataset.
5. For the remaining missing baseline observations after applying the imputation rule # 4, values on the baseline day following trial medication exposure will be included as a baseline value in the dataset.

Regards,

David

David

Telecon at 9:30 AM

In response to the 2nd deficiency letter for NDA 21-829 (received Oct. 16) Schwarz has drafted a proposal for a revised Dataset (see attached). We would like the opportunity to have a short teleconference with the biostatistician(s) to ensure that our proposal fully meets the expectations of the reviewer(s). I believe we would need less than 30 minutes and we will only have a small number of people, likely myself and two biostatisticians present.



Incomplete  
response Letter #2.

David  
19-767-3227  
David.Dobrowski@schwarzbiosciences.com



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.  
Attention: Betsy Waldheim  
Head, U.S. Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

We acknowledge receipt on August 28, 2006 of your August 25, 2006, submission to your new drug application (NDA) for Neupro (rotigotine) 2mg/24 hr., 4 mg/24 hr., 6 mg/24hr., transdermal system.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our February 28, 2006, action letter and our September 24, 2006, incomplete response letter still need to be addressed:

**CLINICAL**

The deficiencies in the data set of laboratory values noted in our previous letter have not been completely rectified. The BASEVAL variable is still listed as missing in 173,970 observations. Although it is possible that for some of these observations there was no other laboratory value obtained for that subject that could be considered a baseline value, this does not appear to be the case for many of these observations. Specifically, we identified 63,334 observations where BASEVAL is given as missing even though a laboratory value was obtained from that subject in the week preceding the subject's entry into the trial.

We request that you make the necessary corrections to the data set, or explain why the values that appear to us to be baseline values are not included as baseline values in the data set. Please resubmit the data set of laboratory values correcting the deficiencies noted (or submit your explanation for the deficiencies noted). Once we have received your submission, we will be able to reconsider your response to the approvable letter for completeness. You do not need to resubmit the other portions of your response.

NDA 21-829

Page 2

If you have any questions regarding these comments, please call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Division Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

-----  
**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/

-----  
Russell Katz  
10/16/2006 08:32:36 AM

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, October 13, 2006 9:54 AM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21829 Neupro - Patient Information Comments from DSRCS

**Attachments:** PPI DRSCS Comments to Sponsor 101306.doc

Betsy,

The attached, is a copy of the Patient Information label comment for NDA 21829 Rotigotine:



PPI DRSCS  
Comments to Sponsor

We have the following comment:

Although voluntary, we recommend that you package the Patient Information leaflet containing instructions for use with the unit-of-use Neupro cartons for patient receipt. See a copy of the recommended Patient Information leaflet attached.

Regards,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*  
New email address: [teresa.wheelous@fda.hhs.gov](mailto:teresa.wheelous@fda.hhs.gov)

## Wheelous, Teresa A

---

**From:** Best, Jeanine A  
**Sent:** Thursday, October 12, 2006 10:40 AM  
**To:** Wheelous, Teresa A  
**Subject:** RE: Word copies of Neupro PPI Review

**Follow Up Flag:** Follow up  
**Due By:** Friday, October 13, 2006 12:00 AM  
**Flag Status:** Flagged

**Attachments:** neuproPPI0806clean2.doc; neuproPPI0806marked2.doc

Hi Teresa,

I found an error in the review. Please use these corrected review copies, especially for info to be shared with the sponsor. I inadvertently used the name of another product I was working on — under the section "General Information About Neupro".

Sorry,  
Jeanine



neuproPPI0806clean2.doc (2 MB)... neuproPPI0806marked2.doc (2 MB...)

*Jeanine Best, MSN, RN, PNP  
Patient Product Information Specialist  
FDA/CDER/OSE/DSRCS  
1903 New Hampshire Ave.  
Bldg 22/Room 4472  
Silver Spring, MD 20993-0002  
Phone: 301-796-0086  
Fax: 301-796-9835  
jeanine.best@fda.hhs.gov*

---

**From:** Wheelous, Teresa A  
**Sent:** Thursday, October 12, 2006 9:40 AM  
**To:** Best, Jeanine A  
**Subject:** RE: Word copies of Neupro PPI Review

Thanks Jeanine

-----Original Message-----

**From:** Best, Jeanine A  
**Sent:** Thursday, October 12, 2006 9:32 AM  
**To:** Wheelous, Teresa A  
**Subject:** Word copies of Neupro PPI Review

Hi Teresa,  
Attached are the Word copies of my Neupro PPI review.

Jeanine

<< File: neuproPPI0806clean.doc >> << File: neuproPPI0806marked.doc >>

*Jeanine Best, MSN, RN, PNP  
Patient Product Information Specialist  
FDA/CDER/OSE/DSRCS*

10903 New Hampshire Ave.  
Bldg 22/Room 4472  
Silver Spring, MD 20993-0002  
Phone: 301-796-0086  
Fax: 301-796-9835  
[jeanine.best@fda.hhs.gov](mailto:jeanine.best@fda.hhs.gov)

**SCHWARZ**  
**PHARMA**

October 02, 2006

Russell Katz, M.D.  
Director  
Division of Neurology Products (HFD-120)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

**RE: NDA 21-829 Neupro<sup>®</sup> (rotigotine transdermal system) (SPM 962)  
For the treatment of early stage Parkinson's disease  
Submission Sequence 0021**

**Amendment to Pending Application: Resubmission, Complete Response**

Dear Dr. Katz:

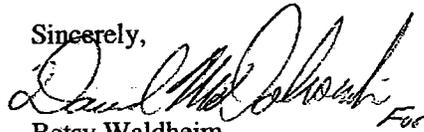
Reference is made to our New Drug Application 21-829 Neupro<sup>®</sup> (rotigotine transdermal system) for the treatment of early stage Parkinson's disease. Reference is also made to correspondence dated September 24, 2006 in which the Division notified Schwarz Biosciences of deficiencies in the response filed August 28, 2006.

The purpose of this submission is to provide a complete response to the deficiency letter. The submission contains the revised data set of laboratory values as requested by the Division.

This submission consists of 1 CD and is approximately 250 megabytes in size. All files were determined to be virus free using McAfee VirusScan Enterprise V 8.0.0, Virus Definitions 4861, Date 09/27/2006 and and F-Secure Anti-Virus 2006 6.12, Build 90, Virus Definition File updated September 28, 2006.

We look forward to working with the Division to facilitate the approval of Neupro<sup>®</sup> for the treatment of signs and symptoms of early-stage idiopathic Parkinson's disease. Should you have any questions regarding this submission, please contact me at (919) 767-2560 (phone) and (919) 767-3139 (fax) or in my absence David Dobrowski, Associate Director, Regulatory Affairs at (919) 767-3227.

Sincerely,



Betsy Waldheim  
Head, US Regulatory Affairs

SCHWARZ BIOSCIENCES, Inc.

Mail P.O. Box 110167 · Research Triangle Park · NC 27709 · Via Courier 8010 Arco Corporate Drive · Suite 100 · Raleigh · NC 27617 · USA  
Phone +1 919 767 2555 · Toll Free +1 866 724 2467 · Fax +1 919 767 2570 · www.schwarzpharma.com

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, September 29, 2006 3:10 PM  
**To:** 'David Dobrowski'  
**Subject:** RE: NDA 21-829 & IND 47,852

David,

The safety team agrees with this interpretation. We would consider forced titration trials to be fixed-dose even if back titration due to tolerability is allowed.

Teresa

-----Original Message-----

**From:** David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Thursday, September 28, 2006 11:46 AM  
**To:** Wheelous, Teresa A  
**Subject:** RE: NDA 21-829 & IND 47,852

Hello Teresa,

We have a question on the 1st bullet point in the Acknowledgment letter (08/24/06) describing the DOSEASN variable. We are seeking concurrence in interpretation of the Division's statement of clarification on the term "fixed-dose studies".

Schwarz has defined a fixed-dose trial as a trial without titration or with a forced titration. In addition, in both cases no adjustment of dose during maintenance was allowed based on either efficacy or tolerability.

The following trials have been conducted without titration: SP503, SP534 Part 1, SP629, and SP673 and are considered fixed-dose.

The following trials had a forced titration design: SP506, SP511, SP533, SP534 part 2, SP535, SP540, SP591, SP630, SP651, SP666, and SP709. In all these trials (except SP651, SP666, SP709) back titration based upon tolerability was allowed. All these trials are considered as fixed-dose trials based upon our interpretation of the clarification note in the Division's letter.

In all other trials, the rotigotine dose could be adjusted based on the clinical response to trial medication (ie. efficacy and/or tolerability). For example, in the Phase III trial SP512, subjects were assigned to only one dosage level of rotigotine (13.5mg/day), but the dose could be adjusted during the titration Phase. Thus, this trial is not considered a fixed-dose trial.

Is our interpretation of the Division's clarification of "fixed-dose" correct?

Best Regards,

David  
919-767-3227

>>> "Wheelous, Teresa A" <teresa.wheelous@fda.hhs.gov> 09/26/06 5:03 PM  
>>

PGP Decrypted Message

\* PGP Signed by an unverified key: 09/26/2006 at 10:58:30 PM

David,

Attached is our letter for NDA 21-829, and as for IND 47,852, we are working on a written response.

Teresa

-----Original Message-----

From: David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
Sent: Tuesday, September 26, 2006 3:30 PM  
To: Wheelous, Teresa A  
Subject: NDA 21-829 & IND 47,852

Hello Teresa,

Two small items I'm following up on.

The first is, should we expect to receive a letter classifying the complete response to the rotigotine NDA 21-829 soon?

The second is in regard to a proposed compulsive behavior CRF page submitted for review to IND 47,852 (Serial No. 510) on September 12th. Does the Division have any comments or intend to comment on the proposed CRF page?

Thanks and Best Regards,

David  
919-767-3227

\* FDA HHS GOV Secure Server (proxy) <Teresa.Wheelous@fda.hhs.gov>  
\* Issuer: FDA HHS GOV - Unverified



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.  
Attention: Betsy Waldheim  
Head, U.S. Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

We acknowledge receipt on August 28, 2006 of your August 25, 2006, submission to your new drug application (NDA) for Neupro (rotigotine) 2mg/24 hr., 4 mg/24 hr., 6 mg/24hr., — 24 hr transdermal system.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

**CLINICAL**

Our examination of the data set of laboratory values submitted as part of your response to the 28 February 2006 approvable letter did not fully address our stated requests and shows the following deficiencies that hinder our analysis of the requested laboratory data. These deficiencies render your response incomplete.

- The DOSEASN variable is incorrectly given a missing value for subjects in the fixed-dose SP506 study. The only studies that have subjects with non-missing values are SP503, SP534, and SP673. Please provide the missing values for subjects in Study SP506. Please also verify that there are no other fixed-dose studies that list missing values for this variable. As a point of clarification, any study that does not adjust the rotigotine dose according to a subject's clinical response, including studies that have only one dosage level for subjects assigned to rotigotine or assign subjects to a series of dosages, should be considered a fixed-dose study for these purposes.
- The DOSEREC variable is listed as missing for subjects assigned to rotigotine who had yet to receive the drug before the laboratory specimen was obtained; it should be listed as 0. This variable should be listed as a missing value only if the dose of rotigotine is unknown.
- The values for STARTDT and STARTROT variables do not match for subjects initially assigned to rotigotine. Our instructions stated that the STARTROT should be "[s]ame as STARTDT for subjects originally randomized to rotigotine." Please make the necessary corrections to the data set.

NDA 21-829

Page 2

- The BASEVAL variable is given as missing for all observations other than the baseline observations themselves. This value should be listed in *all* observations in order to facilitate comparison of each observed value with the baseline value.

Please resubmit the data set of laboratory values correcting the deficiencies noted above. Once this data set is submitted, we will be able to reconsider your response to the approvable letter for completeness. You do not need to resubmit the other portions of your response.

If you have any questions regarding these comments, please call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Division Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/

-----  
Russell Katz  
9/24/2006 12:38:40 PM

**Wheelous, Teresa A**

---

**From:** Betsy Waldheim [Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Monday, September 11, 2006 10:45 AM  
**To:** Wheelous, Teresa A  
**Subject:** NDA 21-829 Rotigotine

**Follow Up Flag:** Follow up  
**Flag Status:** Red

**Attachments:** compulsive behaviorsrev.doc; emfinfo.txt



compulsive behaviorsrev.doc (2..  
emfinfo.txt (775 B)

Dear Teresa,

At the End of Review meeting for rotigotine (April 13, 2006), one of the FDA participants commented that active surveillance for compulsive behaviors (e.g., gambling) for ongoing trials should be instituted. [See FDA meeting minutes on Question 2: Compulsive Behaviors]

We have developed the attached question in response to this request from the Division. This information will be collected at each clinic visit. We believe this would adequately track any further incidences of compulsive behavior. Can you tell me if the Division thinks this assessment is sufficient or if there are any additional suggestions.

Thank you.  
Betsy Waldheim

## Wheelous, Teresa A

---

**From:** Kapcala, Leonard P  
**Sent:** Wednesday, September 06, 2006 5:31 PM  
**To:** Wheelous, Teresa A  
**Subject:** FW: NDA 21-829: Rotigotine "Track Changes" version of label

**Follow Up Flag:** Follow up  
**Due By:** Saturday, September 09, 2006 12:00 AM  
**Flag Status:** Flagged

**Attachments:** Track changes label 092006.doc; emfalert.txt



Track changes label emfalert.txt (2 KB)  
092006.doc...

Hi Theresa,

I believe that you received this. I'd suggest send this tracked changes version of the label to all people involved with this.

Thanx.

Len

-----Original Message-----

**From:** David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Wednesday, September 06, 2006 10:52 AM  
**To:** Kapcala, Leonard P  
**Cc:** Wheelous, Teresa A  
**Subject:** NDA 21-829: Rotigotine "Track Changes" version of label

Dr. Kapcala,

Attached is a track changes version of the label. This version shows the changes to the label from the FDA version in the approvable letter (02/06) to the version submitted in the complete response by Schwarz (08/06, Submission # 0019).

Please let me know if you need any further information or have questions on the complete response.

Best Regards,

David  
919-767-3227

**Wheelous, Teresa A**

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Thursday, August 31, 2006 10:55 AM  
**To:** Wheelous, Teresa A  
**Subject:** NDA 21-829 Labeling WORD Versions

**Attachments:** annotated-package-insert-response.doc; patient-information-leaflet-peel.doc; patient-information-leaflet-tear.doc; draft-package-insert-response.doc; emfalert.txt



annotated-package-insert-response.doc   patient-information-leaflet-peel.doc   patient-information-leaflet-tear.doc   draft-package-insert-response.doc   emfalert.txt (2 KB)

-insert-respo...

leaflet-pe...

leaflet-te...

t-response....

Hello Teresa,

Attached are the WORD versions of the Annotated Label, Patient Information Leaflet for Pouches, Patient Information Leaflet for Pouches, and the Draft Package Insert. These Files will also be submitted to the eCTD.

Our plan is to send the 7 desk copies directly to you via FedEx to your address in Silver Spring. This will avoid any confusion going through the document room with an unofficial submission. Is this acceptable for you?

Best Regards,

David  
919-767-3227

**SCHWARZ**  
**PHARMA**

August 25, 2006

Russell Katz, M.D.  
Director  
Division of Neurology Products (HFD-120)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

**RE: NDA 21-829 Neupro<sup>®</sup> (rotigotine transdermal system) (SPM 962)  
For the treatment of early stage Parkinson's disease  
Submission Sequence 0019**

**Amendment to Pending Application: Complete Response to Action Letter**

Dear Dr. Katz:

Reference is made to our New Drug Application 21-829 Neupro<sup>®</sup> (rotigotine transdermal system) for the treatment of early stage Parkinson's disease. Reference is also made to correspondence dated February 28, 2006 in which the Division notified Schwarz Biosciences that the review of the above referenced application was complete and approvable.

The purpose of this submission is to provide a complete response to the approvable letter. Reference is made to an end-of-review telephone conference with the Division on April 13, 2006 in which clarity was sought on items in the approvable letter. Our complete response includes the agreements made during this conference call.

**Reviewer's Guide**

Our responses to each item in the approvable letter are provided by discipline as follows; CMC Responses (Module 1.11.1), Non-clinical Responses (Module 1.11.2), Clinical Responses (Module 1.11.3).

Per the agreement made during the end-of-review conference, Schwarz submitted on April 24, 2006, a justification supporting the validity of the Goettingen minipig study to assess the potential for rotigotine to induce preneoplastic changes. A copy of this submission is provided in Module 1.6.3.

Schwarz has proposed revisions to the package insert provided by FDA in the approvable letter. To justify our proposed revisions to the package insert, the following documents are provided in Module 5.3.5.3; \_\_\_\_\_ Labeling Justification Clinical, and Labeling Justification ClinPharm.

The original NDA contained labeling for a \_\_\_\_\_ mount carton for each of the \_\_\_\_\_ patch strengths. Labeling was also included for a \_\_\_\_\_ . These presentations have been deleted in this amendment as there is no longer marketing interest in these presentations.

SCHWARZ BIOSCIENCES, Inc.

Mail P.O. Box 110167 · Research Triangle Park · NC 27709 · Via Courier 8010 Arco Corporate Drive · Suite 100 · Raleigh · NC 27617 · USA  
Phone +1 919 767 2555 · Toll Free +1 866 724 2467 · Fax +1 919 767 2570 · www.schwarzpharma.com

C

3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

## Wheelous, Teresa A

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**From:** Wheelous, Teresa A  
**Sent:** Tuesday, April 18, 2006 11:33 AM  
**To:** 'Betsy Waldheim'  
**Subject:** FW: Explanation for Schwarz of NDA 21-829 rotigotine effects on hemoglobin

**Attachments:** rotighgb.xpt

Betsy,

The following is the info promised from the safety reviewer during our rotigotine telecon last week.

