CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

Trade Name: Neupro patch

Generic Name: Rotigotine transdermal system

Sponsor: UCB Inc.

Approval Date: April 2, 2012

Indications: For the treatment of signs and symptoms of Parkinson's disease and the treatment of moderate-to-severe primary Restless Legs Syndrome.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21829/S-001 and S-002

SUPPLEMENT APPROVAL

UCB Inc.
Attn: Ellery Mangas
Associate Director, Regulatory Affairs
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

Dear Mr. Mangas:

Please refer to both of your Supplemental New Drug Applications (sNDAs) dated December 2, 2012, received December 2, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Neupro (rotigotine transdermal) Patch.

We acknowledge receipt of your amendments dated January 23, 2012, February 23, 2012, February 24, 2012, March 27, 2012, March 29, 2012 and March 30, 2012 for both supplements. The December 2, 2011 submissions constituted a complete response to our April 21, 2010, action letter.

We also refer to our approval letter dated April 2, 2012 which contained the following error: REQUIRED PEDIATRIC ASSESSMENTS section did not list "Final Protocol Submission" and "Study Completion" milestone dates for each required study.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain April 2, 2012, the date of the original approval letter.

The "Prior Approval" supplemental new drug application S-001 proposes an added indication to treat "the signs and symptoms of moderate to severe primary Restless Legs Syndrome (RLS)" and supplemental application S-002 proposes an added indication to treat "the signs and symptoms of advanced Parkinson's disease (APD)."

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

S-001 Restless Leg Syndrome

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the requirement to study RLS in children ages 12 years and younger because prevalence estimates for children in this age group with primary RLS requiring treatment is low,

making clinical trials impractical. The efficacy of rotigotine in children with secondary RLS has not been studied.

We are deferring submission of your pediatric studies for ages 13 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1885-1 Conduct a PK/PD study in adolescents ages = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

Final Protocol Submission:	June 2012
Study Completion:	April 2014
Final Report Submission:	November 2014

1885-2 Conduct a clinical trial to assess the efficacy and safety of rotigotine transdermal (Neupro) in adolescents ≥13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. Develop age appropriate dose(s) in order to then identify the lowest maximally effective dose in this age group.

Final Protocol Submission:	September 2015
Study Completion:	July 2024
Final Report Submission:	February 2025

1885-3 Conduct a long-term safety study of adolescents ages =13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. The study must provide a descriptive analysis of safety data in pediatric patients during at least 12 months of continuous treatment with rotigotine transdermal at individualized doses in association with the trial described in the pediatric efficacy study.

Final Protocol Submission:	June 2012
Study Completion:	September 2026
Final Report Submission:	April 2027

Submit final study reports to this NDA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment(s)**".

S-002 Advanced Parkinson's disease

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Studies are impossible or highly impracticable because Parkinson's disease typically occurs in adults over the age of 40 and it does not occur in the pediatric population.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

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

ENCLOSURE(S):
Content of Labeling

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

/s/

RUSSELL G KATZ
04/02/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

OTHER ACTION LETTER(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-829/S-001 and S-002

COMPLETE RESPONSE

UCB, Inc.
Attention: Deborah Hogerman
Senior Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Ms. Hogerman:

Please refer to your supplemental new drug applications dated September 21, 2007 (S-001) and October 5, 2007 (S-002), both received October 11, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro (rotigotine transdermal) Patch.

We acknowledge receipt of your amendments dated July 17, 2009 and January 7, 2010. The July 17, 2009 submissions constituted a complete response to our December 15, 2008 action letter.

Supplemental application S-001 proposes an added indication to treat "the signs and symptoms of advanced Parkinson's disease (APD)" and supplemental application S-002 proposes an added indication to treat "the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS)."

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. Although we have concluded that you have provided substantial evidence of effectiveness for Neupro in patients with advanced Parkinson's disease and in patients with RLS, we describe below our reasons for not being able to approve these supplements at this time, and our recommendations for addressing these issues.

PRODUCT QUALITY

As described in our letter to NDA 21-829 dated April 21, 2010, we continue to have concerns that the currently proposed patch may develop crystals over time.

Specifically, we acknowledge that the data from your recently submitted stability studies suggest that, when patches are stored at (b) (4) the degree of crystallization is (b) (4). However, data from your validation batches, stored under identical conditions, suggest that batches that met your proposed release specification of (b) (4) crystallization developed relatively extensive crystallization at less than 12 months, as judged by your analysts (b) (4)

You assert that there was agreement between your analysts on their assessments of the degree of crystallization for these patches, and that this outcome validates your proposed method of quantitating the degree of crystallization. However, FDA analysts examining patches from this same batch at greater than 18 months post manufacture, and using your method as well as microscopic examination, noted <1% crystallization in all patches. Although we are at a loss to explain the markedly discrepant results between your findings and the Agency's findings, the fact that the patches examined by Agency analysts did not have significant crystallization prevented us from being able to validate your methodology. Given our inability to independently validate your methodology for quantitating the degree of crystallization, we have no reassurance that any batch that you determined met the upper limit of your proposed specification of (b) (4) at 12 months did, in fact, reliably meet that limit.

However, even if we were confident that a (b) (4) level of crystallization could reliably be quantitated (and, again, we are not confident that this is the case), we are not convinced that any batch that met your release specification of (b) (4) would, in fact, be within the (b) (4) limit at 12 months, given the results determined by your analysts at 12 months in the validation batches, as described above.

Further, we note that your temperature excursion and cycling stability studies demonstrated that increased crystallization occurred as early as one week when stored at room temperature and increased to (b) (4) after 11 weeks at (b) (4). These findings increase our concern that significant crystallization can occur when the product is shipped to areas of higher temperatures and humidity and not immediately stored at (b) (4). Of course, our inability to validate your methodology further increases our concerns about the results of these studies.

For these reasons, we strongly reiterate our recommendation that the definitive resolution of the crystallization issue is to reformulate the drug product in order to prevent the formation of crystals. The use of (b) (4) in the manufacture of the drug product clearly does not satisfactorily limit the potential for crystallization, and your attempts to limit the degree of crystallization have, to date, been unsuccessful in our view. The Agency recommends that the reformulated product should be crystal free throughout its shelf-life, well controlled using validated analytical methods, and crystal-free under appropriate conditions as assessed in adequate temperature excursion and cycling stability studies.

CLINICAL

1. We acknowledge that you have responded to our requests conveyed in the Complete Response letter of December 15, 2008. As a result of our analyses of your response, we may include several statements in labeling about several adverse events.

2. In your response to this letter, please include a revised Pediatric Plan for the Restless Legs Syndrome (RLS) indication. Your revised plan should include a proposal for studies in pediatric patients ages 13 years and older.

LABELING

1. We reserve comment on the proposed labeling until the application is otherwise adequate. However, to facilitate review of your proposed labeling, we ask that you resubmit the content of labeling [21 CFR 314.50(l)(1)(i)] in *MS Word* format. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

   Please include a tracked changes version (in WORD) of the label in PLR format using the last approved label as the base document.

2. Please submit updated carton and container labeling for the 1mg/24 hours, 3mg/24 hours and 8mg/24 hours patch strengths in your resubmission.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the Safety Update, incorporate new safety data as follows:

   - Present new safety data about deaths from the studies for all proposed indications using the same format as in the original NDA submission.

   - Present tabulations of the new safety data separately and also combined with the original NDA data and with each of the previous Safety Updates.

   - Include a tabular summary of the mortality rate according to indication and list all cause mortality, death due to myocardial infarction, all cardiac-related deaths, and non-cardiac-related deaths. Present the mortality rate by cause from the original NDA, separately in each Safety Update, and cumulatively in each Safety Update combined with all previous safety data.

   - Present narrative summaries and a tabular summary for all new deaths from all clinical trials involving Neupro. This tabular summary should provide the following information in a single row: patient ID, country, age/gender, treatment/dose/study phase, day after starring treatment, fatal/nonfatal, and a hyperlink to the narrative summary and CRFs. Narratives should provide sufficient detail to permit an adequate understanding of the adverse event. Guidelines for narrative summary content provided in the Guidance for Industry- Premarket Risk Assessment (http://www.fda.gov/cder/guidance/6357fnl.pdf), published in 3/05.

3. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

4. Provide a summary of worldwide post-marketing experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

5. Provide a summary and discussion of the published literature since the last presentation of the published literature. Include a copy of each publication cited.

6. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21829	SUPPL-2	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS

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

/s/

RUSSELL G KATZ
04/21/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-829/S-001 and 002

COMPLETE RESPONSE

UCB, Inc.
Attention: Deborah Hogerman
Senior Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Ms. Hogerman:

Please refer to your supplemental new drug applications dated September 21, 2007 and October 5, 2007, received October 11, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro (rotigotine transdermal) Patch.

We acknowledge receipt of your amendments dated October 17, 2007, and February 8, May 7, June 4, July 15, September 8 and 9, and October 3, 2008.

Supplemental application 001 proposes an added indication to treat "the signs and symptoms of advanced Parkinson's disease (APD)" and supplemental application 002 proposes an added indication to treat "the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS)."

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. Although we have concluded that you have provided substantial evidence of effectiveness for Neupro in patients with advanced Parkinson's disease and in patients with RLS, we describe below our reasons for not being able to approve these supplements at this time, and our recommendations for addressing these issues.

PRODUCT QUALITY

1. As you know, after you submitted these supplements, you informed the Agency of crystal formation in the marketed patches. This crystallization appeared as early as (b) (4) after manufacture in some cases. Over time, extensive crystallization occurred, resulting in product failure, and withdrawal of the product from the market. The crystallization occurred (b) (4) (b) (4) . In order to ensure that crystallization does not occur in the future, we strongly recommend that you reformulate the product. You must provide the following information about any reformulated product before it can be approved:

Drug Substance
1) Physical and chemical characterization of the (b) (4) used,
2) Data to support any revisions to the manufacturing process and in process controls,
3) Specifications with justification for any new specifications proposed,
4) Batch release data, and
5) Stability data from three production scale batches, stored under long term (marketed) conditions through retest period and six months under accelerated conditions.

Drug Product
1) Components and composition,
2) Unit and batch formula,
3) Batch release data,
4) Data to support any revisions to the manufacturing process, In process controls,
5) Specifications with justification for any new specifications proposed, and
6) Stability data from three production scale batches, stored under long term (marketed) conditions through the shelf life and six months under accelerated conditions.

Once you have submitted adequate information to establish the reliability of the new product, you will need to establish that the plasma levels of rotigotine produced by this new product are comparable (bioequivalent) to those produced by the product used in the clinical trials (both for the original approval as well as for the data in these two supplements). In the absence of such data, it would be difficult, if not impossible, to conclude that the previously generated clinical data apply to the newly formulated product.

CLINICAL

2. Please conduct analyses of female reproductive endocrine testing (e.g., serum/plasma LH, FSH, estradiol, progesterone) of all patients in RS1 pool (i.e., all RLS patients in double-blind phase of studies 790 and 792) according to whether the patients are considered pre-menopausal or post-menopausal at the time of screening/randomization. It is not clear if you have applied the same reproductive endocrine testing reference range for patients with the same reproductive status (i.e., pre-menopausal or post-menopausal) considering that we believe that you have utilized a central laboratory for all these tests. If a central laboratory was utilized for all RS1 pool patients, the same reference range should be applied to each individual patient based upon their pre-menopausal or post-menopausal status.

   Initially, please categorize all patients in the RS1 pool as to whether they are pre-menopausal or post-menopausal. After this categorization, please conduct and present all the various, central tendency and outlier analyses of pool RS1 for the different perspectives (e.g., mean absolute values over time, mean change from baseline over time, shift analysis over time, incidence of "low" or "increased" value at any time during the study, and similar respective analyses for "markedly abnormal" values). Please show

results for these analyses **for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page** so that a comparison across treatments can be easily interpreted.

If we do not have a correct understanding about the apparent deficiencies in these analyses, it may be helpful to contact us for clarification about what is needed and what should be done in your resubmission of your Complete Response.

3. Please review all Case Report Forms (CRFs) for TEAEs (in RS1 pool for RLS) that suggest any change in libido and have not been characterized as either essentially increased or decreased. Most likely, a change in libido would either reflect a change such as increased or decreased libido. Please consider recharacterizing any TEAE suggesting a change/alteration in libido that is not specific (e.g., libido abnormal or libido altered) to a more specific characterization such as libido increased or decreased.

   Once all libido-related TEAEs have been reviewed and possibly recharacterized, present the incidence of all similar AE terms suggesting either increased or decreased libido for the RS1 pool according to randomized treatment (i.e., for placebo and each specific rotigotine dose and also for "any" dose) for these TEAEs occurring at any time during the double-blind phase. If these various AE terms can be considered as reflecting either increased or decreased libido, please present the incidence of all these similarly related AE terms suggesting the possibility of increased or decreased libido.

   Please show results for these analyses **for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page** so that a comparison across treatments can be easily interpreted.

4. Please have your clinicians review all Case Report Forms (CRFs) for TEAEs (in RS1 pool for RLS) that suggest any change in menses (e.g., non-specific characterizations such as menstrual disorder, menses abnormal, menstruation irregular or other such non-specific characterizations) that have not been characterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea, menstruation delayed). Once these CRF reviews have been completed, have your clinicians determine whether these various menstrual TEAEs can be recharacterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea). Typically, a significant change in menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea) suggests that there is anovluation.

   After all menstrual TEAEs have been reviewed and possibly recharacterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea), present the incidence of

all similar AE terms suggesting that menses are anovulatory according to randomized treatment (i.e. for placebo and each specific rotigotine dose and also for "any" dose) for these TEAEs occurring at any time during the double-blind phase.

Please show results for these analyses **for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page** so that a comparison across treatments can be easily interpreted.

5. Please conduct and submit analyses of TEAEs that might possibly reflect events (regardless of level of severity) suggestive of the occurrence of hypotension/orthostatic hypotension/postural dizziness for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's disease and for pool RS1 (double-blind phase of studies 790 and 792). Search for a variety of AE terms that might be suggestive of orthostatic hypotension / postural dizziness despite the fact that the AE may not have been coded as such. You have used the following AE search terms for searching for possible "severe" hypotension or orthostatic hypotension (i.e., blood pressure orthostatic, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, dizziness postural, and orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension). Please add the following AE search terms including: dizziness, vertigo, light-headedness, postural light-headedness, impaired balance, and feeling drunk.

   Analyses should be conducted according to randomized treatment (i.e. for placebo and each specific rotigotine dose and also for "any" dose) for TEAEs occurring at any time during the double-blind phase, for SAEs occurring at any time during the double-blind phase, and for TEAEs causing study discontinuation at any time during the double-blind phase.

6. Please conduct and submit subgroup analyses of TEAEs occurring in certain subgroups (i.e., age, gender, concomitant medication such as vasodilator/hypotensive agents) for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792). Your subgroup analyses of TEAEs only considered the frequency of TEAEs for rotigotine treatment relative to each subgroup comparison and did not consider the frequency for placebo treatment in each subgroup analysis

   To conduct these analyses, please present a summary analysis of the incidence of the treatment effect (e.g., % for specific rotigotine dose - % for placebo) for each TEAE according to various level terms (e.g., SOC, high level and high level group terms, and preferred term as presented previously) in each requested subgroup. Please show results for each subgroup immediately below the other subgroup for each AE term **for each specific rotigotine dose and "any" rotigotine dose on the same page** so that a comparison across treatments can be easily interpreted.

LABELING

7. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

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

12/15/2008 01:50:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEUPRO safely and effectively. See full prescribing information for NEUPRO.

Neupro (Rotigotine Transdermal System)
Initial U.S. Approval: 2007

----------RECENT MAJOR CHANGES----------

Indications and Usage, Parkinson's Disease (1.1) 04/2012
Indications and Usage, Restless Legs Syndrome (1.2) 04/2012
Dosage and Administration, Advanced-Stage Parkinson's Disease (2.1) 04/2012
Dosage and Administration, Restless Legs Syndrome (2.2) 04/2012
Warnings and Precautions (5) 4/2012

----------INDICATIONS AND USAGE----------

Neupro is a dopamine agonist indicated for the treatment of:

- Signs and symptoms of Parkinson's disease (1.1)
- Moderate-to-severe primary Restless Legs Syndrome (1.2)

----------DOSAGE AND ADMINISTRATION----------

Apply once a day to the skin; press firmly in place for 30 seconds, making good contact. Do not place Neupro on oily, irritated, or damaged skin, or where it will be rubbed by tight clothing. Do not use the same site more than once every 14 days. The prescribed dose may be achieved using single or multiple patches. (2)

- **Parkinson's disease:** Initially, 2 mg/24 hours for early-stage disease or 4 mg/24 hours for advanced-stage disease. The dose may be increased as needed by 2 mg/24 hours at weekly intervals, up to 6 mg /24 hours for early-stage disease and up to 8 mg/24 hours for advanced-stage disease. (2.1)
- **Restless Legs Syndrome:** Initially, 1 mg/24 hours, increased as needed by 1 mg/24 hours at weekly intervals, up to 3 mg/24 hours. (2.2)

To discontinue treatment, reduce the dose gradually until complete withdrawal of Neupro. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Transdermal System: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg and 8 mg rotigotine per 24 hours. (3)

----------CONTRAINDICATIONS----------

History of hypersensitivity to rotigotine or components of the transdermal patch. (4)

----------WARNINGS AND PRECAUTIONS----------

- Contains sodium metabisulfite that may cause allergic-type reactions in those with sulfite sensitivity. (5.1)
- Falling asleep during activities of daily living, including the operation of motor vehicles and somnolence may occur. (5.2)
- Hallucinations/psychotic -like behavior and dyskinesia may occur. (5.3, 5.9)
- Symptomatic postural hypotension and syncope may occur, especially during dose escalation. (5.4, 5.5)
- Application site reactions can occur, and may be severe. (5.10)
- Elevation of blood pressure and heart rate may occur. (5.7)
- Intense urges may cause impulse control and compulsive behaviors. (5.6)
- Monitor patients for these adverse reactions. If these adverse reactions occur, lowering the dose or discontinuing Neupro may be beneficial. (5)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥ 5 % greater than placebo) for the highest recommended doses of Neupro for treatment of Parkinson's disease were nausea, vomiting, somnolence, application site reactions, dizziness, anorexia, hyperhidrosis, insomnia, peripheral edema, and dyskinesia. (6.1)
- Most common adverse reactions (≥ 5 % greater than placebo) for the highest recommended dose of Neupro for Restless Legs Syndrome were application site reactions, nausea, somnolence, and headache.(6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 866-822-0068 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 04/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Parkinson's Disease (PD)

Neupro (Rotigotine Transdermal System) is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of Neupro was demonstrated in randomized, controlled trials in patients with early-stage Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced-stage Parkinson's disease on concomitant levodopa.

1.2 Restless Legs Syndrome (RLS)

Neupro (Rotigotine Transdermal System) is indicated for the treatment of moderate-to-severe primary restless legs syndrome.

2 DOSAGE AND ADMINISTRATION

Neupro is applied once a day. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time every day, at a convenient time for the patient. Because Neupro is administered transdermally, food is not expected to affect absorption and it can be applied irrespective of the timing of meals. No dosage adjustment is necessary for patients who have moderate impairment of hepatic function or mild to severe impairment of renal function. The application site for Neupro should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days and should not be placed on skin that is oily, irritated, or damaged, or where it will be rubbed by tight clothing. If it is necessary to apply Neupro to a hairy area, the area should be shaved at least 3 days prior to Neupro application. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 30 seconds, making sure there is good contact, especially around the edges. If the patient forgets to replace Neupro, or if the transdermal system becomes dislodged, another transdermal system should be applied for the remainder of the day. The prescribed dose may be achieved using single or multiple patches. *[Refer Patients to Instructions for Use in the Patient Information Section at the end of the Full Prescribing Information].*

2.1 Parkinson's Disease

Early-Stage Parkinson's Disease

Neupro should be started at 2 mg/24 hours for patients with early-stage Parkinson's disease. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose was 4 mg/24 hours. The highest recommended dose for early-stage Parkinson's disease is 6 mg/24 hours.