Teresa

---

**From:** Stone, Marc  
**Sent:** Monday, April 17, 2006 10:13 AM  
**To:** Wheelous, Teresa A  
**Cc:** Racoosin, Judith A  
**Subject:** Explanation for Schwarz of rotigotine effects on hemoglobin

Explanation for Schwarz of rotigotine effects on hemoglobin

### Mixed effects model



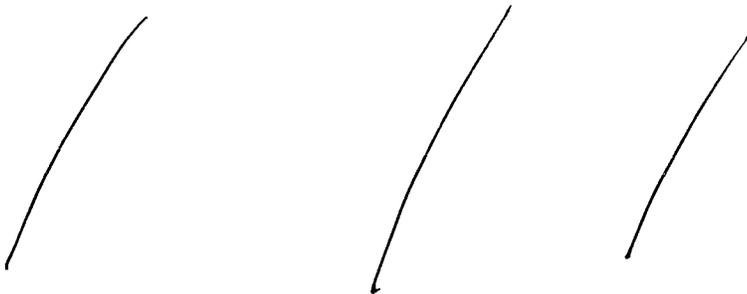
rotighgb.xpt (634  
KB)

I am attaching a SAS Transport file (rotighgb.xpt) that is a reduced version of the large laboratory dataset. This file contains only the blood hemoglobin measurements for subjects assigned to rotigotine or placebo, excludes hemoglobin measurements obtained before baseline and includes a smaller number of fields. Five additional fields were added:

**start** The date of collection for the subject's baseline specimen  
**time** Time in days between collection of this specimen and the baseline collection (calculated as  $\text{time} = \text{lbdtm} - \text{start}$ )  
**id** Unique subject identifier (usubjid) formatted as number  
**tri** Clinical Study (studyid) formatted as number  
**rti** Time on rotigotine (calculated as  $\text{rti} = \text{trtsafn} * \text{time}$ )

The mixed effects model compares the slopes of change in hemoglobin from baseline (lbbchgn) over time for rotigotine and placebo (rti and time) as the fixed effect and includes study (tri) and subject (id) as random effects with subject nested within study. Because change from baseline is, by definition, known to be zero at baseline, the model is calculated with a zero intercept.

The model was calculated using Stata SE 9.1 and gives this output



## MEMORANDUM OF TELECON MINUTES

**MEETING DATE:** April 13, 2006  
**TIME:** 8 AM – 9AM  
**APPLICATION:** NDA 21-829 ROTIGOTINE  
**TYPE OF MEETING:** End of Review  
**MEETING CHAIR:** Dr. Russell Katz

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Dr. Robert Temple – Office Director  
Dr. Russell Katz – Division Director  
Dr. Marc Walton – Deputy Division Director  
Dr. John Feeney – Group Leader  
Dr. Leonard Kapcala – Medical Reviewer  
Dr. Judith Racoosin – Safety Team Leader  
Dr. Gerald Boehm – Safety Reviewer  
Dr. Lois Freed – Pharmacology / Toxicology Team Leader  
Dr. Paul Roney – Pharmacology / Toxicology Reviewer  
Dr. Martha Heimann – CMCM

### SCHWARTZ BIOSCIENCES ATTENDEES AND TITLES:

Babak Borojjerdi, M.D., Clinical Program Medical Scientist  
David Dobrowski, Associate Director Regulatory Affairs  
Eric Foster, Sr. Director, International Project Management  
Irs Loew-Friedrich, Global Head Research and Development  
Steve Pollock, VP Regulatory Affairs  
Kenneth Sommerville, MD, VP Neurology  
Corinne vanDorp, Ph.D., Senior Scientist Pharmacology/Toxicology  
Susan Sisk, Medical Writer  
John Whitesides, Clinical Program Director  
HansMichael Wolff, Ph.D., Pharmaceutical Development  
Franz Woltering, Associate Senior Director, Biostatistics  
Betsy Waldheim, Head, US Regulatory Affairs

### BACKGROUND:

Schwarz BioSciences, Inc. requested a meeting/teleconference (end-of-review conference) with the Division of Neurology Drug Products to discuss the action letter, dated February 28, 2006. The purpose of this meeting is for Schwarz BioSciences, Inc. to discuss with the Division questions on the approvable letter issued by the Division and to gain clarity on further steps needed to obtain approval of our application.

**DISCUSSION QUESTIONS:**

**CLINICAL**

**Cardiac Arrhythmia**

- 1. With respect to the request for the reanalysis of cardiac arrhythmia related adverse events, it is our intent to recode (by blinded cardiologist) these events in all phase 2 and 3 trials to MedDRA. We propose to conduct this reanalysis on all double-blind, placebo (and active) controlled studies in (early and advanced) Parkinson's disease. Since the doses used in RLS studies are substantially lower than those used in our PD studies and the population healthier than in patients with Parkinson's disease, we do not intend to include data from RLS studies in this reanalysis. Is this acceptable?**

We agree with focusing on the phase 2/3 trials and including the double blind, placebo and active controlled trials. However, we are also interested in cardiac arrhythmia events occurring in the open label trials. Because these cardiac arrhythmia events occurred infrequently, we need as much information about them as possible, and that would include getting information about events occurring in open label.

Additionally, we believe cardiac arrhythmia events occurring in RLS trials (controlled and open label) should be included in the analysis as well. RLS patients are relatively healthy, and we would want an accurate picture of the risk of cardiac arrhythmia in this population because we would normally not be willing to tolerate a substantial toxicity (such as ventricular arrhythmia) for a symptomatic therapy in otherwise healthy patients.

ECG tracings should be available upon request.

The analysis of cardiac arrhythmia adverse events occurring in open label trials can be limited to those events that resulted in death or discontinuation or that met the regulatory definition for a serious adverse event.

**Compulsive Behavior**

- 2. We propose to conduct this analysis in the double-blind, placebo controlled studies for early and advanced Parkinson's studies. Is this acceptable?**

Part of your analysis should include a comparison of risk by treatment observed in the randomized controlled trials that you identify above. In addition, we ask that you provide an analysis that includes all compulsive behavior events in rotigotine subjects identified from all trials and in all indications. We expect that you will identify relatively few compulsive behavior events since patients were not asked about these behaviors during trials. Excluding certain indications from the analysis would decrease even further the opportunity to identify these events.

Active surveillance for compulsive behaviors (e.g., gambling) for ongoing trials should be instituted.

**Weight Gain**

3. **With respect to the request for an investigation of subjects who experienced increases in weight of more than 10% of baseline, we propose to perform this analysis in the double-blind, placebo-controlled studies for early and advanced Parkinson's studies as uncontrolled data would be difficult to interpret. Is this acceptable?**

No. Our request is for individual clinical assessments of all rotigotine-treated subjects who experienced substantial weight gain while taking the drug. This would be similar to what is done for subjects who die or experience other serious adverse events. Because these are individual assessments, the difficulty of interpretation should be the same whether or not the subject was in a controlled study.

Open label experience should also be included.

**Laboratory Abnormalities**

4. **Request #1, under lab abnormalities, is for individual patient profiles for all patients who had declines in hemoglobin and/or hematocrit. We believe the FDA is interested in reviewing the patients in Pool S1 (SP506, SP512, SP513) that experienced declines from baseline to study endpoint (end of double-blind maintenance/early termination). We will also present subsequent de-escalation data and open-label extension data for those patients (SP512 open-label, and SP513 open-label).**

**a) Does the FDA concur?**

We concur with focusing on patients in pool S1, including all their on-drug time. This would include placebo patients who took rotigotine in the open label extension.

**b) We intend to present this data in a table, is this acceptable?**

We would prefer that you present this data in graphical format. Each patient should have a plot that shows the changes in hemoglobin and hematocrit over time. It would also be helpful to include one plot that shows all patients' individual curves (color coded by treatment to distinguish placebo from rotigotine or active control).

If you want to submit the data in tabular form as well, that is acceptable.

**Additional Clarification**

Although this was not mentioned in your letter, we would like to clarify our Request #3 under Laboratory Abnormalities. The phrase "unblinded clinical studies" refers to any studies where the treatment assignment of subjects is known. This would include all open label studies as well as any studies that were originally blinded but have reached the point where the blinding is broken. In other words, we would like the laboratory data for all studies with the exception of any ongoing studies that are still in the double-blind phase.

The sponsor is requested to provide a graphical format (plot) for each individual patient as well as a group plot.

5. Request #2, under lab abnormalities, appears to be for the early Parkinson's disease pool SI (SP506, SP512 DB, SB 513 DB) and S6 (SP512 OL and SP513 OL). Please clarify if our interpretation is correct.

Yes, your interpretation is correct.

#### NONCLINICAL

6. FDA's Nonclinical Comment #3: In regard to the minipig studies, Schwarz worked very closely with the Division to gain agreement on the design of the transdermal minipig study protocol. We consider this study valid for many reasons. The agency rationale for the study was to detect histopathological changes in the skin, not detectable in clinical trials (IN 47,852, Serial No. 143). These are local changes in the skin, not related to the systemic effects of the drug substance or the drug product. The concentration of rotigotine in the patches is the same for all dose regimens. Therefore, local effects, (e.g., formation of preneoplastic skin lesions) would be related to the concentration of rotigotine in the skin only, not patch size. In the pig, only limited space is available for patch application. With patch administration to the same site every 8th day, eschar formation was observed in both the rotigotine patch-treated sites and placebo-treated sites. Due to the limited number of application sites, the administration of more than one patch to each side of the animals would have resulted in a higher frequency of application, which would have resulted in formation of edema and finally necrosis as already observed in the first pig study. The rotational application of 4.5mg (10 cm<sup>2</sup>) patches to pig skin is considered to be valid, as local toxicity in the form of eschar formation was observed. A full response will be provided in the response to the NDA approvable letter, however Schwarz feels that in working with the agency we fulfilled the objective of the intended trial. If the FDA wants additional information, Schwarz would be willing to discuss this as a Phase 4 commitment. Does the FDA concur with this proposal?

#### Discussion

The Division stated that it remains concerned about the potential for rotigotine to induce neoplastic changes at the application site. The Division noted that the Approvable letter stated that if the Sponsor could provide additional information to demonstrate that higher doses could not have been achieved, then the Division would consider this issue adequately addressed. If not, a repeat study would need to be conducted prior to approval.

The Sponsor stated that the Division had previously concurred with the protocol for the transdermal minipigs study in a communication on March 13, 2003, and asked if documentation could be provided to the Division by fax following the telecon. The Division agreed.

#### CMC

7. We plan to submit the following additional stability data:
  - (a) 2 lots packaged in the — pouch stored at 25°C for — (note: elated to date of manufacture, age of both batches will be —)

(b) lots (validation batches) packaged in the \_\_\_\_\_ pouch stored under accelerated conditions for \_\_\_\_\_, 30°C and 40°C)

(c) \_\_\_\_\_ packaged in the \_\_\_\_\_ pouch stored at 25°C for 24 months, i.e., in total 24 month stability data of \_\_\_\_\_ consecutive lots in the \_\_\_\_\_ pouch are available

Provided the data consistently meet specifications, Schwarz will request approved packaging to include both pouch systems with a 24 month expiration date for product stored in either the \_\_\_\_\_ and in the \_\_\_\_\_ pouch. Does the FDA concur with this position?

The Division stated that the primary concern at this point is the history of stability failures with regard to \_\_\_\_\_. The following points will be considered in establishing an expiration dating period for either pouch configuration:

- Long-term stability data for the \_\_\_\_\_ pouch are limited to \_\_\_\_\_ data on \_\_\_\_\_ lots manufactured using the proposed backing film and \_\_\_\_\_ process. In previous studies, significant changes in release strength were observed between the \_\_\_\_\_ and 24-month test points.
- Accelerated stability data do not appear to be a reliable predictor of long-term stability. A number of batches were within specified limits after \_\_\_\_\_ at accelerated conditions, but failed at 24 months in long-term studies.
- Due to the previous differences in product stability between the \_\_\_\_\_ pouch, different expiration dating periods may be assigned for each configuration.

The sponsor clarified that the \_\_\_\_\_ consecutive lots packaged in the \_\_\_\_\_ pouch for which 24 months of data will be available were manufactured with the to-be-marketed \_\_\_\_\_

The Sponsor was advised that updated labeling would be needed if approval of the \_\_\_\_\_ pouch is requested.

#### FINAL SAFETY UPDATE

8. Laboratory data and ECGs will be covered in depth in response to your requests as outlined in the above clinical section. In addition to including these analyses for all data in the original NDA submission, our analyses will also include new data with a cut-off date of October 31, 2005. Therefore, do you agree that it is sufficient to just provide adverse event data in the final safety update?

Yes we agree that it is sufficient to just provide adverse event data in the final safety update. We expect that your presentation of adverse event data includes separate discussions of deaths, serious adverse events, discontinuation for adverse events and common adverse event.

Narratives for RLS data and CRS for all treatment groups should be provided.

9. In reference to request #2, we assume that the request in the first bullet refers to a presentation of the new data for the period from our cut-off date of December 31, 2003 in the original NDA submission to our new cut-off date of October 31, 2005. We interpret the second bullet to be requesting the new data in bullet one be combined with all of the data from the original submission. Is our interpretation correct?

Yes, your interpretation is correct.

10. In reference to request #2, 4th bullet, we intend to present cumulative safety information for the other indications which include advanced Parkinson's disease and RLS. Is this acceptable?

Given the differences in the populations treated and the differences in rotigotine doses administered, we would expect separate presentations for the advanced Parkinson's disease data and the RLS data.

Phase 1 data should also be presented separately.

**ADDITIONAL DISCUSSION ITEMS**

- The sponsor would like to

\_\_\_\_\_

\_\_\_\_\_

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

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Russell Katz  
6/2/2006 11:58:47 AM

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  /   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

## Wheelous, Teresa A

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**From:** Betsy Waldheim [Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Thursday, March 16, 2006 3:41 PM  
**To:** Wheelous, Teresa A  
**Subject:** NDA 21-829 Rotigotine

**Attachments:** 16Mar06\_GCMR.pdf; emfalert.txt



Untitled Attachment 16Mar06\_GCMR.pdf; emfalert.txt (758 B)  
f (324 KB)

Dear Teresa,

Attached is a copy of the letter that is being sent to you by overnight courier. We are requesting a meeting/teleconference in order to obtain clarification on some of the points in the Feb. 28th approvable letter. We are committed to providing the FDA with exactly what is needed in order to gain approval.

Please let me know if you have any questions. We look forward to obtaining this clarification.

Many thanks,  
Betsy

**Wheelous, Teresa A**

---

**From:** Betsy Waldheim [Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Monday, March 06, 2006 7:21 AM  
**To:** Kapcala, Leonard P  
**Cc:** Wheelous, Teresa A  
**Subject:** Re: FW: NDA 21-829 Rotigotine

**Attachments:** emfalert.txt



Untitled Attachmentemfalert.txt (758 B)

Hi Dr. Kapcala,

Thank you very much for sending these tables. We will provide the information exactly as you want it.  
Have a great day!  
Betsy

>>> "Kapcala, Leonard P" <leonard.kapcala@fda.hhs.gov> 03/03/06 3:39 PM  
>>>

Hi Betsy,

Theresa asked me to forward the tables to you. Here they are. We are expecting that these specific tables will be filled with the respective data along with the data source tables that would be expected to be many, many pages for each of these single tables.

Please let us know if there are any questions about these.

Would you please confirm that you received them? Thanx.

Have a great weekend!

Best regards,

Len

301-796-1098

-----Original Message-----

**From:** Wheelous, Teresa A  
**Sent:** Friday, March 03, 2006 2:34 PM  
**To:** Kapcala, Leonard P  
**Subject:** FW: NDA 21-829 Rotigotine

Len,

Since I'm on leave, please send an electronic copy of the appended tables to Betsy.

thanks,

Teresa

-----Original Message-----

From: Betsy Waldheim [mailto:Betsy.Waldheim@schwarzbiosciences.com]  
Sent: Friday, March 03, 2006 1:26 PM  
To: Wheelous, Teresa A  
Subject: NDA 21-829 Rotigotine

Dear Teresa,

In the approvable letter for rotigotine under Item 3 in the section of Dose Response Analysis of Adverse Events in Study SP506, you offered an electronic copy of the tables that were appended to the letter. We would very much like to have this electronic copy. Many thanks!

Have a nice weekend.  
Betsy



**MEMORANDUM**

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

---

**DATE:** February 28, 2006

**TO:** Russell Katz, MD, Director  
Division of Neurology Drug Products

**THROUGH:** Claudia Karwoski, PharmD, Scientific Coordinator  
Office of Drug Safety

**FROM:** ODS Risk Minimization Action Plan Team  
Nancy Clark, PharmD., BCPP, Regulatory Project Manager, DSRCs  
Mary Dempsey, Project Management Officer, ODS-IO  
Cindy Kortepeter, Pharm.D., Safety Evaluator Team Leader, DDRE  
Charlene M. Flowers, R.Ph, Safety Evaluator, DDRE  
Alina R. Mahmud, R.Ph. Team Leader, DMETS

**DRUG:** Rotigotine Patch

**NDA #:** 21-829

**SPONSOR:** Schwartz Biosciences, Inc.

**SUBJECT:** Review of Proposed Risk Management Plan (RMP) submitted  
September 29, 2004 (date on document 09 Sep 2003)

**PID #:** D060120

The Office of Drug Safety (ODS) received a consult request to review the proposed Risk Management Plan (RMP) for the Rotigotine Patch, as submitted September 29, 2004 (date on document 09 Sep 2003). The Sponsor's RMP submission includes a summary of the risk assessment conducted during the preclinical and clinical development program. We conclude that their proposal does not appear to differ from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance but seems reasonable and appropriate since there were no significant safety issues identified during the clinical review that would warrant a Risk Minimization Action Plan (RiskMAP) or RMP.

Rotigotine is a dopamine agonist with a safety profile similar to that of other dopamine agonists used in the management of Parkinson's disease. If approved, rotigotine will be the first dopamine agonist marketed in a transdermal formulation. As such, application site reactions are the only adverse events unique to this non-ergot dopamine agonist as compared to other agents in this class. DDRE met with the Division of Neurology Products on January 18, 2006 for a Pre-approval Safety Conference (PSC) at which time there was discussion of other safety issues usually encountered with the other non-ergot dopamine agonists and noted that these issues will be addressed in labeling.

There is a separate premarketing consult completed by the ODS Division of Medication Errors and Technical Support (DMETS) that addresses concerns regarding dosing and administration instructions, dose titration, patch color and \_\_\_\_\_

The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. The measures proposed by the sponsor seem reasonable but would appear to be routine given the potential risk. A separate Patient Package Insert (PPI) consult was performed by the ODS Division of Surveillance, Research and Communication Support (DSRCS).

If the sponsor or the review division identifies a safety concern and determines that a Risk Minimization Action Plan (RiskMAP) is warranted or should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

ODS Risk Minimization Action Plan Team

Nancy Clark, PharmD., BCPP, Regulatory Project Manager, DSRCS

Mary Dempsey, Project Management Officer, ODS-IO

Cindy Kortepeter, Pharm.D., Safety Evaluator Team Leader, DDRE

Charlene M. Flowers, R.Ph, Safety Evaluator, DDRE

Alina R. Mahmud, R.Ph. Team Leader, DMETS

\_\_\_\_\_  
Claudia B. Karwoski, Pharm.D., Scientific Coordinator  
Office of Drug Safety, HFD-400

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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/

-----  
Mary Dempsey  
2/28/2006 01:43:55 PM  
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski  
2/28/2006 01:49:37 PM  
DRUG SAFETY OFFICE REVIEWER

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; WO 22, MAILSTOP 4447)**

<b>DATE RECEIVED:</b> February 2, 2006	<b>DESIRED COMPLETION DATE:</b> February 24, 2006	<b>ODS CONSULT #:</b> 05-0110-1
<b>DATE OF DOCUMENT:</b> September 15, 2005	<b>PDUFA DATE:</b> February 28, 2006	

**TO:** Russell Katz, MD  
Director Division of Neurology Products, HFD-120

**THROUGH:** Todd Bridges, RPh., Acting Team Leader  
Denise Toyer, PharmD., Deputy Director  
Carol Holquist, RPh., Director  
Division of Medication Errors and Technical Support, HFD-420

**FROM:** Linda M. Wisniewski, RN, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

<b>PRODUCT NAME:</b> Neupro (Rotigotine Transdermal System) 2 mg/24 hours 4 mg/24 hours 6 mg/24 hours	<b>NDA SPONSOR:</b> Schwarz Pharma
--	------------------------------------

**NDA#:** 21-829

**SAFETY EVALUATOR:** Linda M. Wisniewski, R.N.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Neupro. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Neupro, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
WO 22; Mailstop: 4447  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 7, 2006  
NDA#: 21-829  
NAME OF DRUG: Neupro  
(Rotigotine Transdermal System)  
2 mg/24 hours  
4 mg/24 hours  
6 mg/24 hours

NDA HOLDER: Schwarz Pharma

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neurology Products (HFD-120), for a re-review of the proprietary name, Neupro, regarding potential name confusion with other proprietary or established drug names. 'Neupro' was the subject of ODS Consult 03-0227, dated December 2, 2004. DMETS found the proprietary name 'Neupro' acceptable at that time. Container labels, carton and insert labeling were also provided for review and comment at this time.

PRODUCT INFORMATION

Neupro is a transdermal delivery system which contains rotigotine, a non-ergolinic dopamine agonist. Neupro is a thin, matrix-type transdermal system composed of three layers: backing film, drug matrix, and protective liner. Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease. 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 three or four weeks. Neupro is applied once daily. 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 application site should be rotated on a daily basis. Additionally, the system should be applied to the same application site more than once every 14 days. Neupro is supplied in the following strengths: 10 cm<sup>2</sup> to contain 4.5 mg, 20 cm<sup>2</sup> to contain 9 mg, 30 cm<sup>2</sup> to contain 13.5 mg,

\_\_\_\_\_ Packaging configurations include: \_\_\_\_\_

\_\_\_\_\_ cartons of 7, 30, \_\_\_\_\_ pouches each.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup>, as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Neupro to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Neupro. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Neupro, acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Neupro. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Names identified through Expert Panel as having the potential for confusion with Neupro.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other*
Neupro	(Rotigotine Transdermal System) 2 mg/24 hours 4 mg/24 hours 6 mg/24 hours	Apply one patch daily.	N/A
Lexapro	Escitalopram Oxalate Tablets: 5 mg, 10 mg, 20 mg Oral Solution: 5 mg/5 mL	10 mg to 20 mg once daily	LA
ReoPro	Abciximab for Injection 2 mg/mL	0.25 mg/kg intravenous bolus administered 10-60 minutes before the start of percutaneous coronary intervention, followed by a continuous intravenous infusion of 0.125 mcg/kg/minute for 12 hours.	LA
Nupro® T Prophylaxis Paste with Fluoride and Triclosan®	Sodium Fluoride Prophylaxis Paste 2%	After professional cleaning.	LA/SA
Neuprex	BPI protein (Recombinant rBPI-21)	No information available.	LA

\*Frequently used, not all-inclusive. \*\*L/A (look-alike), S/A (sound-alike).

<sup>1</sup> MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

## B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Neupro were discussed by the Expert Panel (EPD).

## C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Neupro, the primary concerns related to look-alike and sound-alike confusion with Lexapro, ReoPro, Nupro, and Neuprex. Neuprex, which received the orphan drug designation in 1998, is an investigational drug which currently has no product information available. Therefore, DMETS will not evaluate this name further. Additionally, as previously mentioned in ODS Consult 03-0227, DMETS would like to remind the sponsor of a veterinary product line marketed under the name "Nupro".

1. Lexapro may look similar to Neupro when written. Lexapro is indicated for the treatment of Major Depressive Disorder and Generalized Anxiety Disorder. Both names begin with letters that may look similar (Neu vs. Lexa) and end in the same three letters (pro). Although Lexapro has an upstroke for the initial letter "L" this may not be obvious, particularly if both the 'l' and the 'n' are scripted in lower case letters (see below). Although both products are administered once daily, there are product characteristics that may help to differentiate them when ordered. They include strength and dose (2 mg, 4 mg, 6 mg, — vs. 5 mg, 10 mg, and 20 mg), route of administration (transdermal vs. oral), and dosage form (transdermal system vs. tablet and oral solution). Despite the potential for some orthographic similarities, the dose and dosage form will help to differentiate these two products when ordered.

*Neupro*  
*Lexapro*

2. ReoPro may look similar to Neupro when scripted. ReoPro is indicated as adjunct treatment for the prevention of cardiac ischemia complications in percutaneous coronary intervention and in unstable angina with percutaneous coronary intervention within twenty-four hours. Both names begin with letters that may look similar when scripted (Neu vs. Reo) and end in the same three letters (pro). Although the formal presentation of the name ReoPro includes a capital 'P', it is possible that this name will be scripted using all lower case letters and result in similarities in the orthographic appearance of each name (see page 5). Despite the orthographic similarities, there are differentiating product characteristics that may help to minimize confusion involving these two names. They include dose (2 mg, 4 mg, 6 mg. — vs. 0.25 mg/kg to 0.125 mcg/kg), frequency of administration (daily vs. IV bolus followed by IV infusion over 12 hours), strength (2 mg, 4 mg, 6 mg. — vs. 2 mg/mL), route of administration (transdermal vs. intravenous), dosage form (transdermal system vs. injection), and location of use (inpatient or outpatient vs. coronary care unit and cardiac catheterization laboratory). Additionally, orders for ReoPro will likely include the route of administration on an order and a patient specific dose based on the patient's weight. Although the dose may overlap at 2 mg, ReoPro is indicated as adjunct treatment in percutaneous coronary intervention.

For this dose to overlap the patient would need to weigh 8 kg or 17.5 pounds. This weight would most likely indicate the patient was a child. Although it is possible that a child would be ordered this drug, it is unlikely. Additionally, ReoPro will not likely be dispensed directly to patients and will be administered in a controlled setting by appropriately trained personnel who are familiar with the product and its use. If the orthographic presentation of Neupro were to be misinterpreted as ReoPro, the additional information included would help to identify the correct product ordered and minimize confusion. Despite the potential for orthographic similarities, the product characteristics will help to minimize confusion involving this name pair.

*Reopro*  
*neupro*

3. Nupro-T Prophylaxis Paste with Fluoride and Triclosan may sound similar and look similar to Neupro when spoken or scripted. Nupro was approved as a dental device and used as dental prophylaxis paste applied to the teeth after professional dental cleaning. It is possible that a dental professional could refer to the product by its root name, 'Nupro'. Therefore, DMETS will evaluate the root name Nupro. Both names sound similar due to the similar pronunciation of the letters "Nu and Neu", where both contain a long 'u' sound, such as in the words Nubain or neutrophil. Additional phonetic similarities come from identical endings of each name (pro). The similar spellings also contribute to an overall similar orthographic appearance of each name. Although there are phonetic and orthographic similarities with these two names, there are product characteristics that may help to differentiate them when ordered. They include dose (2 mg, 4 mg, 6 mg, vs. appropriate amount), frequency of administration (daily vs. once), strength (2 mg, 4 mg, 6 mg, vs. 2%), route of administration (transdermal vs. applied to teeth), dosage form (transdermal system vs. prophylaxis paste), and user (patient vs. dental health care professional). Nupro is supplied and administered by the dental health professional after a professional cleaning. It would be unlikely that a patient would have a prescription or an inpatient order for it. Additionally, since Nupro-T is considered a dental device, it is unlikely that pharmacy practitioners would receive an order for it or be able to locate it through commonly used references, such as the Red Book. Conversely, it would be unlikely that the dental supply company or supply department of a hospital would receive an order for Neupro, a prescription drug product. Therefore, despite the orthographic and phonetic similarities, the product characteristics will help to differentiate these two products when written.

*Neupro*  
*Nupro*

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Neupro, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

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/s/

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Linda Wisniewski  
2/22/2006 10:48:03 AM  
DRUG SAFETY OFFICE REVIEWER

Todd Bridges  
2/22/2006 10:55:10 AM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
2/22/2006 04:15:26 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
2/22/2006 04:19:30 PM  
DRUG SAFETY OFFICE REVIEWER

## Wheelous, Teresa A

---

**From:** Roney, Paul L  
**Sent:** Friday, February 17, 2006 2:07 PM  
**To:** Wheelous, Teresa A  
**Subject:** Draft PT Rotigotine Review

**Attachments:** Rotigotine PT Review 1.doc

Hi Teresa,

Here is a draft review. Portions of the overall summary need to be written, but the overall PT issues are there.

Paul



Rotigotine PT  
Review 1.doc (9 ...

**Wheelous, Teresa A**

---

**From:** Betsy Waldheim [Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Friday, February 17, 2006 1:40 PM  
**To:** Goldie, Scott  
**Cc:** Wheelous, Teresa A  
**Subject:** Re: CMC Question - NDA 21-829

**Attachments:** emfinfo.txt



Untitled Attachmentemfinfo.txt (607 B)

Dear Scott,

Schwarz intends to market the — pouch packaging configuration and is the configuration we are seeking approval for.

Please let me know if you have any other questions.

Kind regards,  
Betsy

Betsy Waldheim  
Regulatory Affairs  
Schwarz Biosciences, Inc.

>>> "Goldie, Scott" <Scott.Goldie@fda.hhs.gov> 02/17/06 1:27 PM >>>

Ms. Waldheim:

It was good to speak with you today. With regard to the CMC section of your pending application with the FDA, the following point needs clarification:

With regard to your NDA 21-829 for Neupro(r) (rotigotine patch), please clarify whether you are seeking approval to market both the — pouch and — pouch packaging configurations.

The favor of a prompt reply is requested, with the upcoming due date of your application. This email request and your response will be added to the administrative file as a memorandum to the file. If you have any further questions that require immediate attention, please contact me at (301) 796-2055.

Thank you kindly,

Scott N. Goldie, Ph.D.

Regulatory Health Project Manager for Quality  
Division of Pre-Marketing Assessment I.  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, February 17, 2006 1:02 PM  
**To:** Katz, Russell G  
**Subject:** FW: Draft review of 21-829

**Attachments:** NDA 21-829.doc

-----Original Message-----

**From:** Claffey, David  
**Sent:** Wednesday, February 15, 2006 7:35 PM  
**To:** Wheelous, Teresa A  
**Subject:** Draft review of 21-829

Teresa:  
Here is the current draft of our review for NDA 21-829. We need to figure out the expiry period for the product in the next day or two, once that is done, I will send you a final draft.  
Thanks,



NDA 21-829.doc (2  
MB)

David.

## Wheelous, Teresa A

---

**From:** Freed, Lois M  
**Sent:** Friday, February 17, 2006 11:14 AM  
**To:** Wheelous, Teresa A  
**Cc:** Roney, Paul L  
**Subject:** rotigotine

**Attachments:** rotigotineN21829SponProposLabelEDR206 lf.doc

Hi, Teresa.

We spoke with Rusty and he asked that we send our labeling comments (that we have so far) to you so that you can insert it into the most recent version of labeling.

So, here it is.

Thanks,  
Lois



rotigotineN21829Sp  
onProposLabe...

## Wheelous, Teresa A

---

**From:** Katz, Russell G  
**Sent:** Friday, February 17, 2006 10:00 AM  
**To:** Wheelous, Teresa A  
**Subject:** rotigotine label

**Attachments:** rotigitinelabelRK.doc

Teresa-

Here's a version of the label. You can accept the changes, but there will be more during the day, as the pharm/tox and PK comments roll in.

Thanks, and sorry.



rotigitinelabelRK.doc  
c (176 KB)...

Rusty

## Wheelous, Teresa A

---

**From:** Claffey, David  
**Sent:** Wednesday, February 15, 2006 7:35 PM  
**To:** Wheelous, Teresa A  
**Subject:** Draft review of 21-829

**Attachments:** NDA 21-829.doc

Teresa:  
Here is the current draft of our review for NDA 21-829. We need to figure out the expiry period for the product in the next day or two, once that is done, I will send you a final draft.  
Thanks,



NDA 21-829.doc (2  
MB)

David.

## Wheelous, Teresa A

---

**From:** Best, Jeanine A  
**Sent:** Wednesday, February 15, 2006 7:21 AM  
**To:** Wheelous, Teresa A  
**Subject:** Neupro

**Attachments:** neuproIFU.doc; Neupro memo0206.doc

Teresa,  
Attached are the Word copies.(marked and clean).

Jeanine



neuproIFU.doc  
(144 KB)



Neupro  
memo0206.doc (135 K)

*Jeanine Best, MSN, RN, PNP  
Patient Product Information Specialist  
FDA/CDER/ODS/DSRCS  
White Oak/Bldg. 22/Room 4472  
Mail Stop 4447  
phone 301-796-0086  
fax 301-796-9836  
jeanine.best@fda.hhs.gov*

**MEMORANDUM**

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

**DATE:** February 14, 2006

**TO:** Russell Katz, MD, Director  
Division of Neurology Products

**VIA:** Teresa Wheelous, RPh  
Senior Regulatory Management Officer  
Division of Neurology Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Catherine Miller, MT (ASCP)  
Patient Product Information Specialists  
Division of Surveillance, Research, and Communication Support

**THROUGH:** Toni Piazza-Hepp, PharmD, Acting Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** DSRCs Review of Patient Information for Neupro (rotigotine transdermal system), NDA 21-829

**Background and Summary**

The sponsor submitted an NDA on January 19, 2005, for Neupro (rotigotine transdermal system), NDA 21-829. Patient Information titled Patient Information \_\_\_\_\_ was submitted as labeling with the application and revisions were submitted January 30, 2006. This \_\_\_\_\_ contains 1. The January 30, 2006 submission also included \_\_\_\_\_

We have revised and simplified the submitted Patient Information (see attached), \_\_\_\_\_

**Comments and Recommendations**

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

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/s/

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Jeanine Best  
2/14/2006 04:38:00 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
2/14/2006 04:54:02 PM  
DRUG SAFETY OFFICE REVIEWER

Executive CAC

Date of Meeting: January 31, 2006

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Joseph Contrera, Ph.D., OPS, Member  
Abby Jacobs, Ph.D., OND IO, Member  
Barry Rosloff, Ph.D., DPP, Alternate Member  
Lois Freed, Ph.D., DNP, Supervisor  
Paul Roney, Ph.D., DNP, Presenting Reviewer

Author of Draft: Paul Roney, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 21-829  
Drug Name: Rotigotine  
Sponsor Schwarz Pharma

### **Background Information**

#### **Mouse Carcinogenicity Study**

CD-1 mice were administered rotigotine subcutaneously at doses of 0 (saline), 0 (oily vehicle), 3, 10 or 30 mg/kg/48 hours for two years. There were no drug-related effects on survival rate (36, 30, 36, 38, 34% in males; 24, 42, 46, 28, 32% in females). Body weight tended to be lower in the 10- and 30-mg/kg groups (compared to vehicle controls), but was not significantly affected in either males (8-9% at the HD) or females (4-6% at the HD). Injection site findings included fluid-filled blisters, edema, and fibrosis, and were likely attributable to vehicle. No significant increase in tumor incidence was observed in either male or female mice.

#### **Rat Carcinogenicity Study**

Sprague-Dawley rats were administered rotigotine subcutaneously at doses of 0 (saline), 0 (oily vehicle), 0.3, 1 or 3 mg/kg/48 hours for two years. There were no drug-related effects on survival rate (70, 78, 74, 72, and 80% in males; 46, 50, 56, 64, and 56% in females). Dose-related decreases in body weight (compared to vehicle controls) were observed in both males (8-17% at the HD) and females (7-9% at the HD). Injection site findings included fluid-filled blisters, edema, and fibrosis, and were likely attributable to vehicle. In males, a statistically and biologically significant increase was observed in the incidence of testicular Leydig cell adenomas at all dose levels. In females, a statistically and biologically significant increase in uterine tumors (adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma) was observed in the mid and high dose

groups, and the increased incidence in the low dose group was also considered biologically significant because of its rarity in historical controls. No significant increase in any other tumors was observed in either male or female rats.

**Executive CAC Recommendations and Conclusions:**

Mouse:

The Committee concluded that the mouse study was an adequate evaluation of the carcinogenic potential of rotigotine and that it was negative for drug-related neoplasms.

Rat:

The Committee concluded that the rat study was an adequate evaluation of the carcinogenic potential of rotigotine and that it was positive for drug-related neoplasms:

(a) testicular Leydig cell adenomas were increased in male rats at all doses. The Committee considered this finding to be of questionable clinical significance because the endocrine mechanisms believed to be involved in the production of Leydig cell hyperplasia and adenomas in rats are not relevant to humans.

(b) uterine tumors (adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma) were increased in female rats at all doses.