Advanced-Stage Parkinson's Disease

Patients with advanced-stage Parkinson's disease may be initiated at 4 mg/24 hours. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours. The recommended dose for advanced-stage Parkinson's disease is 8 mg/24 hours.

2.2 Restless Legs Syndrome

Neupro should be started at 1 mg/24 hours. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 1 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose was 1 mg/24 hours. The highest recommended dose is 3 mg/24 hours.

2.3 Discontinuation of Treatment

For patients with Parkinson's disease, the daily dose should be reduced by a maximum of 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of Neupro is achieved.

For patients with RLS, the daily dose should be reduced by 1 mg/24 hours preferably every other day, until complete withdrawal of Neupro is achieved.

3 DOSAGE FORMS AND STRENGTHS

Transdermal System: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg and 8 mg rotigotine per 24 hours.

4 CONTRAINDICATIONS

Neupro is contraindicated in patients who have demonstrated hypersensitivity to rotigotine or the components of the transdermal system.

5 WARNINGS AND PRECAUTIONS

Patients should be monitored for developing adverse reactions described in this section. If any of these adverse reactions develop, lowering or discontinuing the dose of Neupro may be beneficial.

5.1 Sulfite Sensitivity

Neupro contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.2 Falling Asleep During Activities of Daily Living and Somnolence

Patients with early and advanced Parkinson's disease and with Restless Legs Syndrome treated with Neupro have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on Neupro, some did not perceive warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after initiation of treatment. In trials of Restless Legs Syndrome, 2 % of patients treated with the highest recommended Neupro dose (3 mg/24 hours) reported sleep attacks vs 0 % of placebo patients.

Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment.

Somnolence is a common occurrence in patients receiving Neupro. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for somnolence was 16% for early Parkinson's disease, 4 % for advanced Parkinson's disease, and 6 % for Restless Legs Syndrome. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving, operating machines, or working at heights during treatment with Neupro. Patients who have already experienced somnolence and/or an episode of sudden sleep onset should not participate in these activities during treatment with Neupro.

Before initiating treatment with Neupro, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase this risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Neupro should ordinarily be discontinued *[see Dosage and Administration (2.3)]*

If a decision is made to continue Neupro, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.3 Hallucinations / Psychotic-Like Behavior

There was an increased risk for hallucinations in patients with advanced-stage Parkinson's disease treated with Neupro. For the highest recommended Neupro dose, the incidence of the treatment difference (Neupro % - Placebo %) for hallucinations was 4% for patients with advanced-stage Parkinson's disease, and this difference increased with increasing dose. Hallucinations were of sufficient severity to cause discontinuation of treatment (mainly during the dose escalation/titration period) in 3% of advanced-stage Parkinson's disease patients treated with the highest recommended dose of Neupro

compared with 1 % of placebo treated patients. Hallucinations have also been reported in post-marketing reports.

Post-marketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during Neupro treatment or after starting or increasing the dose of Neupro. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium. These various manifestations of psychotic-like behavior were also observed during the clinical development of Neupro for early and advanced-stage Parkinson's disease and Restless Legs Syndrome.

Patients with a major psychotic disorder should ordinarily not be treated with Neupro because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of Neupro *[see Drug Interactions (7.1)]*.

5.4 Symptomatic Hypotension

Dopaminergic agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, resulting in postural/orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge. For these reasons, both Parkinson's and RLS patients being treated with dopaminergic agonists ordinarily (1) require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and (2) should be informed of this risk.

Mild-moderate decreases in systolic blood pressure ($\geq$ 20 mm Hg) and in diastolic blood pressure ($\geq$ 10 mm Hg) occurred more frequently (Neupro % $\geq$ 5 % greater than placebo %) in all patients (i.e., early and advanced-stage Parkinson's disease and Restless Legs Syndrome) with the highest recommended Neupro dose. These decreases in systolic and diastolic blood pressure were observed when supine, standing, and changing from supine to standing position. More severe decreases in systolic blood pressure (> 40 mm Hg) and in diastolic blood pressure ($\geq$ 20 mm Hg) also occurred more frequently (Neupro % $\geq$ 2 % greater than placebo %) in patients with early and advanced-stage Parkinson's disease during measurements when supine, standing and/or changing from supine to standing position. Some threshold decreases in blood pressure described earlier appeared to be dependent on the dose of Neupro and were also observed at the final study visit.

An analysis using a variety of adverse reaction terms suggestive of orthostatic hypotension, including dizziness/postural dizziness and others, showed an increased risk for all patients treated with Neupro. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for adverse reactions suggestive of hypotension/orthostatic hypotension was 18 % for early Parkinson's disease, 4 %for advanced Parkinson's disease, and 1 % for Restless Legs Syndrome.

This increased risk for symptomatic hypotension and decreases in blood pressure was observed in a setting in which patients were very carefully titrated, and patients with clinically relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been excluded from this study. The increased risk for significant decreases in blood pressure or orthostatic hypotension occurred especially in the dose escalation/titration period.

5.5 Syncope

Syncope has been reported in patients using dopamine agonists, and for this reason patients should be alerted to the possibility of syncope. Because the studies of Neupro excluded patients with clinically relevant cardiovascular disease, patients with severe cardiovascular disease should be treated with caution.

5.6 Impulse Control / Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including Neupro, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro *[see Patient Counseling Information (17.6)]*.

5.7 Elevation of Blood Pressure and Heart Rate

Some patients treated with Neupro exhibited moderately severe increases in systolic blood pressure (> 180 mm Hg) and/or in diastolic blood pressure (> 105 mm Hg) while supine and/or standing. In patients with advanced-stage Parkinson's disease, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 2 % for systolic blood pressure > 180 mm Hg and of 4 % for diastolic blood pressure > 105 mm Hg. In patients with Restless Legs Syndrome, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 4 % for diastolic blood pressure > 105 mm Hg.

Mild-moderate increases in systolic blood pressure (≥ 20 mm Hg) and in diastolic blood pressure (≥ 10 mm Hg) occurred more frequently (Neupro % ≥ 5 % greater than placebo %) in all patients (i.e., early and advanced-stage Parkinson's disease and Restless Legs Syndrome) with the highest recommended Neupro dose. These increases in systolic and diastolic blood pressure were observed when supine, standing, and changing from supine to standing position. More severe increases in systolic blood pressure (> 40 mm Hg) and in diastolic blood pressure (≥ 20 mm Hg) also occurred more frequently (Neupro % ≥ 2 % greater than placebo %) in patients with early and advanced-stage Parkinson's disease and with Restless Legs Syndrome during measurements when supine, standing and/or changing from supine to standing position. Some threshold increases in blood pressure described earlier appeared to be dependent on the dose of Neupro and were also observed at the final study visit.

In the placebo-controlled trials, there was an increased risk for hypertension as an adverse reaction with the highest recommended dose for advanced-stage Parkinson's disease (Neupro 3 % vs placebo 0 %) and for Restless Legs Syndrome (Neupro 4 % vs placebo 0 %).

Some patients treated with Neupro exhibited moderately increased pulse (> 100 beats per minute) while supine and/or standing. In patients with advanced-stage Parkinson's disease, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 2 % for increased pulse. In patients with Restless Legs Syndrome, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 5 % for increased pulse.

These findings of blood pressure and heart rate elevations should be considered when treating patients with cardiovascular disease.

5.8 Weight Gain and Fluid Retention

Patients taking the highest recommended Neupro dose for early-stage Parkinson's disease had a higher incidence (2 %) of substantial weight gain (more than 10% of baseline weight) than subjects taking placebo (0 %). In advanced-stage Parkinson's disease, the incidence of weight gain more than 10 % of baseline weight was 9 % Neupro (for highest recommended dose) and 1 % placebo. This weight gain was frequently associated with the development of peripheral edema in patients with Parkinson's disease, suggesting that Neupro may cause substantial fluid retention in some Parkinson's patients. Although the weight gain was usually well-tolerated in subjects observed in the Parkinson's clinical studies, it could cause greater difficulty in patients who may be especially vulnerable to negative clinical consequences from fluid retention such as those with significant congestive heart failure or renal insufficiency.

For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for peripheral edema was 1% for early Parkinson's disease, and 8% for advanced Parkinson's disease. These treatment differences increased further with treatment at Neupro dosing above the highest recommended doses.

5.9 Dyskinesia

Neupro may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate pre-existing dyskinesia. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for dyskinesia was 7 % for patients with advanced-stage Parkinson's disease, and this incidence increased with increasing dose. There was also an increased risk (Neupro 3 % vs placebo 0 %) for discontinuation from the study because of dyskinesia for the highest recommended Neupro dose in these same patients.

5.10 Application Site Reactions

Application site reactions (ASRs) were reported at a greater frequency in the Neupro-treated patients than in placebo patients in the double-blind, placebo-controlled dose-response studies with Neupro. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for various ASRs was 15 % for early-stage Parkinson's disease, 23% for advanced-stage Parkinson's disease, and 39 % for Restless Legs Syndrome. ASRs exhibited a dose-dependent relationship for all doses for patients with early and advanced-stage Parkinson's disease and Restless Legs Syndrome ASRs

were also of sufficient severity to cause study discontinuation for patients with early-stage Parkinson's disease (Neupro 3 % vs placebo 0 %), advanced-stage Parkinsons's disease (Neupro 2 % vs placebo 0 %, and Restless Legs Syndrome (Neupro 12 % vs placebo 0 %) who were treated with the highest recommended Neupro dose.

Of ASRs in Neupro-treated patients, most were mild or moderate in intensity. The signs and symptoms of these reactions generally were localized erythema, edema, or pruritus limited to the patch area and usually did not lead to dose reduction. Generalized skin reactions (e.g., allergic rash, including erythematous, macular-papular rash, or pruritus), have been reported at lower rates than ASRs during the development of Neupro.

In a clinical study designed to investigate the cumulative skin irritation of Neupro, daily rotation of Neupro application sites has been shown to reduce the incidence of ASRs in comparison to repetitive application to the same site. In a clinical study investigating the skin sensitizing potential of Neupro in 221 healthy subjects, no case of contact sensitization was observed. Localized sensitization reactions were observed in a study with healthy subjects by continuously rotating a 0.5 mg/24 hours transdermal system, after induction of maximal irritational stress was achieved by repetitive transdermal system application to the same site. If a patient reports a persistent application site reaction (of more than a few days), reports an increase in severity, or reports a skin reaction spreading outside the application site, an assessment of the risk and benefits for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

5.11 Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using Neupro for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

5.12 Augmentation and Rebound in RLS

Augmentation is a worsening of RLS symptoms during treatment, leading to an increase in overall symptom severity or earlier time of symptom onset each day compared to before initiation of treatment. Dopaminergic medicinal products, including rotigotine, may result in augmentation.

Rebound, an exacerbation of RLS symptoms, is considered to be an end of dose effect, related to the half-life of the therapeutic agent. Reports in the published literature indicate discontinuation or wearing off of dopaminergic medications can result in rebound.

5.13 Magnetic Resonance Imaging and Cardioversion

The backing layer of Neupro contains aluminum. To avoid skin burns, Neupro should be removed prior to magnetic resonance imaging or cardioversion.

5.14 Heat Application

The effect of application of heat to the transdermal system has not been studied. However, heat application has been shown to increase absorption several fold with other transdermal products. Patients should be advised to avoid exposing the Neupro application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

5.15 Withdrawal-Emergent-Hyperpyrexia and Confusion

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, rhabdomyolysis, and/or autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. Therefore it is recommended that the dose be tapered at the end of Neupro treatment as a prophylactic measure *[see Dosage and Administration (2.3)]*

5.16 Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

5.17 Binding to Melanin

As has been reported with other dopamine agonists, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident after a single dose of rotigotine, but was slowly cleared over the 14-day observation period.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in the Warnings and Precautions section of labeling.

- Sulfite Sensitivity *[see Warnings and Precautions (5.1)]*
- Falling Asleep During Activities of Daily Living and Somnolence *[see Warnings and Precautions (5.2)]*
- Hallucinations / Other Psychiatric Disorders *[see Warnings and Precautions (5.3)]*
- Symptomatic Hypotension *[see Warnings and Precautions (5.4)]*
- Syncope *[see Warnings and Precautions (5.5)]*
- Impulse Control / Compulsive Behaviors *[see Warnings and Precautions (5.6)]*
- Elevation of Blood Pressure and Heart Rate *[see Warnings and Precautions (5.7)]*
- Weight Gain and Fluid Retention *[see Warnings and Precautions (5.8)]*
- Dyskinesia *[see Warnings and Precautions (5.9)]*
- Application Site Reactions *[see Warnings and Precautions (5.10)]*
- Melanoma *[see Warnings and Precautions (5.11)]*
- Augmentation and Rebound in RLS *[see Warnings and Precautions (5.12)]*
- Heat Application *[see Warnings and Precautions (5.14)]*
- Withdrawal-Emergent-Hyperpyrexia and Confusion *[see Warnings and Precautions (5.15)]*
- Fibrotic Complications *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions (number of unique patients experiencing an adverse reaction associated with treatment / total number of patients treated) observed in the clinical trials of a drug cannot be directly compared to incidence of adverse reactions in the clinical trials of another drug and may not reflect the incidence of adverse reactions observed in practice.

Adverse Reactions Incidence in Controlled Clinical Studies in Early-Stage Parkinson's Disease

The safety of Neupro was evaluated in a total of 649 early-stage Parkinson's disease patients who participated in three double-blind, placebo-controlled studies with durations of 3 to 9 months. Additional safety information was collected in short term studies, and two open-label extension studies in patients with early-stage Parkinson's disease.

The incidence of adverse reactions in a randomized, double-blinded, placebo-controlled, fixed-dose trial is shown in Table 1. Incidences for the non-recommended 8 mg/24 hour dose are also shown.

In the double-blind, placebo-controlled, Dose-Response study in patients with early-stage Parkinson's disease, the most commonly observed adverse reactions ($\geq$ 5 % greater than placebo) for the highest recommended dose of Neupro (6 mg/24 hours) were nausea, vomiting, somnolence, application site reactions, dizziness, anorexia, hyperhidrosis, and insomnia.

In this trial, 12% of patients treated with the highest, recommended Neupro dose (6 mg/24 hours) discontinued treatment because of adverse reactions, compared with 6% of patients who received placebo.

Table 1 Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Trial of Patients with Early-Stage Parkinson's Disease (Dose-Response Study) Where Incidence Was ≥ 2 % in 6 mg/24 hours Neupro Group and Greater Than the Incidence in Placebo-Treated Patients

Adverse Reactions	Placebo N=64 %	Neupro dose			
		2 mg/24h N=67 %	4 mg/24h N=64 %	6 mg/24h N=65 %	8 mg/24h N=70 %
Ear and labyrinth disorders					
Tinnitus	0	0	2	3	0
Gastrointestinal disorders					
Nausea*	13	34	38	48	41
Vomiting*	3	10	16	20	11
Anorexia	0	0	2	8	4
Dyspepsia	0	2	2	3	0
General disorders and administration site conditions					
Application and instillation site reactions	19	24	21	34	46
Fatigue	3	8	18	6	13
Oedema peripheral*	2	2	3	3	4
Infections and infestations					
Upper respiratory tract infection	0	3	5	2	0
Sinusitis	0	2	0	2	1
Injury, poisoning and procedural complications					
Contusion*	0	2	0	2	4
Investigations					
White blood cells urine positive	2	3	3	3	1
Electrocardiogram T wave abnormal	0	0	2	3	0
Weight decreased*	0	0	0	2	3
Metabolism and nutrition disorders					
Anorexia	0	2	2	6	1
Decreased appetite*	0	0	0	3	3
Musculoskeletal and connective tissue disorders					
Muscle spasms*	2	3	2	3	4
Nervous system disorders					
Dizziness	11	21	14	22	20
Dizziness postural	0	2	2	2	1
Somnolence*	3	12	14	19	20
Lethargy	0	2	2	2	1
Balance disorder	0	0	2	3	0
Psychiatric disorders					
Insomnia	6	5	10	11	7
Early morning awakening*	0	0	0	2	3
Abnormal dreams*	0	2	5	3	7
Depression	0	5	3	2	0
Reproductive system and breast disorders					
Erectile dysfunction*	0	0	0	2	3
Respiratory, thoracic and mediastinal disorders					

Pharyngolaryngeal pain	0	2	2	2	0
Hiccups*	0	2	2	2	3
Skin and subcutaneous tissue disorders					
Hyperhidrosis	3	3	3	11	3
Erythema*	3	3	6	5	6
Rash pruritic*	0	0	0	2	3

*Dose-related

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAEs=treatment-emergent adverse events

The incidence of certain adverse reactions with Neupo treatment was notably increased compared to placebo treatment (i.e., Neupro % - placebo % = ≥ 5 %) in either the titration or maintenance phases of the Dose-Response trial. During the titration phase, an increased incidence (in descending order of % treatment difference) was observed for nausea, somnolence, vomiting, application site reactions (ASRs), dizziness, sweating increased, anorexia and vision abnormal. During the maintenance phase, an increased incidence was observed for nausea, and ASRs. Some adverse reactions developing in the titration phase persisted (≥ 7 days) into the maintenance phase. These "persistent" adverse reactions included ASRs, anorexia, somnolence, nausea, and vision abnormal.

Adverse Reactions Incidence in Controlled Clinical Studies in Advanced-Stage Parkinson's Disease

The safety evaluation of Neupro was based on a total of 672 Neupro-treated subjects with advanced-stage Parkinson's disease who participated in 3 double-blind, placebo-controlled studies (2 fixed-dose trials and one flexible dose trial) with durations of 3 to 7 months. Patients received concomitant levodopa in these studies. Additional safety information was collected in earlier short-term studies, and 2 open-label extension studies in subjects with advanced-stage Parkinson's disease.

The incidence of adverse reactions in a randomized, double-blinded, placebo-controlled, fixed-dose trial is shown in Table 2. Incidences for the non-recommended 12 mg/24 hour dose are also shown.

In the Dose-Response, placebo controlled trial for advanced-stage Parkinson's disease, the most common adverse reactions (≥ 5 % greater than placebo) for the highest recommended dose of Neupro (8 mg) were application site reactions, nausea, somnolence, and headache.

In this trial, approximately 15 % of patients treated with the highest, recommended Neupro dose (8 mg/24 hours) discontinued treatment because of adverse reactions, compared with 9 % of patients who received placebo.