The Committee noted that plasma exposures (AUC) at the LD and MD were lower or similar to that expected in humans at proposed therapeutic doses.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\n  
/Division File, DNP  
/LFreed, DNP  
/PRoney, DNP  
/TWheelous, DNP  
/ASeifried, OND IO

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/s/

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David Jacobson-Kram  
2/3/2006 10:04:05 AM

## Wheelous, Teresa A

---

**From:** Wheelous, Teresa A  
**Sent:** Monday, January 23, 2006 1:38 PM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21-829 Rotigotine Safety Question 1/23/06

Betsy,

The following is a question from the safety reviewer for NDA 21-829 Rotigotine:

Please identify any events in rotigotine treated subjects that represent compulsive gambling, compulsive eating, hypersexuality or any other compulsive behaviour. For any such events please provide the rotigotine subject number, the number of the study where the event was identified, the preferred term to which the event was coded, and a brief description of the event.

Thank you,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Regulatory Management Officer*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-2250*  
*(fax) 301-796-9842*

## Wheelous, Teresa A

---

**From:** Kapcala, Leonard P  
**Sent:** Monday, January 23, 2006 10:43 AM  
**To:** Katz, Russell G; Feeney III, John J; Racoosin, Judith A; Boehm, Gerard A; Stone, Marc; Kavanagh, Ronald E; Siddiqui, Ohidul I; Jin, Kun; Roney, Paul L; Freed, Lois M  
**Cc:** Wheelous, Teresa A  
**Subject:** FW: NDA 21-829; CHMP Assessment



Untitled Attachment CHMP Assesment emfalert.txt (613 B)  
report.doc (1 M...

Gang,

FYI.  
Here is an attached EMEA positive opinion doc and comments that was sent to me from the sponsor.

Len

-----Original Message-----

**From:** David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Monday, January 23, 2006 8:18 AM  
**To:** Kapcala, Leonard P  
**Subject:** NDA 21-829; CHMP Assessment

. Kapcala,

Please find the attached EMEA positive opinion and comments. since issuance of the opinion we have not made an official submission other than revised packaging.

## Wheelous, Teresa A

---

**From:** Kapcala, Leonard P  
**Sent:** Friday, January 20, 2006 4:23 PM  
**To:** Wheelous, Teresa A  
**Subject:** FW: NDA 21-829 ; Labeling

**Follow Up Flag:** Follow up  
**Due By:** Monday, January 30, 2006 12:00 AM  
**Flag Status:** Flagged

**Attachments:** neutro PIL text only.doc; draft-package-insert.doc; emfalert.txt



Untitled Attachment neutro PIL text draft-package-inseremfalert.txt (613 B)  
only.doc (109 ... t.doc (234 ...

HI Theresa,

FYI. David sent these WORD docs of the proposed label and the patient info leaflet. I've asked him to submit these to the EDR officially. The docs in the EDR are PDF format.

I told David : "As I understand what you sent, the patient information leaflet has only text and does not have the graphics of the PDF doc in the EDR but that the WORD doc is identical to the PDF in the EDR. Is this correct?" I'm awaiting a response.

Len

-----Original Message-----

**From:** David Dobrowski [mailto:David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Friday, January 20, 2006 3:21 PM  
**To:** Kapcala, Leonard P  
**Subject:** NDA 21-829 ; Labeling

Dr. Kapcala,

Attached is the WORD text version of the patient information leaflet and package insert.

Also, please note that myself and most of US Regulatory here at Schwarz will be out of the office Monday - Wens. (Jan. 23 - 26) at an off site meeting. I will not be able to access Secure email. I will be able to access un-encrypted email and will be limited in our availability via phone.

Have a nice weekend.

Best Regards,

David  
919-767-3227

6

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## Wheelous, Teresa A

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**Subject:** NDA 21-829 Rotigotine Safety Meeting  
**Location:** CDER White Oak 4270 Conference Room 4th Floor

**Start:** Wed 1/18/2006 9:00 AM  
**End:** Wed 1/18/2006 10:00 AM

**Recurrence:** (none)

**Meeting Status:** Meeting organizer

**Required Attendees:** Wheelous, Teresa A; Katz, Russell G; Feeney III, John J; Racoosin, Judith A; Stone, Marc; Heimann, Martha R; Broadbent, Thomas A; Roney, Paul L; Kapcala, Leonard P; Temple, Robert; Siddiqui, Ohidul I; Kavanagh, Ronald E; Currier, Carolanne; Flowers, Charlene M; Freed, Lois M; Baweja, Raman K; Kavanagh, Ronald E; Currier, Carolanne; Birdsong, Sandra; Kortepeter, Cindy

**Optional Attendees:** Uppoor, Ramana S; Jin, Kun; Yasuda, Sally

**Resources:** CDER White Oak 4270 Conference Room 4th Floor

Due Date - Feb. 28, 2005

H

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## Memorandum of Communication/Telephone Conversation

NDA # 21-829  
Date: 05 January 2006  
Product Name: neupro (rotigotine transdermal system)  
Sponsor: Schwarz BioSciences  
Subject: Product stability data and stability commitments  
Conversation with: Betsy Waldheim  
Telephone #: (919) 767-2560

I called Betsy Waldheim of Schwarz Biosciences (12/28/05) and requested additional stability data as missing from eCTD sections 3.2.P.8.3.1 through 3.2.P.8.3.8. I also requested complete stability commitments as required by 21 CFR 314.81.

Ms. Waldheim sent the requested information by e-mail (1/4/2006). The formal eCTD submission will follow. The information has been forwarded to DPA1 management for review.

### Text of message:

Dear Tom,

Attached is the file containing the updated stability data for rotigotine. The eCTD lifecycle submission will follow.

Please let me know if you have any other requests or questions.

Thank you!  
Betsy Waldheim

---

Thomas A. Broadbent, Ph.D.  
Review Chemist  
FDA / CDER / ONDQA / DPA1

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/s/

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Thomas Broadbent  
1/5/2006 03:34:21 PM  
CHEMIST

**Wheelous, Teresa A**

---

**From:** Boehm, Gerard A  
**Sent:** Tuesday, January 17, 2006 11:43 AM  
**To:** Wheelous, Teresa A  
**Subject:** Rotigotine slides

**Attachments:** JR edits JB rotig slides.ppt



JR edits JB rotig  
slides.ppt (...)

Hi Teresa,

Judy asked me to email the attached slides to you for tomorrow's rotigotine meeting.

Thanks,

Jerry

## Wheelous, Teresa A

---

**From:** David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
**Sent:** Thursday, December 22, 2005 4:00 PM  
**To:** Wheelous, Teresa A  
**Cc:** Waldheim, Betsy  
**Subject:** NDA 21-829 Adverse Event Response

**Attachments:** fda-response-22dec2005-tbl.pdf; emfalert.txt



Untitled Attachment fda-response-22dec2005-tbl.pdf (687 B)  
c2005-tbl.pdf...

Teresa,

The attached PDF file is the requested Adverse Event dose-response analysis, per the email request to B. Waldheim on 12/20. The data are from Pool S1 and the analysis is limited to AEs occurring in at least 5% of subjects. This submission will be sent to the division today as an electronic life cycle submission to the NDA as submission sequence 0014.

Best Regards,

David Dobrowski  
US Regulatory Affairs  
Schwarz Biosciences  
919-767-3227

David Dobrowski  
US Regulatory Affairs  
Schwarz Biosciences  
301-767-3227

## **Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Tuesday, December 20, 2005 10:14 AM  
**To:** 'Betsy Waldheim'  
**Subject:** NDA 21-829 Rotigotine Adverse Event dose response Analysis Request - 12/20/05

Betsy,

The following is a safety information request:

We request an additional adverse event dose-response analysis. Using data for pool S1 studies, we would like you to calculate adverse event incidence by dose.

### Numerator- Adverse events by dose

For the numerator of the incidence calculation we ask that you classify the AEs by dose using the same methodology that you used previously (assign AE to dose the subject was taking at the time of the event). The analysis can be limited to AEs occurring in at least 5% of subjects.

### Denominator- Person time for each dose

For the denominator of the incidence calculation we ask that you allot each subject's rotigotine exposure time into the appropriate dose categories. For example, a rotigotine subject with 75 days in a study might have been exposed to 4.5mg for 10 days, 9mg for 10 days, 13.5 mg for 30 days and 18 mg for 25 days. Each subject's time would be attributed to the appropriate dose category. After allotting each subject's time to the appropriate dose categories, sum the time in each dose category to arrive at the total duration for each dose.

### Incidence calculation

For the incidence calculation, we ask that you divide the number of AEs at a given dose by the total time for that dose.

Thank you,

*CDR Teresa Wheelous, R. Ph.  
Sr. Regulatory Management Officer  
FDA  
Division of Neurology  
10903 New Hampshire Avenue, Bldg. #22  
Silver Spring, MD 20993-0002  
(telephone) 301-796-2250  
(fax) 301-796-9842*

## Wheelous, Teresa A

---

**From:** Boehm, Gerard A  
**Sent:** Tuesday, December 20, 2005 7:38 AM  
**To:** Wheelous, Teresa A  
**Subject:** Rotigotine question



Rotigotine adverse  
event dose ...

Teresa,

Please forward the attached question about rotigotine to the appropriate people at Schwarz.

Thanks

Jerry

## Wheelous, Teresa A

---

**From:** Betsy Waldheim [Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Thursday, December 15, 2005 4:48 PM  
**To:** Wheelous, Teresa A  
**Subject:** RE: NDA 21829 Rotigotine Info Request



Untitled Attachment malignancy-tables emfalert.bt (758 B)  
Final.pdf (1...

Dear Teresa,

Attached is the requested information on treatment emergent malignancies from the rotigotine development program. We will be providing this to you as an eCTD life-cycle submission as well.

Let me know if you or the reviewer have any questions.

Regards,  
Betsy Waldheim

>>> "Wheelous, Teresa A" <WHEELLOUST@cdcr.fda.gov> 12/6/2005 3:24:15 PM

>>>

Thank you

-----Original Message-----

**From:** Betsy Waldheim [mailto:Betsy.Waldheim@schwarzbiosciences.com]  
**Sent:** Tuesday, December 06, 2005 3:14 PM  
**To:** Wheelous, Teresa A  
**Subject:** Re: NDA 21829 Rotigotine Info Request

Dear Teresa,

are working on this and as soon as I have an idea as to timing for submitting the response I'll let you know.

Thanks,  
Betsy

MEMORANDUM

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

---

CLINICAL INSPECTION SUMMARY

DATE: 11/1/05

TO: Teresa Wheelous, Regulatory Project Manager  
Leonard Kapcala, M.D., Clinical Reviewer  
Division of Neurology Products, HFD-120

THROUGH: Ni A. Khin, M.D.  
Branch Chief  
Good Clinical Practice Branch 1, HFD-46  
Division of Scientific Investigations

FROM: Carolanne Currier, CSO  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-829

APPLICANT: Schwarz Biosciences, Inc.

DRUG: Neupro® (rotigotine transdermal system)

CHEMICAL CLASSIFICATION: 1

THERAPEUTIC CLASSIFICATION: S

INDICATION: Treatment for early Parkinson's Disease

CONSULTATION REQUEST DATE: 4/22/05

PDUFA GOAL DATE: 2/28/06

I. BACKGROUND:

Schwarz Biosciences, Inc., submitted NDA 21-829, Neupro® (rotigotine transdermal system) for early-stage idiopathic Parkinson's disease to FDA for marketing approval. Two protocols (SP506 and SP512 [part 1]) were identified as pivotal to the application.

SP506 was a multi-center, randomized, double-blind, placebo controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of escalating transdermal doses of rotigotine (SPM 962) in subjects with early-stage Parkinson's disease. The dose-ranging study was conducted over 12-weeks. There was a 28-day screening period which included a 4 to 7 day open-label run-in using placebo. Subjects were randomized to receive 1 of 4 target doses (4.5, 9.0, 13.5, or 18.0mg) during a 28-day titration period, followed by a 49-day maintenance period, a 7-day run-out (de-escalation) period, and a 2-week safety follow-up period. The primary outcome variable was efficacy of rotigotine as measured by a change in the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II + III score from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77).

SP512, Part 1 was a multi-center, multinational, phase III, randomized, double-blind, placebo controlled trial of the efficacy and safety of the rotigotine patch in subjects with early-stage idiopathic Parkinson's disease. This trial was a 2-arm parallel group trial. Subjects were required to be diagnosed with idiopathic Parkinson's Disease  $\leq 5$  years, have a UPDRS at baseline  $\geq 10$ , a Hoehn and Yahr stage  $\leq III$ , a Mini Mental State Examinations (MMSE)  $\geq 25$ , and at least 2 motor or postural signs of Parkinson's. Subject received doses of 4.5, 9.0, or 13.5mg/day for 175 days, following a 4-week screening period and a 30-day titration phase. A de-escalation phase of up to 4 days was followed by a 4 week safety follow-up period. The primary efficacy variable was the change in the sum of scores from the ADL and the Motor Examination sections in the UPDRS (parts II + III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase.

DSI issued 5 domestic inspection assignments to verify the data for these two protocols. The inspection results are summarized in the following table, and detailed in the RESULTS section below:

Name (site)	City, State	Protocol	Insp. Date	Letter Issued	Class.	Data Acceptable?
Mayank Pathak, M.D.	Fountain Valley, CA	SP506	7/5-7/05	---	Pending EIR	Yes*
Paul Tuite, M.D.	Minneapolis, MN	SP506	7/5-15/05	9/30/05	VAI	Yes**
John Murphy, M.D.	Danbury, CT	SP512	7/6-13/05	8/9/05	VAI	Yes**
Paul Nauseida, M.D.	Milwaukee, WI	SP512	6/28-7/6/05	8/16/05	NAI	Yes
Ray Watts/Marian Evatt	Atlanta, GA	SP512	7/11-15/05	8/16/05	NAI	Yes

\* Pending final review of EIR. \*\* Possible exception of a few subjects – see below.

## II. RESULTS (by protocol/site):

### Protocol 506

#### 1. Mayank Pathak, M.D. – Data acceptable pending final review of EIR.

- a. What was inspected: Dr. Pathak screen 23 subjects and randomized 16. The source documents, CRFs, and all study-related records for all 16 subjects were reviewed during the inspection. In addition records for 6 non-randomized subjects were reviewed.



- a. Subject 7104 had a baseline QTc interval of 364. The visit 2 QTc interval was 427 (+63 msec). The \_\_\_\_\_ printout reported a normal ECG with no withdrawal criteria met.
- b. Subject 7109 had a baseline QTc interval of 355. The visit 2 interval was 427 (+72 msec). The first \_\_\_\_\_ printout indicated the ECG was normal with no withdrawal criteria met. A second report of the ECG dated the same day and time (although it was not a copy) was available in the file with the same QTc interval of 427 msec. This 2<sup>nd</sup> version indicated that withdrawal criteria were met. Subject 7109 also had reports of QTc intervals of 428 and 429 taken 7 minutes apart on 7/12/00 (visit 6). Both reports from \_\_\_\_\_ indicated that the protocol withdrawal criteria were met.

The above two subjects continued in the study despite having the out-of-range QTc interval increase over baseline. It is unclear whether the initials indicating review of the ECG reports are those of Dr. Tuite. It was not until after the study was completed (2/22/01), that the CRO \_\_\_\_\_ discovered the protocol violations and submitted data clarification forms reiterating that withdrawal criteria had been met. None of the subjects had repeat ECGs an hour later or were withdrawn per protocol. In addition, none of the deviations were reported to the sponsor; they did not show up on the line listings of protocol deviations obtained from the sponsor for inspection background material. We recommend that the data for these two subjects be reviewed for any safety impact on the study. With the possible exception of these two subjects, the data appear acceptable.

#### Protocol SP512

#### 3. John Murphy, M.D. – Data Acceptable

- a. What was inspected: Dr. Murphy screened 12 subjects at his site. There were no screen fails and no dropouts; all 12 subjects completed the study. Study records for all subjects were reviewed for inclusion/exclusion criteria, randomization, concomitant medication use, protocol adherence, accuracy of data transcription from ECGs and lab reports, AE reporting, IRB and sponsor correspondence, and drug accountability. Primary efficacy endpoints (change in UPDRS from baseline to end of study) were compared to data listings provided by the sponsor.
- b. Limitations of the inspection: None
- c. General observations/commentary: All UPDRS scores were entered directly onto CRFs. The CRF data was identical to that provided in line listing by the sponsor. There was no evidence of under-reporting of AEs. There were some protocol deviations. Twenty-one visits for 9 subjects occurred from 18 days early to 42

days late outside the study visit window (see appendix for details). In addition 3 subjects (12802, 12805, and 12811) were started or restarted on CNS-active drugs (sertraline and clonazepam) during the trial (protocol required a 28-day stable dosing of CNS active drugs). Also, subject 12811 had been taking Sinemet for a 7-month period prior to study entry (protocol had a 6-month limit).

4. Paul Nausieda, M.D. – Data acceptable

- a. What was inspected: Dr. Nausieda enrolled 12 subjects; 8 were randomized to rotigotine, 4 to placebo. Study records for all subjects were reviewed for inclusion/exclusion criteria, randomization, concomitant medication use, protocol adherence, accuracy of data transcription from ECGs and lab reports, AE reporting, IRB and sponsor correspondence, and drug accountability. Primary efficacy endpoints (change in UPDRS from baseline to end of study) were compared to data listings provided by the sponsor.
- b. Limitations of the inspection: None
- c. General observations/commentary: Two subjects (#15611 and #15612) were withdrawn early due to SAEs; one for anxiety and one for symptomatic hypotension. All subjects signed informed consents prior to study entry. All primary efficacy endpoint data (UPDRS scores) recorded on CRFs were compared to a data listing provided by the sponsor and found to be identical. Source documents were compared to CRFs for 5 subjects. A few very minor discrepancies were found during the record review. One subject was entered into the study even though he had received Sinemet for 6 months and 2 days at some point prior to the study (the protocol stated anyone who had received carbidopa/levidopa for longer than 6 months was not eligible). In addition, the study coordinator had mistakenly coded the timing of BP readings as protocol deviations, when in fact they were taken correctly. In general, the data appear acceptable.

5. Ray Watts, M.D./Marian Evatt, M.D.

- a. What was inspected: The inspection assignment identified Dr. Ray Watts and the original investigator for the study, and Dr. Alan Freeman as his successor. The inspection revealed that Dr. Marian L. Evatt was the current principal investigator. Dr. Watts had screened 19 study subjects. Two subjects failed screen and 17 were randomized and completed the study. Study records for 14 subjects were reviewed for inclusion/exclusion criteria, randomization, concomitant medication use, protocol adherence, accuracy of data transcription from ECGs and lab reports, AE reporting, IRB and sponsor correspondence, and drug accountability.
- b. Limitations of the inspection: None

- c. General observations/commentary: Primary efficacy endpoints (change in UPDRS from baseline to end of study) were compared to data listings provided by the sponsor and found to be identical. All subjects signed informed consents prior to study entry. All AEs were reported appropriately. A few minor problems were found during the record review; 2 subjects were exempted from PK sampling by the sponsor because of poor venous access; 2 subjects had one study visit outside the protocol time frame (+1 day); and 2 subjects took prohibited medications (subject 14702 took lorazepam one time for a job interview, and subject 14709 was on Wellbutrin for the entire study. Both instances were approved in writing by the sponsor and reported to FDA as protocol deviations.) From the records reviewed, the data appear acceptable.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

With the possible exception of subjects 7104 and 7109 at Dr. Tuite's site for the SP506 study, and the 4 subjects at Dr. Murphy's site for the SP512 study, it appears the subjects whose records were reviewed at the 5 sites were eligible for the studies. Efficacy data from all studies appear to have been reported accurately. The Review Division Medical Officer should note the unreported adverse events from Dr. Tuite's file for the SP506 study.

After final review of the EIR for the Pathak SP506 study, if there are any significant changes from the above evaluation, a revised summary will be forwarded immediately.

With the above exceptions, the remaining data at the 5 sites could be used to support an approval decision for the NDA.

*{See appended electronic signature page}*

Carolanne Currier, CSO  
Good Clinical Practice Branch I

#### CONCURRENCE:

Supervisory comments

*{See appended electronic signature page}*

Ni A. Khin, M.D.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

DISTRIBUTION:

NDA 21-829

HFD-170/ (through DFS)

HFD-45/Division File / Reading File

HFD-45/Program Management Staff

HFD-46/Khin/Currier

HFD-46/GCPB1 File#s 11596, 19681, 11580, 11608, (Pathak number TBD upon receipt)

o:\cac\2005\Rotigotine.PDUFA.N21829.CIS.doc

cac:11/1/05

## APPENDIX

The following chart illustrates the scheduling deficiencies that occurred at Dr. Murphy's site for Study SP512. Visit 2 was to occur 4 weeks after visit 1; the remaining visits were supposed to be scheduled in relation to visit 5. Visits 5 through 11 had a two-week scheduling window.

Subject #	Visit #	Study Day Visit Supposed to Occur	Study Day Visit Occurred	Number of Days Early or Late (outside the protocol window)
12808	2	28 days after visit 1	70 days after visit 1	42 late*
12810	2	28 days after visit 1	35 days after visit 1	7 late
12801	10	134-148 days after visit 5	154 days after visit 5	6 late
12801	11	162-176 days after visit 5	184 days after visit 5	8 late
12803	9	106-120 days after visit 5	104 days after visit 5	2 early
12808	9	106-120 days after visit 5	105 days after visit 5	1 early
12808	11	162-176 days after visit 5	147 days after visit 5	15 early
12809	7	50-64 days after visit 5	67 days after visit 5	3 late
12810	9	106-120 days after visit 5	102 days after visit 5	4 early
12810	10	134-148 days after visit 5	123 days after visit 5	11 early
12810	11	162-176 days after visit 5	144 days after visit 5	18 early
12811	7	50-64 days after visit 5	48 days after visit 5	2 early
12811	8	78-92 days after visit 5	74 days after visit 5	4 early
12811	9	106-120 days after visit 5	95 days after visit 5	11 early
12811	10	134-148 days after visit 5	123 days after visit 5	12 early
12811	11	162-176 days after visit 5	145 days after visit 5	17 early
12812	7	50-64 days after visit 5	48 days after visit 5	2 early
12812	8	78-92 days after visit 5	74 days after visit 5	4 early
12812	9	106-120 days after visit 5	101 days after visit 5	5 early
12812	10	134-148 days after visit 5	125 days after visit 5	9 early
12812	11	162-176 days after visit 5	151 days after visit 5	11 early

\*Due to subject hospitalization. Subject entered study without re-screening; records indicate nothing had changed since original screening.

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

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Carolanne Currier  
11/1/2005 01:09:53 PM  
MANGMNT ANALYST

Ni Aye Khin  
11/1/2005 05:54:22 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.  
Attention: Betsy Waldheim  
Head, US Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

Please refer to your January 19, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro (rotigotine) 2, 4, 6, — mg/24hrs Transdermal Patches.

On September 14, 2005, we received your September 13, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 28, 2006.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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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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Russell Katz  
10/3/2005 12:36:39 PM

## **Nighswander, Robbin M**

---

**Subject:** Telecon with Schwarz  
**Location:** CDER WOC2 3FL-D Conf Room  
**Start:** Wed 9/7/2005 10:00 AM  
**End:** Wed 9/7/2005 11:00 AM  
**Recurrence:** (none)  
**Meeting Status:** Meeting organizer  
**Required Attendees:** Nighswander, Robbin M; Katz, Russell G; Racoosin, Judith A; Boehm, Gerard A  
**Resources:** CDER WOC2 3FL-D Conf Room

Telecon with Schwarz to discuss narratives for rotigotine:

They will call in at 10:15 am

Call-in # 1 877-915-0980 and passcode: 358641

## Nighswander, Robbin M

---

From: David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
Sent: Tuesday, September 06, 2005 4:33 PM  
To: Robbin Nighswander FDA  
Subject: Teleconference attendees



Untitled Attachmentemfalert.txt (658 B)

Hello Robbin,

I received the phone number for the telecon tomorrow at 10:15am. To save a little time tomorrow with introductions, below is a tentative list of participants from our side which I can send you a final list after meeting if there are any changes.

David Dobrowski - Assoc Director, US Regulatory Affairs  
Betsy Waldheim - Head, US Regulatory Affairs  
Eric Föster - Sr. Director, International Project Management  
Steven Neilson - Clinical Trial Manager, Parkinson's Disease  
Rolf Horstmann, MD., Senior Director, Clinical Pharmacology  
Kenneth Sommerville, MD, Vice President Clinical Development, Neurology  
Mike Litzinger, Statistician

Best Regards,

David  
919-767-3227

## Nighswander, Robbin M

---

From: David Dobrowski [David.Dobrowski@schwarzbiosciences.com]  
Sent: Friday, September 02, 2005 8:45 AM  
To: Robbin Nighswander FDA  
Subject: RE: NDA 21-829, safety reviewer comments #4



Untitled Attachmentfalert.txt (658 B)

Good Morning Robbin,

The email request for information we received yesterday included the request for narratives for "all adverse events leading to discontinuation, please submit them at this time." We are identifying the events and would propose to submit all adverse events leading to discontinuation which meet the following criteria:

- Phase II and Phase III trials (double blind and open label)
- Rotigotine treated subjects
- early parkinsons trial subjects (no RLS or Advanced trial subjects)

Please call me if this is not acceptable to the safety reviewer.

Thanks and Best Regards,

David Dobrowski  
919-767-3227

## Nighswander, Robbin M

---

**From:** Nighswander, Robbin M  
**Sent:** Thursday, September 01, 2005 1:27 PM  
**To:** 'David.Dobrowski@Schwarzbiosciences.com'  
**Subject:** Rotigotine Questions #4

David:

My email appears to be working again as I did not get an error message this morning when I sent an earlier email "Questions #3". Please let me know if you received that email and this one.

"During our review of the rotigotine NDA and Safety Update we have been unable to locate many narratives for subjects who withdrew for adverse events. Upon further review we found that in the Summary of clinical safety under section 2.7.4.2.2.2 you state that you provide narratives for subjects who discontinued from trials SP534 Part I, SP534 Part II, and SP535.

Did you submit narratives for all adverse events leading to discontinuation or only the studies identified above?

If you have submitted narratives for all adverse events leading to discontinuation, please identify their location within the submissions.

If you have not submitted narratives for all adverse events leading to discontinuation, please submit them at this time.

In our review of the Safety Update, we discovered an apparent discrepancy between tables 53.1 and 54.1.2. Table 53.1 presents the frequencies for adverse events leading to discontinuation. Table 54.1.2 is a listing of subjects who experienced the adverse events leading to discontinuation. Table 54.1.2 includes more and different events than does table 53.1. For example, Table 53.1 identifies under the Application Site disorder Body system only two events: Application site reaction, and Dermatitis contact. Table 54.1.2 includes patients with the following AEs under the Application site Body system: Application site edema, Application site reaction, and Dermatitis contact. There are additional such discrepancies between these two tables. Please explain why there are more and different adverse events leading to discontinuation in the listing table 54.1.2 compared to 53.1."

Please call if you have questions.

Thanks

Robbin Nighswander  
Supervisory Regulatory Project Manager  
Division of Neurology Products  
(301) 594-5531

FOOD AND DRUG ADMINISTRATION  
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
5600 FISHERS LANE [HFD-120]  
ROCKVILLE, MARYLAND 20857  
FAX: [301] 594-2858-/594-2859  
COVER SHEET

NOTE: THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone at [301]-594-2850 or return it to us at the above address by mail, Attention [HFD-120]. Thank you in advance.

DATE: 8/30/05

TIME: 4<sup>15</sup> pm

PLEASE DELIVER THE FOLLOWING PAGES TO:

David P. Branski Schwartz Pharma

FAX NUMBER: (919) 767-2570

FROM: Robbin Nykswander

Total number of pages, including cover page (2)

If you do not receive all pages or have any problems with receiving, call [301]594-2850.

MESSAGE: Questions - as discussed on phone,

Thanks

## Rotigotine Questions 2

Subject 513 Part II 105610/805609 had an SAE of ventricular arrhythmia. The narrative provided no final diagnosis and limited information about treatment. Please provide additional information about this case including the final diagnosis and any additional test results or treatments.

In the Safety Update (p.29), you reported that for the early stage Parkinson's disease controlled and open label trials (pool S3), adverse event was the most common reason for discontinuation (15%, 159/1093). In the same submission, in the adverse event section (p.62) you report that 16% (173/1093) of rotigotine subjects discontinued for AEs. Please explain this apparent discrepancy.

Please provide treatment duration (mean and standard deviation), daily dose (mean and standard deviation), maximum daily dose (mean and standard deviation), and dose of longest duration (mean and standard deviation) for pools P11, P12, AS1, and RLS. Please include data accrued through the 120-Day Safety Update.

Please provide person-years exposure for all treatment groups (rotigotine, placebo, and active comparator) for each pool (S1-S6, P11, P12, AS1, and RLS) through the 120-Day Safety Update.



**FILING COMMUNICATION**

NDA 21-829

Schwarz BioSciences, Inc.  
Attention: Betsy Waldheim  
Head, U.S. Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

Please refer to your January 19, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (rotigotine) transdermal 2, 4, 6, — mg/24 hours.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on March 28, 2005, in accordance with 21 CFR 314.101(a).

At this time, we request that you submit the following information:

As you know, fibrosis and fibrotic complications have been associated with the use of dopaminergic agonists in Parkinson's disease. Please examine your safety databases for all subjects and across all indications (early and advanced Parkinson's disease, RLS, etc.) for any cases of fibrotic or potentially fibrotic complications associated with the use of rotigotine. Several important adverse event (AE) search terms include: pulmonary fibrosis, pleural fibrosis, interstitial lung disease, alveolitis, alveolitis fibrosing, pleurisy, pleural effusion, retroperitoneal fibrosis, peritoneal fibrosis, mediastinal fibrosis, retroperitonitis, mitral valve incompetence, mitral valve stenosis, mitral valve disease, tricuspid valve incompetence, tricuspid valve disease, aortic valve stenosis, aortic valve incompetence, aortic valve disease, valvular heart disease; valvulopathy, pericarditis, pericardial effusion, and related terms. At a minimum, these are AE search terms and related terms that we recommend should be used. Retroperitoneal fibrosis could potentially present as hydropnephrosis and renal obstruction due to ureteral obstruction from the retroperitoneal fibrosis. Thus, you can see how the phenomenon of fibrosis could occur but might not be clearly captured as such because only hydropnephrosis/renal obstruction may have been coded as the key AE terms. Consequently, we recommend that you devise a comprehensive search strategy and use additional, potentially relevant AE terms associated with fibrosis or fibrotic complications in order to assemble a comprehensive list of search terms.

Your comprehensive analysis should include : 1) a presentation of narratives of possible cases of fibrosis or fibrotic complications from your safety databases, and a discussion of the evidence

that the cases may have been caused or exacerbated by rotigotine exposure; 2) summary tables (based upon the time of onset of fibrosis or fibrotic complication) of these cases in your safety databases presented according to treatment in placebo-controlled (e.g. any rotigotine exposure vs placebo; and rotigotine by dose vs placebo) and open-label experience (e.g. any rotigotine exposure and rotigotine by dose) as 3 different datasets (1- cases with a reasonable likelihood that fibrosis or fibrotic complications have been caused or exacerbated by rotigotine exposure, 2- cases without a reasonable likelihood that fibrosis or fibrotic complications have been caused or exacerbated by rotigotine exposure, 3- a comprehensive dataset including the previous 2 datasets), individual subject listings and discussion of the summary table data; 3) analysis of the concomitant use of other drugs that enhance dopaminergic tone and that were associated with your cases and discussion; and 4) a presentation and discussion of all possible cases of fibrosis or fibrotic complications associated with rotigotine exposure from published reports irrespective of whether the cases are included in your safety databases (please indicate when a published cases is included in your safety database).

Please also provide an executive summary of these analyses and your conclusion(s) about the possibility of whether fibrosis or fibrotic complications may be caused or exacerbated by rotigotine exposure and propose language for this adverse reaction in the label.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301)594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

-----  
Russell Katz  
6/8/05 02:22:18 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation I**

**FACSIMILE TRANSMITTAL SHEET**

DATE: June 15, 2005

<b>To:</b> Betsy Waldheim	Teresa Wheelous
<b>Company:</b> Schwartz	<b>From:</b> Division of Division of Neuropharmacological Drug Products
<b>Fax number:</b> fax 919-767-2570	Phone number: (301) 594-2850
<b>Phone number:</b> 919-767-2560	Phone number: (301) 594-2850
<b>Subject:</b> NDA 21-829 STAT INFO REQUEST	
<b>Total no. of pages including cover:</b> 3	

Betsy,

I send you an email earlier this week which requested some statistical information. Just in case you did not receive that email I am faxing the same info request to you.

Please provide Tables 1 & 2 (see following pages) and the SAS codes for these two tables.

Thanks,

Teresa

**Document to be mailed:**  YES  NO

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 594-2850. Thank you.

Table 1: Observed Cases ANCOVA Results for Change from Baseline to End of Maintenance Phase for UPDRS Subtotal (Part II+III)- ITT Population

Day/ Treatment Group	Study#SP512 (Part 1)					Study# SP513 (Part 1)					
	N	Least Square Means	SE	Diff .from Placebo	p-value (Vs. Placebo)	Treatment Group	N	Least Square Means	SE	Diff. from Placebo	p-value (Vs. Placebo)
Day 29 MP*						Day 29 MP*					
Placebo				--	--	Placebo				--	--
Rotigotine						Rotigotine					
						Ropinirole					
Day 57 MP*						Day 57 MP*					
Placebo						Placebo					
Rotigotine						Rotigotine					
						Ropinirole					
Day 85 MP*						Day 85 MP*					
Placebo						Placebo					
Rotigotine						Rotigotine					
						Ropinirole					
Day 113 MP*						Day 113 MP*					
Placebo						Placebo					
Rotigotine						Rotigotine					
						Ropinirole					
Day 141 MP*						Day 141 MP*					
Placebo						Placebo					
Rotigotine						Rotigotine					
						Ropinirole					
End of MP*						End of MP*					
Placebo						Placebo					
Rotigotine						Rotigotine					
						Ropinirole					

\*MP=Maintenance Period.

Table 2: LOCF ANCOVA Results for the Secondary efficacy measures- ITT Population.

Study / Secondary measures	Treatment	Least Squares			
		Mean	SE	Difference from placebo	P-value
<b>Study#SP512 (Part 1)</b>					
UPDRS Part II only (activities of daily living): Change from baseline	Placebo				
	Rotigotine				
UPDRS Part III only (motor examination): Change from baseline	Placebo				
	Rotigotine				
<b>Study#SP513 (Part 1)</b>					
UPDRS Part II only (activities of daily living): Change from baseline	Placebo				
	Rotigotine				
	Ropinirole				
UPDRS Part III only (motor examination): Change from baseline	Placebo				
	Rotigotine				
	Ropinirole				

Use ANCOVA with adjustment terms for geographic region of investigational center and baseline score in both tables.

Please send the SASCODES and the data sets (SAS exportable files), so that the FDA reviewer will be able to reproduce both tables.



NDA 21-829

INFORMATION REQUEST LETTER

Schwarz BioSciences, Inc.  
Attention: Betsy Waldheim  
Head, US Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

Please refer to your 19 January 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for neupro (rotigotine transdermal system) 2, 4, 6 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Questions, comments and requests regarding rotigotine drug substance:

1. Reporting of the process validation of rotigotine production is incomplete. Please provide the release test data and any available stability data for the consecutive commercial production scale batches of rotigotine for process validation and evaluation.
2. Potential contamination of the drug substance with \_\_\_\_\_ has not been investigated. These are of concern because of their potential genotoxicity. Please test the process validation batches for the presence of \_\_\_\_\_ and \_\_\_\_\_. Please include a description of the test method and an assessment of its sensitivity with the report of results.
3. \_\_\_\_\_ has not been qualified as a drug substance impurity. We recommend that the acceptance criterion for \_\_\_\_\_ be expressed as a limit of \_\_\_\_\_ NMT \_\_\_\_\_.
4. The modifications of \_\_\_\_\_ in testing rotigotine have not been justified. Please justify the modification of these methods, the reduction of recommended sample sizes in particular.
5. Data from the current stability protocol is of limited applicability to the current drug substance manufacturing process. Please update the report for the current stability protocol, the data for batch WE12799, in particular.
6. The retest period for rotigotine drug substance is not clear. Section S.7.1 proposes a retest period of \_\_\_\_\_. Your communication of May 10, 2005 implies that the retest period is \_\_\_\_\_. Please clarify the proposed retest period.