Table 2 Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Trial of Patients with Advanced-Stage Parkinson's Disease (Dose-Response Study) Where Incidence Was ≥ 2 % in 8 mg/24 hours Neupro Group and Greater Than the Incidence in Placebo-Treated Patients

Adverse Reaction	Placebo N=120 %	Neupro dose	
		8 mg/24h N=118 %	12 mg/24h N=111 %
Gastrointestinal disorders			
Nausea	19	28	22
Vomiting	6	10	8
Constipation	6	9	5
Diarrhea	5	7	5
General disorders and administration site conditions			
Application and instillation site reactions [a]*	13	36	46
Edema peripheral*	1	9	14
Asthenia	3	4	3
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	1	2	2
Arthralgia	7	11	8

Nervous system disorders			
Somnolence	28	32	32
Dizziness	15	23	14
Dyskinesia*	7	14	17
Headache	8	10	8
Paraesthesias/Dysesthesias*	3	5	6
Tremor	3	4	3
Psychiatric disorders			
Disturbances in initiating and maintaining sleep[a] *	6	9	14
Hallucinations *	3	7	14
Nightmare*	2	3	5
Respiratory, thoracic and mediastinal disorders			
Cough	1	3	3
Nasal congestion	0	3	3
Sinus congestion	0	3	2
Skin and subcutaneous tissue disorders			
Hyperhidrosis	0	3	1
Erythema	1	3	2
Vascular disorders			
Hypertension*	0	3	5

*Dose-related

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAEs=treatment-emergent adverse events

[a] The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions, and disturbances in initiating and maintaining sleep

The incidence of certain adverse reactions with Neupo treatment was notably increased compared to placebo treatment (i.e., Neupro % - placebo % = ≥ 5 %) in either the titration or maintenance phases of the Dose-Response trial. During the titration phase, an increased incidence (in descending order of % treatment difference) was observed for nausea, hallucinations, constipation, dyskinesia, dizziness. During the maintenance phase, an increased incidence was observed for ASRs, peripheral edema, and dyskinesia. Some adverse reactions developing in the titration phase persisted (≥ 7 days) into the maintenance phase. A notably "persistent" adverse reaction was ASRs.

Adverse Reactions Incidence in Controlled Clinical Studies in Restless Legs Syndrome

The safety evaluation of rotigotine was based on a total of 745 Neupro-treated subjects with RLS who participated in 2 double-blind, placebo-controlled studies with maintenance durations of 6 months. Additional safety information was collected in earlier short term studies, and 3 open-label extension studies in subjects with RLS.

The incidence of adverse reactions in two randomized, double-blinded, placebo-controlled, fixed-dose trials are shown in Table 3.

In the two randomized, double-blinded, placebo-controlled, fixed-dose trials for RLS, the most common adverse reactions (≥ 5 % greater than placebo) for the highest recommended dose of Neupro (3 mg) were application site reactions, nausea, somnolence, and headache.

In the two Dose-Response, placebo controlled trials, 24 % of Neupro-treated patients treated with the highest recommended dose (3 mg) discontinued treatment because of adverse reactions, compared with 3 % of patients who received placebo.

Table 3 Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Trial of Patients with Restless Legs Syndrome (North American and Foreign Multinational Studies) Where Incidence Was ≥ 2 % in 2 mg or 3 mg/24 hours Neupro Groups and Greater Than the Incidence in Placebo-Treated Patients

Adverse Reaction	Placebo N=217	Neupro Dose

		0.5 mg/24h N=99 %	1 mg/24h N=215 %	2 mg/24h N=211 %	3 mg/24h N=220 %
Ear and labyrinth disorders					
Vertigo	1	0	4	3	1
Gastrointestinal disorders					
Nausea	10	18	15	23	21
Dry mouth*	4	3	3	3	7
Constipation	3	6	3	2	5
Vomiting*	1	2	2	4	4
Dyspepsia*	1	2	1	2	3
General disorders and administration site conditions					
Application and instillation site reactions [a]*	4	23	27	38	43
Asthenic conditions [a]*	8	11	7	14	12
Infections and infestations					
Nasopharyngitis	7	5	10	7	8
Sinusitis*	1	2	1	2	3
Investigations					
Serum ferritin decreased*	1	2	1	1	2
Musculoskeletal and connective tissue disorders					
Muscle spasms	1	3	1	4	1
Nervous system disorders					
Headache	11	21	15	18	16
Somnolence*	4	8	5	8	10
Dizziness	6	7	5	9	6
Psychiatric disorders					
Disturbances in initiating and/or maintaining sleep [a]*	3	2	4	3	10
Sleep disorder*	1	0	2	3	3
Abnormal dreams*	0	2	1	2	3
Sleep attacks*	0	0	1	0	2
Skin and subcutaneous tissue disorders					
Pruritus	3	9	4	3	7
Hyperhidrosis*	2	1	3	5	3
Erythema*	1	1	1	0	2
Vascular disorders					
Hypertension*	0	3	1	1	4
Hot flush	1	4	1	3	0

*Dose-related

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

[a] The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions (i.e., asthenia, malaise, fatigue), and disturbances in initiating and maintaining sleep.

The incidence of certain adverse reactions with Neupo treatment was notably increased compared to placebo treatment (i.e., Neupro % - placebo % = $\geq$ 5 %) in either the titration or maintenance phases of the Dose-Response trial. During the titration phase, an increased incidence (in descending order of % treatment difference) was observed for ASRs, and disturbances in initiating and/or maintaining sleep. During the maintenance phase, an increased incidence was observed for ASRs. Some

adverse reactions developing in the titration phase persisted (≥ 7 days) into the maintenance phase. These "persistent" adverse reactions were ASRs, nausea, and disturbances in initiating and/or maintaining sleep.

6.2 Laboratory Changes

Some clinical laboratory analytes were abnormal for patients treated with the highest recommended Neupro dose in the dose-response trials for patients with early-stage and advanced-stage Parkinson's disease and with RLS.

There was a treatment difference (Neupro % - placebo %) of 6 % for decreased hemoglobin (below the normal reference range) and of 3 % for decreased hematocrit (below the normal reference range) in patients with early-stage Parkinson's disease. There was a treatment difference of 4 % for a decreased hemoglobin (below the normal reference range) and of 3 % for decreased hematocrit (below the normal reference range) in patients with advanced-stage Parkinson's disease. There was a treatment difference of 3 % for a decreased hemoglobin (below the normal reference range) in patients with RLS. There was also a treatment difference of 2 % for markedly decreased hemoglobin and hematocrit in patients with advanced Parkinson's disease and of 1 % for markedly decreased hematocrit in patients with RLS.

There was a treatment difference of 9 % for increased serum BUN (above the normal reference range) in patients with early-stage Parkinson's disease. There was a treatment difference of 1 % for markedly increased serum BUN in patients with advanced-stage Parkinson's disease.

There was a treatment difference of 9 % for decreased serum glucose (below the normal reference range) in patients with early-stage Parkinson's disease and of 3 % in patients with advanced-stage Parkinson's disease. There was a treatment difference of 1 % for markedly decreased serum glucose in patients with advanced-stage Parkinson's disease.

7 DRUG INTERACTIONS

7.1 Dopamine Antagonists

It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of rotigotine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In studies conducted in mice, rats, and rabbits, rotigotine was shown to have adverse effects on embryo-fetal development when administered during pregnancy at doses similar to or lower than those used clinically. Neupro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rotigotine administered subcutaneously (10, 30, or 90 mg/kg/day) to pregnant mice during organogenesis (gestation days 6 through 15) resulted in increased incidences of delayed skeletal ossification and decreased fetal body weights at the two highest doses and an increase in embryo-fetal death at the high dose. The no-effect dose for embryo-fetal developmental toxicity in mice is approximately 6 times the maximum recommended human dose (MRHD) for Parkinson's disease (8 mg/24 hours) on a body surface area (mg/m^2) basis. Rotigotine administered subcutaneously (0.5, 1.5, or 5 mg/kg/day) to pregnant rats during organogenesis (gestation days 6 through 17) resulted in increased embryo-fetal death at all doses. The lowest effect dose is less than the MRHD on a mg/m^2 basis. This effect in rats is thought to be due to the prolactin-lowering effect of rotigotine. When rotigotine was administered subcutaneously (5, 10, or 30 mg/kg/day) to pregnant rabbits during organogenesis (gestation days 7 through 19), an increase in embryo-fetal death occurred at the two highest doses tested. The no-effect dose is 12 times the MRHD on a mg/m^2 basis.

In a study in which rotigotine was administered subcutaneously (0.1, 0.3, or 1 mg/kg/day) to rats throughout pregnancy and lactation (gestation day 6 through postnatal day 21), impaired growth and development during lactation and long-term neurobehavioral abnormalities were observed in the offspring at the highest dose tested; when those offspring were mated, growth and survival of the next generation were adversely affected. The no-effect dose for pre- and postnatal developmental toxicity (0.3 mg/kg/day) is less than the MRHD on a mg/m^2 basis.

8.3 Nursing Mothers

Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation.

Studies have shown that rotigotine and/or its metabolite(s) are excreted in rat milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NEUPRO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients for any indication have not been established.

8.5 Geriatric Use

Of subjects treated with Neupro in clinical studies for the treatment of Parkinson's disease, approximately 50% were 65 years old and over, and approximately 11% were 75 and over. Among subjects treated with Neupro in clinical studies for the treatment of RLS, 26% were 65 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

No overall differences in plasma levels of rotigotine were observed between patients who were 65 to 80 years old compared with younger patients receiving the same rotigotine doses.

8.6 Renal Impairment

The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. There were no relevant changes in rotigotine plasma concentrations. In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 ml/min), exposure to rotigotine conjugates was doubled. No dosage adjustment is recommended.

8.7 Hepatic Impairment

The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in subjects with moderate impairment of hepatic function (Child Pugh classification – Grade B). There were no relevant changes in rotigotine plasma concentrations. No dose adjustment is necessary in subjects with moderate impairment of hepatic function. No information is available on subjects with severe impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Rotigotine is not a controlled substance

9.3 Dependence

Animal studies and human clinical trials with rotigotine did not reveal potential for drug-seeking behavior or physical dependence.

10 OVERDOSAGE

Since Neupro is a transdermal system, overdosing is not likely to occur in clinical practice unless patients forget to remove the previous day's transdermal system; patients should be advised regarding this possibility.

10.1 Overdose Symptoms

The most likely symptoms of overdose would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions, and other signs of excessive dopaminergic stimulation.

10.2 Overdose Management

There is no known antidote for overdosage of dopamine agonists. In case of suspected overdose, the excess transdermal system(s) should immediately be removed from the patient. Concentrations of rotigotine decrease after patch removal. The terminal half-life of rotigotine is 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-

life of 3 hours. If it is necessary to discontinue use of rotigotine after overdose, it should be discontinued gradually to prevent neuroleptic malignant syndrome *[see Warnings and Precautions (5.14)]*. The daily dose should be reduced by 2 mg/24 hours for Parkinson's disease patients and 1 mg/24 hours for RLS patients with a dose reduction preferably every other day, until complete withdrawal of rotigotine is achieved. Before completely stopping use of Neupro in the event of an overdose *[see Dosage and Administration (2.3)]*.

The patient should be monitored closely, including heart rate, heart rhythm, and blood pressure. As shown in a study of renally impaired patients, dialysis is not expected to be beneficial. Treatment of overdose may require general supportive measures to maintain vital signs.

11 DESCRIPTION

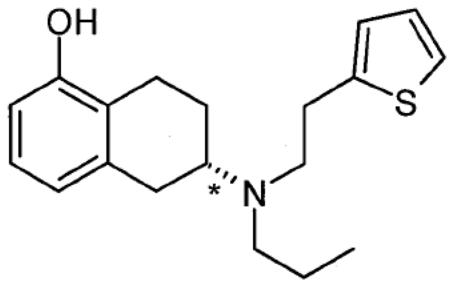
Neupro is a transdermal system that provides continuous delivery of rotigotine, a non-ergoline dopamine agonist, for 24 hours following application to intact skin.

Neupro is available in six strengths as shown in Table 4.

Table 4 Nominal Dose, Drug Content, and Transdermal System Size

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
1 mg/24 hours	2.25 mg	5 cm^2
2 mg/24 hours	4.5 mg	10 cm^2
3 mg/24 hours	6.75 mg	15 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2
8 mg/24 hours	18 mg	40 cm^2

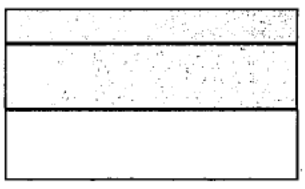
The chemical name of rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol. The empirical formula is $C_{19}H_{25}NOS$. The molecular weight is 315.48. The structural formula for rotigotine is:



The asterisk designates the chiral center.

11.1 System Components and Structure

Neupro is a thin, matrix-type transdermal system composed of three layers as shown in Figure 1:



Backing film

Drug matrix

Protective liner

Figure 1: System Schematic

1. A flexible, tan-colored backing film, consisting of an aluminized polyester film coated with a pigment-layer on the outer side. The backing provides structural support and protection of the drug-loaded adhesive layer from the environment.
2. A self-adhesive drug matrix layer, consisting of the active component rotigotine and the following inactive components: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.
3. A protective liner, consisting of a transparent fluoropolymer-coated polyester film. This liner protects the adhesive layer during storage and is removed just prior to application.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rotigotine is a non-ergoline dopamine agonist. The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine receptors within the caudate-putamen in the brain. The precise mechanism of action of rotigotine as a treatment for Restless Legs Syndrome is unknown but is thought to be related to its ability to stimulate dopamine receptors.

12.2 Pharmacodynamics

Cardiac Electrophysiology

There is no indication of a QT/QTc prolonging effect of Neupro in doses up to 24 mg/24 hours. The effects of Neupro at doses up to 24 mg/24 hours (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg IV, single dose) parallel-group trial with an overall treatment period of 52 days in male and female patients with advanced-stage Parkinson's disease. Assay sensitivity was confirmed by significant QTc prolongation by moxifloxacin.

12.3 Pharmacokinetics

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2). Rotigotine is primarily eliminated in the urine as inactive conjugates. After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

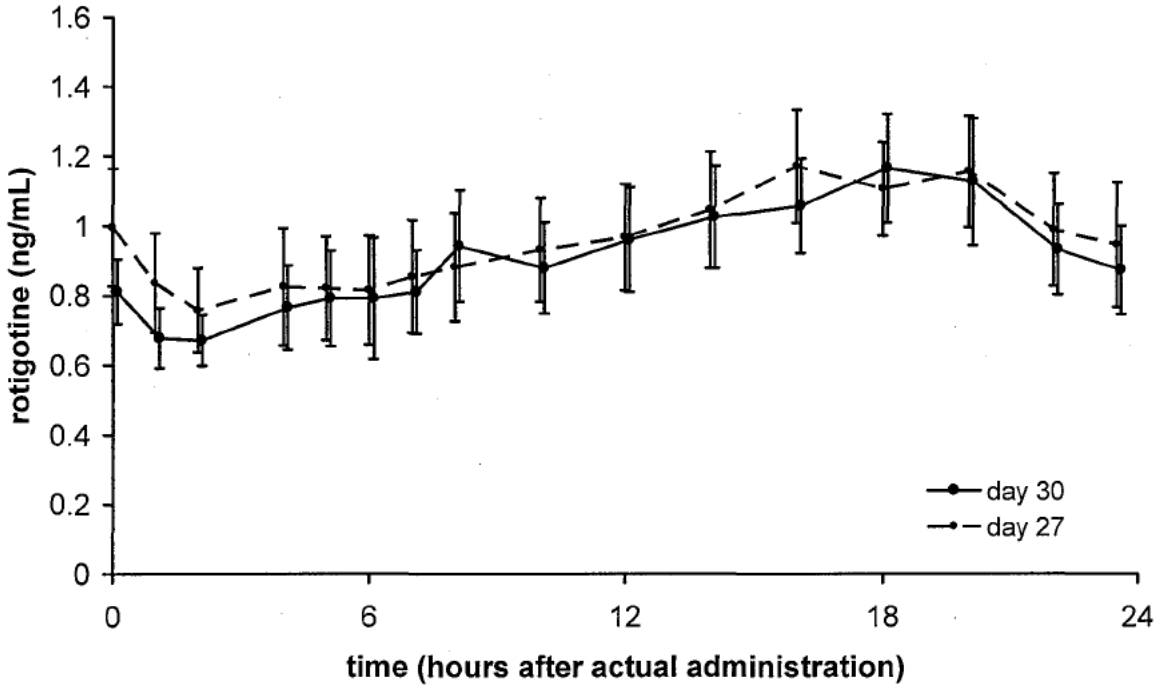
Absorption and Bioavailability

When single doses of 8 mg/24 hours are applied to the trunk, there is an average lag time of approximately 3 hours until drug is detected in plasma (range 1 to 8 hours). T_{max} typically occurs between 15 to 18 hours post dose but can occur from 4 to 27 hours post dose. However, there is no characteristic peak concentration observed. Rotigotine displays dose-proportionality over a daily dose range of 1 mg/24 hours to 24 mg/24 hours. In the clinical studies of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of maintenance treatment. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease. In a single trial conducted in patients with early-stage Parkinson's disease differences in bioavailability ranged from less than 1% (abdomen vs hip) to 46% (shoulder vs thigh) with shoulder application showing higher bioavailability.

Because rotigotine is administered transdermally, food should not affect absorption, and the product may be administered without regard to the timing of meals.

In a 14-day clinical study with rotigotine administered to healthy subjects, steady-state plasma concentrations were achieved within 2 to 3 days of daily dosing.

Figure 2 Average (±95% CI) Neupro Plasma Concentrations in Patients with Early-stage Parkinson's Disease After Application of 8 mg/24 hours to 1 of 6 Application Sites (shoulder, upper arm, flank, hip, abdomen, or thigh) on 2 Different Days During the Maintenance Phase



Distribution

The weight normalized apparent volume of distribution, (Vd/F), in humans is approximately 84 L/kg after repeated dose administration.

The binding of rotigotine to human plasma proteins is approximately 92% *in vitro* and 89.5% *in vivo*.

Metabolism and Elimination

Rotigotine is extensively metabolized by conjugation and N-dealkylation. After intravenous dosing the predominant metabolites in human plasma are sulfate conjugates of rotigotine, glucuronide conjugates of rotigotine, sulfate conjugates of the N-despropyl-rotigotine and conjugates of N-desthienylethyl -rotigotine. Multiple CYP isoenzymes, sulfotransferases and two UDP-glucuronosyltransferases catalyze the metabolism of rotigotine.

After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A smaller proportion is excreted in feces (~23%). The major metabolites found in urine were rotigotine sulfate (16% to 22%of the absorbed dose), rotigotine glucuronide (11% to15%), and N-despropyl-rotigotine sulfate metabolite (14% to 20%) and N-desthienylethyl-rotigotine sulfate metabolite (10% to 21%). Approximately 11% is renally eliminated as other metabolites. A small amount of unconjugated rotigotine is renally eliminated (<1% of the absorbed dose).

Drug Interaction Studies

CYP Interactions

In vitro studies indicate that multiple CYP-isoforms are capable of catalyzing the metabolism of rotigotine. In human liver microsomes, no extensive inhibition of the metabolism of rotigotine was observed when co-incubated with CYP isoform specific inhibitors. If an individual CYP isoform is inhibited, other isoforms can catalyze rotigotine metabolism.

Rotigotine, the 5-O-glucuronide and its desalkyl and monohydroxy metabolites were analyzed for interactions with the human CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in vitro. Based on these results, no risk for inhibition of CYP1A2, CYP2C9 and CYP3A4 catalyzed metabolism of other drugs is predicted at therapeutic rotigotine concentrations. There is a low risk of inhibition of CYP2C19 and CYP2D6 catalyzed metabolism of other drugs at therapeutic concentrations.

In human hepatocytes in vitro, there was no indication for induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4.

Rotigotine is metabolized by multiple sulfotransferases and two UDP-glucuronosyltransferases (UGT1A9 and UGT2B15). These multiple pathways make it unlikely that inhibition of any one pathway would alter rotigotine concentrations significantly.

Protein Displacement, Warfarin

In vitro, no potential for displacement of warfarin by rotigotine (and vice versa) from their respective human serum albumin binding sites was detected.

Digoxin

The effect of rotigotine on the pharmacokinetics of digoxin has been investigated in vitro in Caco-2 cells. Rotigotine did not influence the P-glycoprotein-mediated transport of digoxin. Therefore, rotigotine would not be expected to affect the pharmacokinetics of digoxin.