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

John Simmons, Ph.D.  
Division Director  
Division of New Drug Chemistry DNDC I  
Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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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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Martha Heimann  
5/26/05 09:27:00 AM  
Signed for Dr. John E. Simmons.

3-16-05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.  
Attention: Betsy Waldheim  
Head, U.S. Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our November 24, 2004 refusal to file letter for the following:

- Name of Drug Product: (rotigotine) transdermal system
- Review Priority Classification: Standard (S)
- Date of Application: January 19, 2005
- Date of Receipt: January 28, 2005
- Our Reference Number: NDA 21-829

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 29, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **November 28, 2005**.

Under 21 CFR 314.102(c) of the new drug regulations you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. However, since this disease is not found in pediatric patients we are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug Products  
Attention: Division Document Room, 4008  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug Products, HFD-120  
Attention: Document Room 4008  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301)594-5504.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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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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Russell Katz  
3/16/05 09:16:44 AM

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** December 17, 2003

**TIME:** 1:30 PM – 3:30 PM

**LOCATION:** WOC II Conference Room E

**APPLICATION:** IND 47,852 Rotigotine CDS

**TYPE OF MEETING:** Pre-NDA Meeting

**MEETING CHAIR:** Dr. Russell Katz

**MEETING RECORDER:** Teresa Wheelous

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name</u>	<u>Title</u>	<u>Division &amp; HFD</u>
Dr. R. Katz	Division Director	HFD-120
Dr. J. Feeney	Group Leader	HFD-120
Dr. L. Kapcala	Medical Reviewer	HFD-120
Dr. S. Yan	Biometrics Reviewer	HFD-710
Dr. R. Kavanagh	Clinical Pharmacology / Biopharmaceutics Reviewer	HFD-860
Dr. L. Freed	Pharmacology Team Leader	HFD-120
Dr. P. Roney	Pharmacology Reviewer	HFD-120
Dr. J. Racoosin	Safety Team Leader	HFD-120
Dr. M. Heimann	CMC Reviewer	HFD-810
Teresa Wheelous	Project Manager	HFD-120

### SCHWARZ PHARMA ATTENDEES

<u>Name</u>	<u>Title</u>
F. Owen Fields, Ph.D.	Director, US Regulatory Affairs
Harold Jordan, Ph.D.	Head of Regulatory Affairs
Silvia Riffle Friedrich	Assoc. Director, European Reg. Affairs
Susanne Heinig, Ph.D.	Assoc. Director, CMC Regulatory Affairs
Kenneth Sommerville, M.D.	V.P., Clinical Development
Babak Boroojerdi, M.D.	Medical Scientist, Clinical Development
Kate Poole	Director, Clinical Development
Dieter Scheller, Ph.D.	Scientific Director, Preclinical Development
Corinne van Dorp	Sr. Scientist, Preclinical Development
Klaus Hansen, Ph.D.	Sr. Scientist Pharmacokinetics, ADME
Marina Braun, M.D.	Sr. Scientist, Clinical Pharmacology
Franz Woltering	Sr. Assoc. Director, Biostatistics
Patrick Liu, Ph.D.	Director, Biostatistics
Eric B. Foster, M.S.	Associate Director, Reg. Affairs
Betsy Waldheim	Director, Regulatory Affairs

**BACKGROUND:**

The October 15, 2003 meeting request submitted by Schwarz Pharma, Inc. was received October 17, 2003, and the meeting was granted on October 24, 2003. The pre-NDA meeting package dated November 13, 2003, was received on November 14, 2003. The questions listed in the meeting package and the Division's responses to each question follow.

**MEETING OBJECTIVES:**

To gain the Division's input on all of the issues and questions presented for discussion in the treatment of early-stage, idiopathic Parkinson's disease.

**QUESTIONS:****FDA comments on overall plan for the NDA**

Schwarz intends to submit an NDA for the rotigotine transdermal system; the original NDA will seek an efficacy claim for early-stage idiopathic Parkinson's disease.

The original NDA will seek approval for 4.5, 9.0, 13.5, — mg rotigotine transdermal systems. The original NDA will be supported by an overall clinical safety database which is estimated as follows:

- In total, approximately 1,844 subjects will have been exposed to rotigotine by the time of the original NDA clinical safety data cut-off (December 31, 2003); 1021 of these will be early PD patients
- Approximately 121 subjects will have been exposed to (18 mg) for at least a year; all of these will be early PD patients.
- Approximately 136 subjects will have been exposed to the 13.5 mg dose for a year; all of these will be early PD patients.
- Approximately 362 and 196 subjects will have been exposed to the 18 mg and 13.5 mg doses for 6 months, respectively; 272 and 196 of these will be early PD patients.

It is currently estimated that by the time of the four-month safety update clinical data cut-off (approximately July, 2004) approximately 2007 subjects will have been exposed to any dose of rotigotine and 261 subjects will have been exposed to (18 mg) of rotigotine for at least a year (all of these will be early PD patients).

Exposure data should also be presented showing a breakdown by gender, dose, and duration of treatment (e.g. # males exposed for a certain time at a certain dose; # females exposed for a certain time at a certain dose).

**1. Does FDA concur with these overall application plans?**

- The proposed exposure is acceptable. DNDP emphasizes that data from early PD patients treated with the transdermal, silicone rotigotine patch should be presented separately and not included with any analyses of data derived from advanced PD patients, any other subjects, or different formulations of rotigotine.

**Analysis of Trial SP512**

A statistical analysis plan for Trial SP512 has been provided, as has a brief summary of the preliminary results of the trial.

**2. Does FDA suggest that any supplemental analyses of Trial SP512 be included in the original NDA?**

- Six month data including last observation carried forward should be provided.
- Analyses of efficacy data of completers at 3 months are requested.
- Analyses of the primary and secondary efficacy parameters specified by the protocol should be included. Other supplemental analyses are not necessary.

**Analysis of Trial SP513**

A statistical analysis plan for study SP513 has been provided, as has a brief summary of the preliminary results of the study.

**3. Does FDA suggest that any supplemental analyses of Trial SP513 be included in the original NDA?**

- The analyses provided should show efficacy results over time.
- Analyses of efficacy data of completers at 3 months are requested.
- Analyses of the primary and secondary efficacy parameters specified by the protocol should be included. Other supplemental analyses are not necessary.

**Analysis plan and database for Integrated Summary of Efficacy (ISE)**

A statistical analysis plan to support the Integrated Analysis of Efficacy (ISE) has been provided in this information package.

**4. Does FDA concur with the approach proposed for pooling? Does FDA suggest any additional/alternative analyses be included in this analysis plan?**

- Except for efficacy results displayed by demographic characteristics, DNDP is not interested in pooled efficacy analyses.
- The main subgroup analyses of interest to DNDP are gender, age, and race. The age breakdown of major interest to DNDP is < 65 years old and  $\geq$  65 years old.

**Analysis plan and database for Integrated Summary of Safety (ISS)**

A statistical analysis plan to support the Integrated Analysis of safety (ISS) has been provided in this information package.

**5. Does FDA concur with the approach proposed for pooling? Does FDA suggest any additional/alternative analyses be included in this analysis plan?**

- Analyses of safety data should be analyzed and presented separately for pivotal, placebo-controlled studies and for open-label studies. DNDP is not interested in combined analyses of safety experience observed in large, placebo-controlled and open-label studies.
- DNDP is interested in the following pooled groups for the ISS analyses :
  - All phase 2b/3 randomized, double-blind, placebo-controlled studies (506, 512, 513) with the transdermal silicone rotigotine patch
  - All open-label experience of early Parkinson's disease patients treated with the transdermal silicone rotigotine patch and all patients treated in studies 534 (parts I and II), 535, and 540 with the transdermal silicone rotigotine patch
- The sponsor proposes to present safety data without consideration of dose. However, additional analysis based on dose are desired and requested for all pivotal studies (506, 512, and 513). Study 506, a randomized, fixed-dose study, may be most helpful in determining dose related adverse events. In addition, data from studies (512,513) in which patients were titrated to an "optimal" rotigotine dose should also be shown according to dose (focusing on the dose at the specific time of safety data collection).
- SAE narratives should be grouped together and contain hyperlinks. A table of contents for all SAE narratives should include pt's ID and study #, demographic information (age, gender), description of SAE, outcome if fatal, and volume and page location.
- Include the adverse event coding dictionary as PDF and SAS files.
- In addition to standard subgroup analyses (e.g. gender, age, race) of treatment-emergent (TE) adverse events (AEs) and serious adverse events (SAEs), please also provide subgroup analyses based upon concomitant medication use of vasodilator/hypotensive drugs.
- Consider treatment-emergent (TE) AEs/SAEs as those occurring up to 30 days after the last administration of study treatment. We request that you combine the analyses of TE events during treatment and TE events after treatment because we are not interested in such a separate breakdown/analysis.
- Analyze and present the incidence of TEAEs, TESAEs, and study discontinuations according to treatment (placebo, specific rotigotine dose at event, such as 4.5, 9, 13.5, or 18 mg and any rotigotine dose) in a study. Please also provide additional analyses based upon: 1) the occurrence of an event during the titration period; 2) the occurrence of an event during the maintenance period; 3) the occurrence of an event in the titration period and persistence into the maintenance period. You will need to define this last category (e.g. when it is considered "persistent" such as if an event starting in the titration period persists >

7 days into the maintenance period). In these analyses, also show the total number of specific events and the total number of patients experiencing these events.

- Provide analyses (randomized, double-blind, placebo-controlled pivotal trials-506,512,513) of TEAEs, TESAEs, and TE study discontinuations for AEs/SAEs that are of special interest to DNDP. These analyses of special interest represent a conservative approach of assessing the possible frequency of particular events of interest that may not have been captured as a particular event because of AE coding vagaries. These analyses include :
  - **Events possibly suggestive of falls.** Search for a variety of AE terms that might be suggestive of a fall despite the fact that the AE had not been coded as a fall. AE terms (e.g. **some examples but not a complete list**) that might be included in this search are fall, abrasion, laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the event was not a result of a fall. Present the incidence, total number of events, and total number of patients for events that may have been suggestive of a fall for TEAEs, TESAEs, and study discontinuations for a TEAE (further broken down as to whether the event was an SAE or non-serious AE) .
  - **Events possibly suggestive of orthostatic hypotension / postural dizziness.** Search for a variety of AE terms that might be suggestive of orthostatic hypotension / postural dizziness despite the fact that the AE had not been coded as such. AE terms (e.g. **some examples but not a complete list**) that might be included in this search are hypotension, postural hypotension, decreased blood pressure, syncope dizziness, vertigo, postural dizziness, light-headedness, postural light-headedness, impaired balance, and feeling drunk. Present analyses as described for events possibly suggestive of falls.
  - **Events possibly suggestive of sleep attacks.** Search for a variety of AE terms that might be suggestive of a sleep attack despite the fact that the AE had not been coded as such. Present analyses as described for events possibly suggestive of falls.

Requested analyses for laboratory results, orthostatic vital signs, and electrocardiographic data (described more specifically below) apply to presentation of results (within individual study reports) in each of the pivotal studies (506, 512, 513) and also pooled analyses of the 3 pivotal studies in the ISS.

- Present tables and figures showing laboratory results for mean results and mean change from baseline for all analyses over time according to treatment (placebo or rotigotine dose at the time). Tables should show multiple parameters including N, mean, SD, minimum, median, and maximum. Figures representing pictorial representation of tables should show mean and SD data.
- Present shift tables (e.g. shift from low, normal or high at baseline to low, normal or high during treatment at a specific time/visit) showing laboratory results for

ALL analyses over time according to treatment (placebo or rotigotine dose at the time). Low is defined as below the normal reference range and high is defined as above the normal reference range.

- Provide criteria for markedly laboratory result abnormalities (“markedly abnormal” increments and/or decrements of all analytes that might be of interest based upon potential clinical concerns). For example, if serum potassium normal reference range was 3.5 – 5.0 mEq/L, markedly low might be  $\leq 3.0$  mEq/L and markedly high might be  $\geq 5.5$  mEq/L. DNDP recommends that you propose your markedly abnormal laboratory result criteria and submit them to DNDP for review, feedback, and agreement prior to conducting analyses of markedly abnormal laboratory results.
- Present markedly abnormal laboratory result shift tables (e.g. tables showing shift from markedly low, markedly high, or not markedly low or high at baseline to markedly low, markedly high, or not markedly low or high at each specific post-treatment time/visit).
- Present analyses showing the incidence of low and high abnormalities for ALL analytes and the incidence of markedly low and markedly high abnormalities.
- DNDP has several comments/concerns about electrocardiographic data that have and have not been collected. These comments are most relevant to electrocardiographic data collected in the randomized, double-blinded, placebo-controlled, pivotal studies (506, 512, and 513).
- DNDP recommends presenting QTc analyses based upon the Fridericia QT correction formula and the “zero” slope correction method/exponent. QTc correction using the “zero slope” correction method/exponent should be derived from pre-treatment and placebo-treated ECGs for specific studies.
  - You should determine the QTc for “zero slope” in each specific study and apply the specific correction exponent to all data collected in that specific study.
  - QTc adjusted by the “zero slope” method in pivotal studies should utilize the specific exponent determined in a specific study for correcting all electrocardiographic data presented for that specific study. Thus, a different exponent could be applied to each of the 3 pivotal studies.
  - The DNDP has very little experience with the Framingham/linear method and suggests avoiding QT correction with this method.
  - The DNDP recommends against using the Bazett correction method because rotigotine may increase heart rate and this correction method could provide artifactual results.
- Electrocardiographic data collected in study 506 utilized a Holter monitor rather than standard 12 lead ECGs. DNDP is not aware that there has been validation

and acceptance for investigating electrocardiographic data (especially QTc) obtained with the Holter system you used.

- Present tables and figures showing electrocardiographic interval results (PR, QRS, QT, QTc) for mean results and mean change from baseline over time according to treatment (placebo or rotigotine dose at the time). Tables should show multiple parameters including N, mean, SD, minimum, median, and maximum. Figures representing pictorial representation of tables should show mean and SD data. Whenever available, electrocardiographic data (especially QTc) collected at specific times relative to patch application should be analyzed and presented separately.
- Outlier analyses of electrocardiographic interval data (e.g., QTc change from baseline  $\geq 30$  msec  $\geq 60$  Msec, QTc increase  $\geq 500$  msec, etc.) should be presented.
- There are no QTc data assessing the potential effect of rotigotine for prolonging QTc that were collected along with a positive/active control drug for prolonging QTc. The FDA Preliminary Concept Paper (11/15/02) noted that "In addition to the use of a placebo control, a concurrent active control is very valuable to verify the ability of a particular study to detect a relevant change in the QT/QTc interval."
- EKG data (especially QTc) are desired in relation to patch application at steady state for  $T_{max}$  and other times over 24 hours after patch application for various rotigotine doses (up to 18 mg/d).
- EKGs (particularly in the 3 pivotal studies) should be read by central reader(s) blinded to treatment.
- Present separate scatter plots of plasma rotigotine level vs QTc and vs QTc change for each of the pivotal studies, for the pooled, pivotal studies, and also for each of the phase 2a studies (534, 535, 540).
- VS data analyses should be presented as supine, standing, and orthostatic change from supine to standing. Please present these orthostatic VS analyses showing the absolute values at baseline by position and all post-treatment times and the change from baseline for supine VS, standing VS, and orthostatic change from supine to standing.
  - Present tables and figures showing VS results for mean results and mean change from baseline for supine VS, standing VS, and VS changes while going from supine to standing positions (i.e. change of a change) over time according to treatment (placebo or rotigotine dose at the time). Tables should show multiple parameters including N, mean, SD, minimum, median, and maximum. Figures representing pictorial representation of tables should show mean and SD data.

- Present analyses of the frequency of orthostatic hypotension (over time and occurrence at baseline and/or during treatment as shown in Tables 1 and 2 attached at the end of these minutes.
- Present analyses of the frequency of VS outliers (at any visit or at final visit) as shown in Tables 3 and 4 attached at the end of these minutes.
- Present analyses of the frequency of orthostatic hypotension developing during the titration period, and during the maintenance period, and the frequency that orthostatic hypotension develops in the titration period and “persists” into the maintenance period. For these analyses of orthostatic hypotension developing in the titration period and persisting into maintenance period, we suggest that define this last category based upon the occurrence of the same degree of orthostatic hypotension (systolic and/or diastolic) at the last visit in the titration period and the first visit in the maintenance period. Examples of these tables are shown in Tables 5, 6, and 7 attached at the end of these minutes.
- DNDP noted that you do not appear to have collected pharmacokinetic (PK) data showing plasma levels of rotigotine and metabolites at various times (over 24 hours) after patch application at steady state at high daily doses of rotigotine (e.g. 13.5, 18 mg). PK of transdermal drugs is known to vary with the site of patch application and safety responses (e.g. orthostatic VS and 12 lead ECGs) could vary after patch application at various body sites (especially at various sites used in the pivotal trials) at steady state at high daily doses of rotigotine (e.g. 13.5, 18 mg). Relevant to this issue, important, desired safety data (e.g. orthostatic VS and 12 lead ECGs) collected at various times (over 24 hours) after patch application (at various body sites used in the pivotal trials) at steady state at high daily doses of rotigotine (e.g. 13.5, 18 mg) do not exist. Such PK and safety data are highly desired and could be obtained in a randomized, double-blinded, placebo-controlled, clinical pharmacology study.
- Some PK data collected at steady state for low dose rotigotine suggest variable plasma levels of rotigotine at different times after patch application.
  - Data that clearly show T<sub>max</sub> for plasma rotigotine at high daily doses (e.g. 13.5 and 18 mg), do not appear to exist, and would also be desirable.
- If alternative data presentations are considered, the sponsor should obtain division concurrence before submitting the NDA with these alternative presentations.

## **PRECLINICAL PROGRAM**

An overview of the preclinical development program has been provided, as has a proposed Table of Contents for the preclinical sections of the NDA.

6. ***Does FDA concur that the pharmacology, toxicology, and drug metabolism program conducted is sufficient to support the initial NDA?***

- The preclinical information is sufficient to support the initial NDA. The carcinogenicity data should be provided electronically as SAS data sets.
- Relative metabolism across species is requested.
- This is a matter of review. With regards to the drug metabolism program information presented in the background package was insufficiently detailed to evaluate. For example information on induction could not be found.

## CMC

### 7. *Does FDA concur that the proposed contents of the CMC module are sufficient to support the initial NDA?*

- The proposed contents appear sufficient for filing of the initial NDA.
- The sponsor was advised that drug substance and drug product specifications should list all individual impurities that exceed the appropriate identification threshold. Given the formation of the \_\_\_\_\_ as drug product degradants, degradants resulting from the \_\_\_\_\_ should be monitored, and qualified if necessary.
- This is a matter of review, as is selection of the regulatory dissolution method. Dissolution data in at least 3 different media are expected. For transdermal systems water and/or buffers with near neutral pHs are typically included, in addition to more alkaline and acidic pHs. Acceptance ranges are based upon the dissolution characteristics of the batches used in the pivotal efficacy studies. If different batch numbers are used at different stages of production, the final drug product batches should be traceable backwards. Dissolution data to bridge batches used in clinical pharmacology studies with the batches used in the pivotal efficacy studies should also be provided.

## CLINICAL PROGRAM

An overview of the clinical development program has been provided, as has a proposed Table of Contents for the clinical sections of the NDA.

### 8. *Does FDA concur that the clinical pharmacology and clinical safety and efficacy programs outlined in this package are sufficient to support an NDA for the signs and symptoms of early-stage idiopathic Parkinson's disease?*

Based upon a preliminary review of summaries of efficacy and safety data that the sponsor plans to submit in an NDA, the clinical efficacy and safety programs generally appear to be adequate for submission of an NDA for the indication of treatment of early Parkinson's Disease. **However, the DNDP has concerns about the lack of important, desired safety data (e.g. orthostatic VS and 12 lead ECGs) collected at various times (over 24 hours) after patch application at PK steady state for the highest daily doses (e.g. 13.5, 18 mg) of rotigotine.**

## Clinical Pharmacology Program:

- Provide the batch information, including dissolution, used in each study.
- The proposed dissolution method may be inadequate. Based upon the U.S.P., dissolution method for patches should have a pH of around — not the proposed pH. of —
- The number of samples collected should be increased from 6 (level 1) as proposed to 12 (level 2)
- This is a chiral compound and therefore the activity for each enantiomer should be provided. PK data from the patch and not I.V. should be provided. In vivo and in vitro induction data should be provided..
- Bioavailability with the highest proposed to be marketed dose formulation with repeated exposures and at all proposed application sites in the appropriate population should be provided.
- The electronic data sets provided in the original NDA should have groups by dose, site of application, demographics, and relative absorption over time based on site application.
- Because rotigotine absorption can vary with the site of application, detailed absorption data in reference to site application is needed.
- Provide the necessary data to support establishment of steady state. Additional PK study using higher doses should be conducted.
- There are a number of concerns with regard to the clinical pharmacology program that need to be addressed, including the following. Several of these concerns may or may not be adequately addressed depending upon the subjects and design of any population pK analyses.
- Application of the transdermal systems in the clinical pharmacology studies should be to the same site and in the same manner as in the pivotal efficacy and safety studies, including preparing the site and affixing the patch.
- Blood sampling schemes should be sufficient to adequately describe the entire concentration vs. time profile including any absorption lag upon changing patches.
- It's unclear if mass balance studies use high enough doses to provide adequate information on *in vivo* drug metabolism.
- It's unclear if there will be adequate information to assess dose linearity and time invariance, i.e. sufficiently high doses for an adequate application period.

- It's unclear if there will be adequate information to adequately assess the effects of age, gender, and the effect of various ethnicities, (e.g. Hispanic, etc.).
- The drug delivery and dermal tolerability studies appear to be inadequate at least in part due to the use of small patch sizes. These studies typically are bracketed by the largest and smallest patch sizes.
- There is no indication that an adhesion study is being conducted.

### **Table of contents**

The table of contents for the NDA as proposed will conform with the ICH Common Technical Document format. However, as with all application formats, some flexibility in the organization of studies and information is available.

**9. *Given this, Schwarz is seeking any guidance FDA may be able to provide on how to optimally organize the application TOC in such a way as to facilitate review of the application.***

- The table of contents should be hyperlinked to the corresponding page number and the specific pages for various sections should be specified. If the table of contents does not allow for correct location of information then the application may not be able to be filed.
- Lists of all tables/tabulations, figures, and specific detailed identification of items in appendices should be shown in a TOC for each final study report, the ISE, and ISS, along with a hyperlink to the location and the page specification of the location in the TOC.
- Tables/tabulations and figures presented/discussed in text should be hyperlinked to the location of the table/tabulation or figure to allow for easy referencing by the reviewer.
- The format should allow easy navigation and location of all pertinent information. For example if the study report title is the 4<sup>th</sup> level header it should still be possible to view and link to all subheadings of the protocol, appendices, tables, etc. Inability to navigate the NDA without difficulty, and to locate information easily can be a filing issue.

### **Datasets and CRFs**

Case report forms and case report tabulations will be provided in a manner consistent with 21 CFR 314, applicable FDA guidance, and standard practice. Case report forms will be provided for all patients who died or did not complete a study due to an adverse event. Datasets in SAS Transport (XPT) format will be provided (as the case report tabulations) for studies SP506 (the Phase 2b trial), SP512 (the first pivotal trial), SP513 (the second pivotal trial), and for the integrated efficacy and safety databases. As per agreement with FDA (telephone conversation of August 29, 2003), PDF format case report tabulations will not be included in the original application. These will be available upon request. Electronic datasets or PDF format case report tabulations for Phase 2a and Phase 1 studies will not be provided unless these are requested by FDA.

**10. Schwarz seeks confirmation that FDA concurs with these plans.**

- Study reports should be in PDF format and bookmarked.
- Electronic data sets are requested for all PK and PK/PD data along with demographic and dosing information for these studies.

**Designation of Dose**

Most existing transdermal delivery systems express dosage as an approximate amount of drug delivered systemically. This is due to the following factors:

- Virtually all existing transdermal systems deliver drugs which are, or are related to, compounds which are also available as oral or parenteral dosage forms.
- Patients are often switched from oral or parental dosage forms to transdermal dosage forms; in such situations, it is necessary for the transdermal system to express dosage in a way that facilitates the transition from oral or parenteral dosage forms.
- Expression of dose of a transdermal system as the amount of drug systemically delivered facilitates this therapeutic transition; for this reason, for most transdermal systems this method of dose expression is medically appropriate.

However, in the case of rotigotine (which is not orally available, and for which parenteral delivery is impractical), the above factors do not apply, as the drug will only be available in a transdermal system. Expressing dose as the total amount of drug substance in a dosage form is standard for oral dosage forms, including those with limited bioavailability. Further, this method of dose expression has been used in all clinical trial reports and in all clinical summaries. Given this, expressing the dose in this manner may result in less confusion during the review process.

At the same time, global considerations may make it desirable to express the dose in product labeling as the amount systemically delivered. Schwarz believes that either method of expressing dose in product labeling (by the amount in the transdermal system, as well as by the amount systemically delivered) is appropriate.

**11. Does FDA concur that either method of expressing the dose of the product in labeling (by the amount in the transdermal system, or by the amount systemically delivered) is appropriate?**

- The release rate or the amount of delivered drug will be used in labeling.
- Typically the amount of drug in a transdermal system is in excess of the amount released and subsequently available for absorption in order to provide a driving force for pseudo-zero order release. Consequently, the amount of drug absorbed is often the preferred labeling method. However, for a number of practical reasons reports often refer to the amount of drug contained in the product. Therefore in reports and the application the sponsor may utilize the amount of drug in the system for convenience and consistency, although for labeling purposes conversion to the amount delivered may be preferred.

### Need for Advisory Committee

Preparation for an Advisory Committee represents a significant investment of resources and forward planning on both the Agency's and the Sponsor's part. It is understood that if rotigotine raises unique safety or efficacy issues, an opinion from the appropriate Advisory Committee will likely be sought. However, it is our understanding that new chemical entities which act by existing and well-established mechanisms of action, and which do not raise any unique safety or efficacy issues, do not generally require consideration by an Advisory Committee.

12. *Given the efficacy and safety profile of the rotigotine transdermal system as presented in this package, Schwarz seeks to understand FDA's viewpoint on whether an Advisory Committee meeting is likely to be needed to consider the approval of the product. It is understood that issues which arise during NDA review may change FDA's viewpoint on this matter.*

- Currently, an Advisory Committee meeting is not planned.

### Potential for QT interval prolongation

Schwarz believes that the potential of clinically relevant doses of rotigotine to meaningfully prolong the QT interval in Parkinson's patients has been adequately addressed by the existing clinical safety database.

13. *Does FDA concur that the existing clinical database is sufficient to address the potential of rotigotine to prolong QTc intervals?*

- No. DNDP noted that there are important shortcomings in the availability of QTc data (derived from standard 12 lead ECGs) to assess the potential effect of rotigotine for prolonging QTc at various times over 24 hours after patch application at high daily doses of rotigotine (e.g. 13.5 and 18 mg) at PK steady state.

EKG data (standard 12 lead) should be obtained at various times after patch application for daily rotigotine doses up to 18 mg at PK steady state. These data should be read at a central site by one or two readers under conditions in which the reader is blinded to treatment. Intra- and inter-reader variability for reading QTc should be presented. These important, desired electrocardiographic data (and orthostatic VS data) could be obtained in a randomized, double-blinded, placebo-controlled clinical pharmacology study. It may also be possible to collect important, desired PK data assessing the effect of patch application of rotigotine at various body sites (that were used in pivotal studies and that the sponsor wants to specify in the label) in the same clinical pharmacology study.

Important features of such a clinical pharmacology/safety study (details of this potential study were not discussed during the meeting) might include:

- conducting a randomized, double-blind, placebo-controlled clinical pharmacology trial of patients with early Parkinson's disease

- randomization to placebo, or placebo with single dose administration of moxifloxacin only on study day or one of several fixed, daily doses of rotigotine such as 9 mg, 13.5 mg, and 18 mg (? also 4.5 mg) ; N = 15-20 patients/group; patch application would be at a specific body site
- titration of patch treatment at weekly intervals to the maximal, daily rotigotine dose (18 mg) over 4 weeks
- prior to initiating collection of safety/PK data for comparison, "integrated" baseline/pre-treatment ECG and orthostatic VS should be collected based upon several collections over a similar 24 hour period as the time eventually to be studied or at least based upon a minimum of 3 collections of safety data over a period of 1-2 hours; data should be averaged to provide the mean, "integrated" baseline/pre-treatment ECG and VS data to be used for comparison with patch application and administration of moxifloxacin
- administration of moxifloxacin (positive control QTc prolonging drug at a dose of 400 mg expected to produce mild QTc prolongation with a mean QTc of approximately 7 msec greater than placebo) on study day at 4 weeks ; patients not randomized to receive moxifloxacin would receive a double-dummy placebo
- collection of orthostatic VS (supine and standing BP and pulse) and 12 lead ECGs and PK samples at multiple, various times (e.g. 0, + 1, 2, 4, 8, 12, 16, 20, 24 hours) over 24 hours after patch application
- "cross-over" of all patients to applying patch treatment to a second, different site for 7 days
- repeat administration of moxifloxacin or respective placebo and collect ECGs, orthostatic VS, and PK samples at multiple timepoints over 24 hours after patch application as previously 1 week earlier
- repeat "cross-over" of all patients to applying patch treatment to a third body site for 7 days and then collect electrocardiographic, VS, and PK data as previously following administration of moxifloxacin or respective placebo
- repeat "cross-over" of all patients to applying patch treatment to a fourth body site (if desired) for 7 days and repeat collection of safety and PK data as previously after moxifloxacin or respective placebo
- FDA comments on target label. A target label has been provided in this submission. This target label is based on current knowledge of the rotigotine transdermal system, and it has necessarily omitted information to be derived from analyses which have not yet been conducted. This target labeling is being submitted so that FDA feedback on the overall labeling approach can be considered as the actual proposed labeling is developed. Given the early stage of labeling development, Schwarz is only interested in major, substantive comments the Division might have at this early stage.

Schwarz is particularly interested in comments on:

- the presentation of the clinical data;
- the presentation of adverse event information;
- use of a patient package insert focusing on how to apply the product.

***14. Does FDA have any major, substantive comments on the target labeling included in this submission?***

- This is a matter of review.

The following are DNDP requests that were not specifically discussed at the pre-NDA meeting.

- Please submit CRFs for all SAEs.
- DNDP requests supplementary safety analyses of various populations that are specified here. However, for the safety analyses of these populations, it is not necessary to present these analyses with the same level of detail as those conducted and presented in the ISS.
  - Present separate analyses of the safety experience of all Parkinson's disease patients treated with any formulation of rotigotine other than the transdermal silicone patch
  - Present separate analyses of the safety experience of advanced Parkinson's disease patients treated with the transdermal silicone rotigotine patch
  - Present separate analyses of the safety experience of RLS patients exposed to rotigotine
  - Present separate analyses of the safety experience of healthy subjects exposed to rotigotine with a breakdown according to the formulation / route

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Russell Katz

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## MEMORANDUM OF TELECON

**DATE:** November 21, 2001

**APPLICATION NUMBER:** 47,852 Rotigotine CDS

**BETWEEN:**

**Name:** Eric Foster  
**Phone:** (919) 767-2512  
**Representing:** Schwarz Biosciences, Inc.

**AND**

**Name:** Dr. Leonard Kapcala – Medical Reviewer  
Teresa Wheelous, Regulatory Management Officer  
Division of Neuropharmacological Drug Products, HFD-120

**SUBJECT:** Clarification of three bullet points provided in the divisions' End of Phase 2 meeting minutes dated August 16, 2001.

**DISCUSSION:**

In an October 26, 2001 submission, Schwarz Biosciences, Inc. requested three revisions to the End of Phase 2 meeting minutes. The three points of revision are:

**1. Page 4, Question 2 of the division's official minutes**

*"It appears, based on the presentation, and subject to review that all higher doses (9.0 mg, 13.5 mg, 18 mg) were statistically significant vs. placebo group. However, statistically significant differences were not observed between drug treatment groups."*

- Schwarz Biosciences proposed that this bullet be deleted because protocol SP506 was not intended to show statistically significant differences between treatment group.
- **It was agreed during the 11/21/01 teleconference that this bullet would remain unchanged. The summary did not comment about any intention of the study but only described what the statistical outcome was. If the analyses did show statistical differences between dose groups, such a comment would have been noted. The summary merely reflected the outcome of statistical analyses. The sponsor will discuss this with statistical colleagues and re-contact DNDP if they disagree.**

**2. Page 4 and 6, Questions 3 and 7**

**(Q3) Does the division agree that only one additional study is required to support efficacy in early PD? (see protocol outline, 4.7.1 and/or 4.7.2)**

***A Phase 3, randomized, double-blind, placebo-controlled, optimal-dose, multicenter trial in US and Canada of Rotigotine CDS patch in subjects with***

*early stage, idiopathic PD. The primary variable: a responder is defined as a subject with a > 20% decrease from baseline in UPDRS score (II+III) to end of treatment.*

- Yes

*(Q7) Does the division agree with the following primary and secondary variables for early PD patients?*

Primary:

- *Efficacy will be determined by the subject's response to therapy. A responder is defined as a subject with a >20% decrease from baseline in the Unified Parkinson's Disease Score (UPDRS) Part II-III score to end of treatment.*

Secondary:

- *Relative and absolute change in UPDRS score (II-III) from baseline visit to end of treatment.*
- *Absolute change in UPDRS mental, activities of daily living (ADL), motor scores (Parts I, II, and III) from baseline visit to end of treatment.*
- *Change from baseline to end of treatment in UPDRS Part II.*
- *Change from baseline to end of treatment in UPDRS Part III.*
- *The primary and secondary outcome variables are acceptable.*
- *A question was raised as to the Agency's view if only one of the two identical studies (U.S. and non-U.S.) in early PD supported efficacy of Rotigotine. A consensus view for dealing with this problem has not yet been established.*
- Schwarz Biosciences requested the following statement be made: During the discussion of question 7 Schwarz suggested the possibility of using both the dichotomized and the continuous endpoints in the same protocol to satisfy EU and US regulatory requirements. The division noted that a consensus view for dealing with this problem has not yet been established and encouraged Schwarz to submit a proposal for review and comment.
- **It was agreed that the last bullet of question 7 (above) be revised to:**

**A question was raised as to the Agency's view if two different primary efficacy endpoints were utilized in the early and advanced PD trials conducted as separate trials (with identical design except for different primary endpoints) in the US and in non-US sites. A consensus view for dealing with this problem has not yet been established. The division invited Schwarz to submit a proposal relative to this issue for review and comment.**

3. *Page 9, under Dermal Toxicity Study*

*"A 6-month monkey dermal study was started in May 2001"*

- Schwartz would like to revise this bullet to read "A 6-month minipig dermal study was started in May 2001".
- **The change from a 6-month monkey dermal study to a 6-month minipig dermal study was agreed upon.**

The division will make the agreed upon changes officially.

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/s/

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Teresa Wheelous  
12/20/01 07:59:40 AM  
CSO

Leonard Kapcala  
12/20/01 11:22:41 AM  
MEDICAL OFFICER

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** June 14, 2001

**TIME:** 2:30 PM

**LOCATION:** WOC II Conference Room E

**APPLICATION:** IND 47,852 Rotigotine CDS

**TYPE OF MEETING:** End-of-Phase 2

**MEETING CHAIR:** Dr. Russell Katz

**MEETING RECORDER:** Teresa Wheelous

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name</u>	<u>Title</u>	<u>Division &amp; HFD</u>
Dr. R. Katz	Division Director	HFD-120
Dr. J. Feeney	Group Leader	HFD-120
Dr. L. Kapcala	Medical Reviewer	HFD-120
Dr. S. Yan	Biometrics Reviewer	HFD-710
Dr. G. Fetterly	Clinical Pharmacology / Biopharmaceutics Reviewer	HFD-860
Dr. R Upoor	Clinical Pharmacology / Biopharmaceutics Team Leader	HFD-860
Dr. R. Kavanagh	Clinical Pharmacology / Biopharmaceutics Reviewer	HFD-860
Dr. B. Rosloff	Pharmacology Team Leader	HFD-120
Dr. P. Roney	Pharmacology Reviewer	HFD-120
Teresa Wheelous	Project Manager	HFD-120

### SCHWARZ BIOSCIENCES ATTENDEES

<u>Name</u>	<u>Title</u>
Joseph Bianchine, M.D.	Scientific Advisor
Alan Blumberg, Ph.D.	Regulatory Affairs
Eric B. Foster, M.S.	Associate Director, Reg. Affairs
Kathryn H. Poole	Clinical Program Director
David Rudd	Sr. Director Clinical Development
Rolf Horstmann, M.D.	Head of Clinical Pharmacology
Harold Jordan, Ph.D.	Head of Regulatory Affairs
Ute Scharfenecker, Ph.D.	Sr. Scientist Pharmacokinetics/ADME
Patrick Schwarz-Schuetz	Acting Head, Research & Development
Barbara Stegmann, M.D., Ph.D.	Chief Medical Officer
Franz Woltering	Biostatistician

### BACKGROUND:

Schwarz BioSciences, Inc. submitted an End-of Phase 2 meeting package dated May 18, 2001. The questions listed in the meeting package along with the replies and discussion to each question follows.