Cimetidine

Co-administration of rotigotine (up to 4 mg/24 hours) with cimetidine (400 mg b.i.d.), an inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4, did not alter the steady-state pharmacokinetics of rotigotine in healthy subjects.

Levodopa/Carbidopa

Co-administration of levodopa/carbidopa (100/25 mg b.i.d.) with rotigotine (4 mg/24 hours) had no effect on the steady-state pharmacokinetics of rotigotine; rotigotine had no effect on the pharmacokinetics of L-levodopa/carbidopa.

Oral Contraception

Co-administration of rotigotine (3 mg/24 hours) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel).

Omeprazole

Co-administration of the CYP2C19 selective inhibitor omeprazole (40 mg/day) had no effect on the steady-state pharmacokinetics of rotigotine (4 mg/24 hours).

12.6 Pharmacokinetics in Special Populations

Hepatic Insufficiency

There were no relevant changes in rotigotine plasma concentrations in subjects with moderate hepatic impairment (Child Pugh classification – Grade B). No information is available on subjects with severe impairment of hepatic function.

Renal Insufficiency

There were no relevant changes in rotigotine plasma concentrations (up to end stage renal disease requiring hemodialysis). In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 ml/min), exposure to conjugated rotigotine metabolites was doubled .

Gender

Female and male subjects and patients had similar plasma concentrations (body weight normalized).

Geriatric Patients

Plasma concentrations of rotigotine in patients 65 to 80 years of age were similar to those in younger patients, approximately 40 to 64 years of age. Although not studied, exposures in older subjects (>80 years) may be higher due to skin changes with aging.

Pediatric Patients

The pharmacokinetics of rotigotine in subjects below the age of 18 years has not been established.

Race

The pharmacokinetic profile was similar in Caucasians, Blacks, and Japanese. No dose adjustment is necessary based on ethnicity.

12.7 Adhesion

Adhesion was examined in subjects with Parkinson's disease when patches were applied to rotating sites. Similar results were observed for the 4 mg/24 hours (20 cm^2), 6 mg/24 hours (30 cm^2), and 8 mg/24 hours (40 cm^2) patches. An adherence of ≥90% of the patch surface was observed in 71% to 82% of cases. A partial detachment of >10% was observed in 15% to 24% of cases. A complete detachment of the patch was observed in 3% to 5% of cases.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies of rotigotine were conducted in mice at doses of 0, 3, 10, and 30 mg/kg and in rats at doses of 0, 0.3, 1, and 3 mg/kg; in both studies rotigotine was administered subcutaneously once every 48 hours. No significant increases in tumors occurred in mice at doses up to 9 times the maximum recommended human dose (MRHD) in Parkinson's disease (8 mg/24 hours).

In rats, there were increases in Leydig cell tumors and in uterine tumors (adenocarcinomas, squamous cell carcinomas) at all doses. The endocrine mechanisms believed to be involved in the production of these tumors in rats are not considered relevant to humans. Therefore, there were no tumor findings considered relevant to humans at plasma exposures (AUC) up to 4-6 times that in humans at the MRHD.

Mutagenesis

Rotigotine was negative in the *in vitro* bacterial reverse mutation (Ames) and in the *in vivo* micronucleus assays. Rotigotine was mutagenic and clastogenic in the *in vivo* mouse lymphoma *tk* assay.

Infertility

When rotigotine was administered subcutaneously (1.5, 5, or 15 mg/kg/day) to female rats prior to and during mating and continuing through gestation day 7, an absence of implantation was observed at all doses. The lowest dose tested is 2 times the MRHD on a mg/m^2 basis. In male rats treated from 70 days prior to and during mating, there was no effect on fertility; however, a decrease in epididymal sperm motility was observed at the highest dose tested. The no-effect dose (5 mg/kg/day) is 6 times the MRHD on a mg/m^2 basis. When rotigotine was administered subcutaneously to female mice at doses of 10, 30, and 90 mg/kg/day from 2 weeks until 4 days before mating and then at a dose of 6 mg/kg/day (all groups) (approximately 4 times the MRHD on a mg/m^2 basis) from 3 days before mating until gestation day 7, a markedly reduced (low dose) or complete absence of implantation (mid and high doses) was observed. The effects on implantation in rodents are thought to be due to the prolactin-lowering effect of rotigotine. In humans, chorionic gonadotropin, not prolactin, is essential for implantation.

13.2 Animal Toxicology and/or Pharmacology

Retinal Pathology: Albino rats: Retinal degeneration was observed in albino rats in a 6-month toxicity study at the highest dose of rotigotine (plasma exposure [AUC] at least 15 times that in humans at the MRHD. Retinal degeneration was not observed in the 2-year carcinogenicity studies in albino rat (plasma AUCs up to 4-6 times that in humans at the MRHD) or albino mouse, or in monkeys treated for 1 year. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

14 CLINICAL STUDIES

14.1 Parkinson's Disease

The effectiveness of Neupro in the treatment of the signs and symptoms of idiopathic Parkinson's disease was established in five parallel group, randomized, double-blind placebo-controlled trials conducted in the U.S. and abroad. Three of these five trials enrolled patients with early-stage Parkinson's disease (not receiving levodopa), and two enrolled patients with advanced-stage Parkinson's disease who were receiving levodopa. Depending on trial design, patients underwent a weekly titration of Neupro in 2 mg/24 hours increments to either the randomized dose or optimal dose. Back titrations by 2 mg/24 hours decrement of Neupro were permitted for intolerable adverse events. Patch application sites were changed on a daily basis.

Change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS), parts II + III, served as the primary outcome assessment measure in the early-stage studies. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (part I), Activities of Daily Living (ADL) (part II), motor performance (part III), and complications of therapy (part IV). Part II of the UPDRS contains 13 questions relating to ADL, which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for part II. Part III is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability, etc.), scored for different body regions, and has a maximum (worst) score of 108.

Change from baseline in time spent "off" (hours) based on daily diaries was the primary outcome assessment in the two trials of advanced-stage Parkinson's disease (with levodopa).

Studies in Patients with Early-Stage Parkinson's Disease

Patients (N=649) in the three trials of early-stage Parkinson's disease had limited or no prior exposure to levodopa (off levodopa for at least 28 days prior to baseline or levodopa use for no more than 6 months). Patients were excluded from the studies if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine must have been on a stable dose and able to maintain that dose for the duration of the study.

PD-1

This trial was a multicenter, multinational dose-response study in which 316 early-stage Parkinson's disease patients were titrated over 4 weeks to their randomized treatment with either placebo or one of four fixed doses of Neupro (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours). The patches were applied to the upper abdomen and the sites of application were rotated on a daily basis.

Patients underwent a weekly titration (increasing the number of 2 mg/24 hours patches or placebo patches at weekly intervals) over 4 weeks such that the target doses of Neupro were achieved for all groups by the end of 3 weeks and were administered over the fourth week of the titration phase. Patients then continued on treatment for a 7 week maintenance phase followed by a down titration during the last week. Two back titrations by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) at a time were permitted for intolerable adverse events. The mean age of patients was approximately 60 years (range 33 to 83 years; approximately 36% were $\geq$ 65 years) and the study enrolled more men (62%) than women (39%). Most patients (85%) were Caucasian and most randomized patients ($\geq$ 88%) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) scores were similar among all treatment groups, between 27.1 and 28.5 for all groups. The mean change from baseline and difference from placebo for each treatment group is shown in Table 5. Statistically significant mean changes reflecting dose-related improvement were observed at the three highest doses, and the 6 mg/24 hours and 8 mg/24 hours doses had a similar effect.

Table 5 PD-1: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Treatment	Mean Change from Baseline	Difference from placebo
Placebo	-1.4	NA
2 mg/24 hours	-3.5	-2.1
4 mg/24 hours	-4.5	-3.1
6 mg/24 hours	-6.3	-4.9
8 mg/24 hours	-6.3	-5.0

PD-2

This trial was a randomized, double-blind, multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/24 hours, or 6 mg/24 hours), parallel group study in which 277 early-stage Parkinson's disease patients were assigned (2: 1 ratio) to treatment with Neupro or placebo for a period up to about 28 weeks. This trial was conducted in 47 sites in North America (U.S. and Canada). Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Patients underwent a weekly titration (consisting of 2 mg/24 hours increments at weekly intervals) over 3 weeks to a maximal dose of 6 mg/24 hours depending on efficacy and tolerability, and then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 4 days. Back/down titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e., patients with intolerable adverse events had to leave the study). Primary efficacy data were collected after a treatment period of up to approximately 27 weeks.

The mean age of patients was approximately 63 years (range 32 to 86 years; approximately 45% were ≥65 years), approximately two-thirds of all patients were men, and nearly all patients were Caucasian. Approximately 90% of patients randomized to Neupro achieved a maximal daily dose of 6 mg/24 hours; 70% maintained this dose for most (>20 weeks) of the maintenance phase. Most enrolled patients (≥81 %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) was similar in both groups (29.9 Neupro group, 30.0 placebo). Neupro-treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 27 or last visit for patients discontinuing early) of -4.0 (Table 6), and the difference from placebo was statistically significant.

Table 6 PD-2: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Treatment	Mean Change from Baseline	Difference from placebo
Placebo	+1.3	NA
Neupro up to 6 mg/24 hours	-4.0	-5.3

PD-3

This study was a randomized, double-blind multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours), three-arm, parallel-group study using a double-dummy treatment in which 561 early-stage Parkinson's disease patients were assigned to treatment with either placebo or Neupro or active oral comparator in a ratio of 1: 2: 2 for a period up to about 39 weeks. This study was conducted in up to 81 sites in many countries outside of North America. Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Treatment with a patch and placebo was given to all patients in a double-blinded manner such that no one would know the actual treatment (i.e. Neupro, comparator, or placebo).