**Proposed Phase 3 Protocols:**

Because of the different US and non-US regulatory requirements, with Europe requiring an active control arm the sponsor is proposing, two studies in patients with early Parkinson's Disease (PD):

Early PD Studies: (1) SP512 - a 2-arm (placebo and Rotigotine CDS) study in US and Canada, and (2) SP513 – a 3-arm (placebo, Rotigotine CDS, ropinirole active control) study in Europe.

STUDY (phase)	STUDY NAME	WHERE	# of PATIENTS	DOSE	Duration Per Patient
SP 512	Early PD (vs. placebo)	US	240	4.5,9.0, & 13.5 MG (1,2, or 3 x10 cm <sup>2</sup> )	37 weeks +open label
SP513	Early PD (vs. placebo & ropinirole)	EU	450	4.5 to 18.0 mg (10 to 40 cm <sup>2</sup> )	45 weeks

**MEETING OBJECTIVES:**

Discuss the adequacy of Schwarz's Phase 3 proposed program for the continued development of Rotigotine CDS to support a NDA for the treatment of the signs and symptoms

**QUESTIONS:**

- Does the division agree that the results of Protocol SP506 provide adequate evidence of Rotigotine CDS effectiveness for Early Parkinson's Disease and could be considered as evidence for efficacy for an Early Parkinson's Disease indication.
  - The assessment of the results of protocol SP506, a completed Phase 2 trial conducted in Early PD patients, is a review issue, but this protocol is adequate in design to support an effectiveness claim in early PD.
  - The primary outcome measure for this study is the total score of parts II & III of the UPDRS (activities of daily living and motor function).
  - Patients were randomized to fixed doses (4.5 mg, 9, 13.5, 18 mg /day).
  - Doses were titrated in 4.5-mg increments to a maximum dose of 18 mg. This dosage regimen was selected because of the severity of nausea and vomiting that is experienced when higher doses are initiated without titration.

2. Does the division agree that the results from protocol SP 506 adequately demonstrate a dose-response relationship?

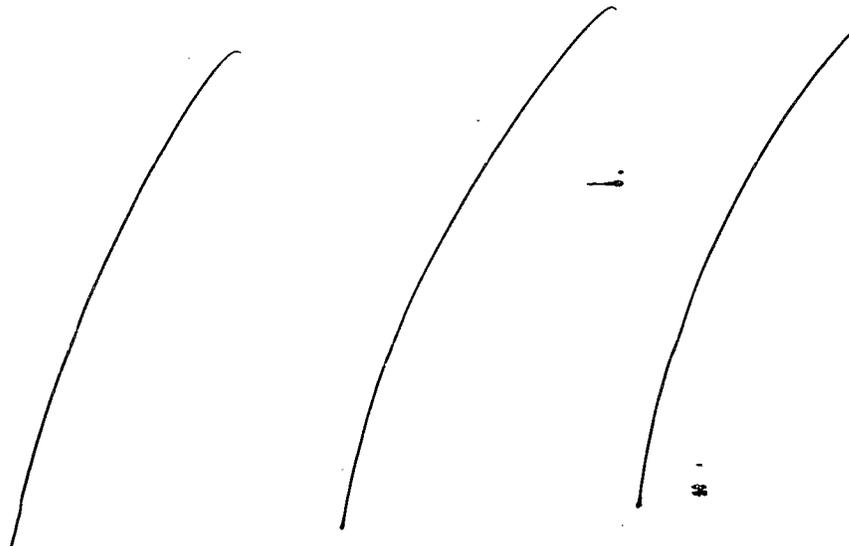
- It appears, based on the presentation, and subject to review that, a dose response relationship is shown by linear regression.
- It appears, based on the presentation, and subject to review that the lowest dose (4.5 mg – 10 cm<sup>2</sup>) showed a trend for statistical significance.
- It appears, based on the presentation, and subject to review that all higher doses (9.0 mg, 13.5 mg, 18 mg) were statistically significant vs. placebo group. However, statistically significant differences were not observed between drug treatment groups.

3. Does the division agree that only one additional study is required to support efficacy in early PD? (see protocol outline, 4.7.1 and/or 4.7.2)

*A Phase 3, randomized, double-blind, placebo-controlled, optimal-dose, multicenter trial in US and Canada of Rotigotine CDS patch in subjects with early stage, idiopathic PD. The primary variable: a responder is defined as a subject with a > 20% decrease from baseline in UPDRS score (II+III) to end of treatment.*

- Yes

4.

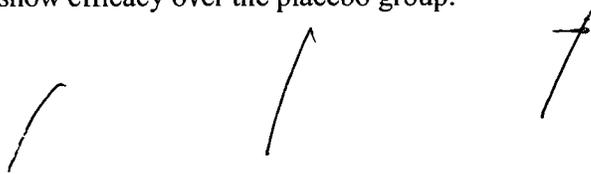


5. Does the division agree with the planned doses for Phase 3 (on the basis of the Phase 2 data)? (see protocol outlines, sect 4.3 and 4.4)

*Based upon the results of the Phase 2 study in early PD (SP506)  
Rotigotine produced therapeutic benefit over placebo in UPDRS II+III*

*in a linear regression dose-response relationship from 4.5 mg (10 cm<sup>2</sup>) up to 13.5 mg (30 cm<sup>2</sup>) and 18.0 mg (40 cm<sup>2</sup>). The first dose showing statistical difference from placebo was 9.0 mg (20 cm<sup>2</sup>). Schwarz believes that the optimal therapeutic dose for early PD subjects*

- It can be problematic in writing labeling when studying dose response based upon optimal individual responses instead of fixed doses (fixed doses are preferred).
- Often, there is not a robust safety experience at the highest dose group, and therefore safety description in labeling for the high dose group is difficult.
- The protocol design should address the need for adequate safety data at the high dose group.
- In an effort to maintain the blind in the comparator study (ropinirole, Rotigotine, placebo), where different drug products with different titration schedules are administered, the sponsor intends to maintain a blind for all groups by using a double dummy design in which all patients receive similar numbers of patches and tablets.
- In study # 511, no statistical significance from placebo was observed for any dose group. Surprisingly, the placebo group maintained improvement even after discontinuation of the placebo patch. However, the drug treatment groups returned toward baseline after discontinuation of treatment patches. The levodopa dose reduction was monitored, but there was not a marked reduction in usage.
- Doses of 9 mg, 18 mg, and 27 mg (20 cm<sup>2</sup>, 40 cm<sup>2</sup>, and 60 cm<sup>2</sup> respectively) did not show efficacy over the placebo group.



**6. Does the division agree with the sponsor's definition of early PD?**

- *Idiopathic PD subjects with  $\leq 6$  months*
- *Concomitant L-dopa therapy,*
- *Hoehn and Yahr stages  $\leq 3.0$ , and*
- *Duration of PD  $\leq 5$  years*
- Based upon the definitions of early PD and advanced PD, there is possible overlap between the two groups.
- The presence of inadequately controlled motor fluctuation is the main distinction between the two groups.

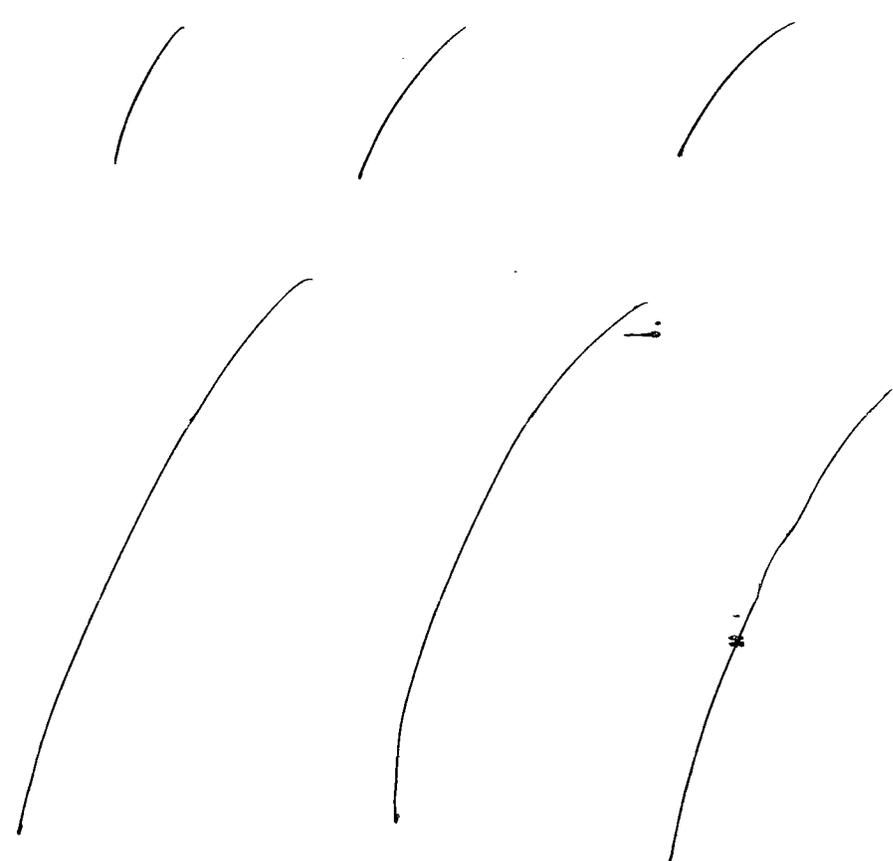
7. Does the division agree with the following primary and secondary variables for early PD patients?

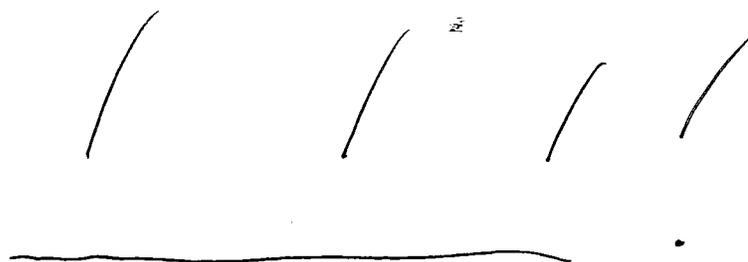
Primary:

- *Efficacy will be determined by the subject's response to therapy. A responder is defined as a subject with a >20% decrease from baseline in the Unified Parkinson's Disease Score (UPDRS) Part II-III score to end of treatment.*

Secondary:

- *Relative and absolute change in UPDRS score (II-III) from baseline visit to end of treatment.*
  - *Absolute change in UPDRS mental, activities of daily living (ADL), motor scores (Parts I, II, and III) from baseline visit to end of treatment.*
  - *Change from baseline to end of treatment in UPDRS Part II.*
  - *Change from baseline to end of treatment in UPDRS Part III.*
- The primary and secondary outcome variables are acceptable.
  - A question was raised as to the Agency's view if only one of the two identical studies (U.S. and non-U.S.) in early PD supported efficacy of Rotigotine. A consensus view for dealing with this problem has not yet been established.





**10. The current development plan will expose approximately 1705 subjects in all phases to Rotigotine. More than 100 subjects will have been exposed for 1 year and more than 300 subjects will have been exposed for a minimum of 6 months to Rotigotine. Does the division agree that this will provide an adequate number of patients for an evaluation of efficacy and safety for the proposed indication?**

- Yes, these numbers more than meet the ICH safety guidelines of 100 subjects for at least 1 year, 300 subjects for at least 6 months, and total of 1500 subjects for exposure of any duration.

#### **OTHER DISCUSSION TOPICS:**

##### **CLINICAL**

##### **QTc, ECG, and Vital Signs**

- Based on a preliminary review of partial data and a draft report for ECG data, QTc prolongation does not seem to be a concern at doses up to 27 mg/day.
- Although mean data are provided in the submitted report, individual patient data are also requested.
- ECG data were obtained essentially at Cmax both prior to patch removal and soon after patch application. The division would like to obtain ECG data during steady state and also during the time around patch changes.
- At least 3 baseline ECGs should be collected in Phase 3 studies.
- Vital signs to include orthostatic (supine and standing) blood pressure/pulse collection are planned for all the studies.

##### **Sleep Attack Safety**

- There have been a couple of apparent sleep attacks and this information should be placed in the informed consent. Investigators should monitor specifically for the occurrence of sleep attacks.
- Sleep attacks appear to be a drug class adverse event. Therefore, it is necessary to question directly and closely for the development of sudden sleep attacks. It is

important to sensitize patients and investigators for reporting about possible sleep attacks.

- If patients fall asleep in passive situations, they may be at risk for falling asleep during active situations.
- Schwarz is considering the addition of the Epworth Sleep Scale and a questionnaire to the protocol.
- A follow-up questioning of the two patients that appear to have experienced sleep attacks is recommended.

#### **Fibrotic Complications**

- Dopamine agonist drugs typically contain a standard section in labeling regarding fibrotic changes. The sponsor may consider literature reports.

#### **Domperidone Use**

- Considering that the use of domperidone (for nausea and vomiting) is not approved in the United States and that domperidone may be associated with QTc prolongation, the sponsor is reminded that use of domperidone is not recommended for inclusion in the pivotal trials to support the NDA.

### **PRECLINICAL**

#### **Incomplete Chronic Toxicology Package**

- The chronic monkey study is pending and is needed to support clinical trials greater than 3 months in duration.

#### **Incomplete Reproduction Package**

- Segment 1 and segment 2 studies were inadequate because of the drug-induced prolactin decrease, which caused the female rats to abort their pregnancies.
- Protocols for additional reproduction studies are currently under review.
- Additionally, there may be an issue regarding the adequacy of the plasma level exposure in the segment 3 study.
- In the absence of reliable segment 1, 2, and 3 data, enrolling women of childbearing potential becomes an issue. It may be necessary to exclude this group from the studies.

#### **Investigator's Brochure**

- ---

The *in vitro* animal mutagenicity study is positive and the *in vivo* study is less sensitive. Accordingly, the positive finding can not be dismissed and the product can not be viewed as being without risk.

**Preclinical Combination (with Sinemet) Toxicology Studies**

- Three-month studies are planned, but have not yet been submitted for review to the Agency. The submission is scheduled for the 4<sup>th</sup> quarter of 2001.
- An outline of the feasibility studies was presented and appears to be acceptable.
- The timing of these studies is out of the ordinary. By the time phase 3 trials are started, combination toxicology studies are ordinarily completed. However, it was decided that the proposed plan was acceptable.
- Apparently there is no acute toxicity concern, but chronic toxicity remains a concern.

**Dermal Toxicity Study**

A 6-month monkey dermal study was started in May 2001.

**CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS****PK Concerns**

- Formal PK study results in women are needed. Data will be gathered from study #506.
- The degree of dose dependence should be included in the PK package.

**Metabolism**

- SPM962 is highly metabolized by various CYP450 isoforms. In addition, 70% of the administered dose is excreted in urine. Thus, renal and hepatic impairment studies will be needed. Please refer to the "Guidances for Industry" on Renal (final) and Hepatic Impairment Studies (draft).
- Studies need to be performed to ascertain the ability of Rotigotine and any major metabolites to either inhibit or induce various CYP450 isoforms.
- In addition to the ongoing radiolabeled <sup>14</sup>C-Rotigotine pharmacokinetic study, the plasma time courses of both parent drug and all major and active metabolites should be assessed quantitatively. As a result of metabolites detected in preclinical studies and their apparent chemical structures characterized by *in vitro* human microsomes and mass spectrometry, the possibility of Phase II conjugates should be determined using human hepatocytes.
- The sponsor has proposed a drug interaction study between Rotigotine and L-dopa to assess the potential interaction with concomitant medications that patients will be taking. In addition, the sponsor has proposed a drug interaction study with cimetidine to assess potential pharmacokinetic interactions with Rotigotine. Once the complete metabolic profile is qualitatively and quantitatively ascertained, additional drug interaction studies may need to be performed since the parent drug is metabolized by various CYP450 isoforms.
- As a result of

\_\_\_\_\_, the sponsor has chosen to proceed into the Phase III clinical studies with the silicone patch. Although the safety and efficacy of Rotigotine in the silicone patch seems to be sufficient in the small clinical studies performed to date, no pharmacokinetic information has been obtained for the parent drug and its metabolites following administration of the silicone patch in patients with Parkinson's Disease, including females. The sponsor has stated that they obtained sufficient pharmacokinetic data from a Phase II Clinical Study including the use of the silicone patch in males and females.

- The sponsor has proposed \_\_\_\_\_ Phase III clinical trials to assess the efficacy of Rotigotine in patients with Early \_\_\_\_\_ Parkinson's Disease. The protocols listed in this submission do not specify the collection times of blood samples to assess the concentration of the drug and its metabolites in relation to administration of the drug. The collection times for blood samples should be specified.
- The sponsor should determine the relative bioavailability of Rotigotine transdermal system at different application sites.
- The sponsor should address the following during drug development:
  - a) In vitro release testing
  - b) Adequate adhesion of patch
  - c) \_\_\_\_\_
  - d) Any major changes between patches used in pivotal clinical trials and to be marketed products may necessitate a Bioequivalency (BE) study.

#### CMC

- A separate CMC meeting is not planned, but should be arranged in order to obtain guidance about the use of cohesives in patch delivery systems.

#### ACTION ITEMS:

Schwarz will consider the Agency's comments.

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Russell Katz  
8/16/01 09:22:06 AM