Patients underwent a weekly dose escalation/titration of patch (consisting of 2 mg/24 hours increments of Neupro or placebo) and a dose escalation of capsules of comparator or placebo over 13 weeks (13 week titration was planned for the comparator treatment) up to a maximal dose of 8 mg/24 hours of Neupro depending on achieving optimal efficacy or intolerability at a lower dose. Patients randomized to Neupro achieved the maximal dose of 8 mg/24 hours after a 4 week titration if maximal efficacy and intolerability had not occurred over a 4 week titration period. Patients then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 12 days. A single back titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) or capsule was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy data were collected after a treatment period of up to approximately 37 weeks of randomized treatment.

The mean age of patients was approximately 61 years (range 30 -86 years; approximately 41% were ≥65 years), nearly 60% of all patients were men, and nearly all patients were Caucasian. About 73% of patients completed the full treatment period. The mean daily dose of Neupro was just less than 8 mg/24 hours and approximately 90% of patients achieved the maximal daily dose of 8 mg/24 hours.

Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2 Neupro, 31.3 placebo, 32.2 comparator). Neupro-treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 37 or last visit for patients discontinuing early) of -6.8 (Table 11), and the difference from placebo treated patients showed a mean change from baseline of –2.3 (see Table 7), a difference that was statistically significant.

Table 7 PD-3: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Treatment	Mean change from baseline	Difference from placebo
Placebo	-2.3	NA
Neupro up to 8 mg/24 hours	-6.8	-4.5

Advanced-Stage Parkinson's Disease

Patients (N=658) in the three trials of Neupro in advanced-stage Parkinson's disease had to be experiencing "on-off" periods at baseline, despite treatment with optimal doses of levodopa. Patients continued concomitant levodopa during the trial; however, reductions in the dosage of levodopa were allowed if patients experienced adverse events that the investigator considered related to dopaminergic therapy. Patients were excluded from the studies if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine must have been on a stable dose and able to maintain that dose for the duration of the study. In the North American trial, COMT-inhibitors were not permitted.

*PD-4*This trial was a multinational, three-arm, parallel group study in which 351 advanced-stage Parkinson's disease patients were titrated over 5 weeks to treatment with either placebo or Neupro (8 mg/24 hours or 12 mg/24 hours) and maintained treatment for 24 weeks followed by a down titration over the last week. This study was conducted in 55 sites in North America (U.S. and Canada).

Mean baseline "off" times were similar among all treatment groups (6.4, 6.8, and 6.3 hours for the placebo, Neupro 8 mg/24 hours and 12 mg/24 hours treatment groups, respectively). Neupro-treated patients experienced a mean change in "off" time from baseline to end of treatment of -2.7 hours for the 8 mg/24 hours treatment arm and -2.1 hours for the 12 mg/24 hours treatment arm (Table 8), and the difference from placebo was statistically significant for both Neupro doses (8 mg/24 hours, 12 mg/24 hours). Onset of treatment benefit began as early as the first week of treatment.

Table 8 PD-4: Mean Change in "off" time (hours) from Baseline at End of Treatment for Intent-to-Treat Population

Treatment	Mean Change From Baseline	Difference from placebo
Placebo	-0.9	NA
8 mg/24 hours	-2.7	-1.8
12 mg/24 hours	-2.1	-1.2

PD-5

This trial was a multinational, flexible dose, three-arm, parallel-group study using a double-dummy treatment in which 506 advanced-stage Parkinson's disease patients were titrated over 7 weeks to treatment with either Neupro from a minimum dose of 4 mg/24 hours up to an optimal dose not exceeding 16 mg/24 hours, active oral comparator, or placebo and maintained treatment for 16 weeks followed by a down titration over 6 days. This study was conducted in 77 sites in many countries outside of North America.

Mean baseline "off" times were similar among all treatment groups (6.6, 6.2, and 6.0 hours for the placebo, Neupro, and comparator treatment groups, respectively). Neupro-treated patients experienced a mean 2.5 hour decrease change in "off" time from baseline to end of treatment (Table 9), and the difference from placebo was statistically significant. Onset of treatment benefit began as early as the first week of treatment. The optimal Neupro dose was established as 4 mg/24 hours for 2% of patients, 6 mg/24 hours for 6%, 8mg/24 hours for 8%, 10 mg/24 hours for 9%, 12 mg/24 hours for 16%, 14mg/24 hours for 11% and 16mg/24 hours for 44%.

Table 9 PD-5: Mean Change in "off" time (hours) from Baseline at End of Treatment for Intent-to-Treat Population

Treatment	Mean Change From Baseline	Difference from placebo
Placebo	-0.9	NA
Up to 16 mg/24 hours	-2.5	-1.6

14.2 Restless Legs Syndrome

The clinical program included 1309 patients with moderate to severe RLS. The efficacy of Neupro in the treatment of Restless Legs Syndrome (RLS) was primarily evaluated in 2 fixed-dose, randomized, double-blind, placebo-controlled trials with maintenance periods of 6 months duration. Patients received Neupro doses ranging from 0.5 mg/24 hours to 3 mg/24 hours or placebo once daily. In these 2 trials, the mean duration of RLS was 2.1 to 3.1 years, mean age was approximately 55 years (range of 19 to 78 years), approximately 68 % were women, and 97% were Caucasian. In both trials, patches were applied to different application sites including the abdomen, thigh, hip, flank, shoulder, and/or upper arm and patch application sites were rotated on a daily basis.

The two outcome measures used to assess the effect of treatment as co-primary efficacy endpoints were the International RLS Rating Scale (IRLS Scale) and a Clinical Global Impression - Improvement (CGI-I) assessment. The IRLS Scale contains 10 items designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence, and impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. The CGI-I is designed to assess clinical progress (global improvement) on a 7-point scale.

RLS-1

This trial was a multicenter, 5-arm, parallel-group, fixed-dose trial of Neupro in subjects with moderate-to-severe RLS. A total of 505 subjects were randomized in this trial, participating at approximately 50 sites in the US. Subjects received placebo or Neupro (0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours). Subjects began treatment at a daily dosage of 0.5 mg/24 hours Neupro and were titrated over a 4 week period to their assigned daily dose followed by a 6 month maintenance period and 7 day down titration period.

Mean baseline IRLS sum score were similar among all treatment groups (23.5, 23.1, 23.2, 23.3, and 23.6 for the placebo, Neupro 0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, and 3 mg/24 hours groups, respectively). Patients experienced a mean change in the IRLS sum score from baseline to the end of treatment for each of the 4 Neupro dose groups. The mean changes from baseline and differences from placebo in IRLS sum score and CGI Item 1 are shown for each treatment group in Table 10. The difference between the 2 highest treatment groups (2 mg/24 hours and 3 mg/24 hours) and placebo were statistically significant. Of the Neupro-treated patients, 23% had an IRLS score of 0 compared to 9.1% of placebo patients at the end of the maintenance period. Onset of treatment benefit was seen with the 1 mg/24 hours dose.

Table 10 RLS-1: ANCOVA Results for Co-primary Endpoints: Change from Baseline to End of Maintenance Period for Intent-to-Treat Population

Variable	Treatment	Mean Change From Baseline	Difference from placebo
IRLS sum score	Placebo	-9.0	NA
	0.5 mg/24 hours	-11.1	-2.2
	1 mg/24 hours	-11.2	-2.3
	2 mg/24 hours	-13.5	-4.5
	3 mg/24 hours	-14.2	-5.2
CGI Item 1	Placebo	-1.4	NA
	0.5 mg/24 hours	-1.8	-0.35
	1 mg/24 hours	-1.7	-0.32
	2 mg/24 hours	-2.1	-0.65
	3 mg/24 hours	-2.3	-0.90

RLS-2

This trial was a multicenter, 4-arm, parallel-group trial of Neupro in subjects with moderate-to-severe RLS. A total of 458 subjects were randomized in this trial, participating at approximately 50 sites in 8 European countries. Patients received placebo or Neupro (1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours). Patients began treatment at a daily dosage of 1 mg/24 hours Neupro and were titrated over a 3 week period to their assigned daily dose followed by a 6 month maintenance period and 7 day down-titration period.

Mean baseline IRLS sum score were similar among all treatment groups (28.1, 28.1, 28.2, and 28.0 for the placebo, Neupro 1 mg/24 hours, 2 mg/24 hours, and 3 mg/24 hours groups, respectively). Patients experienced a mean change in the IRLS sum score from baseline to the end of treatment for each of the 3 Neupro dose groups. The mean changes from baseline and differences from placebo in IRLS sum score and CGI Item 1 are shown for each treatment group in Table 11. The difference between all 3 treatment groups (1 mg/24 hours, 2 mg/24 hours, and 3 mg/24 hours) and placebo were statistically significant. Of the Neupro-treated patients, 24% had an IRLS score of 0 compared to 12% of placebo patients at the end of the maintenance period. Onset of treatment benefit was seen with the 1 mg/24 hours dose.

Table 11 RLS-2: ANCOVA Results for Co-primary Endpoints: Change from Baseline to End of Maintenance Period for Intent-to-Treat Population

Variable	Treatment	Mean Change From Baseline	Difference from placebo
IRLS sum score	Placebo	-8.6	NA
	1 mg/24 hours	-13.7	-5.1
	2 mg/24 hours	-16.2	-7.5
	3 mg/24 hours	-16.8	-8.2
CGI Item 1	Placebo	-1.3	NA
	1 mg/24 hours	-2.0	-0.76
	2 mg/24 hours	-2.4	-1.07
	3 mg/24 hours	-2.5	-1.21

16 HOW SUPPLIED/STORAGE AND HANDLING

Each transdermal system is packaged in a separate pouch.

Each strength is available in cartons of 30 transdermal systems.

1 mg/24 hours	30 transdermal systems	NDC #50474-801-03
2 mg/24 hours	30 transdermal systems	NDC #50474-802-03
3 mg/24 hours	30 transdermal systems	NDC #50474-803-03
4 mg/24 hours	30 transdermal systems	NDC #50474-804-03
6 mg/24 hours	30 transdermal systems	NDC #50474-805-03
8 mg/24 hours	30 transdermal systems	NDC #50474-806-03

Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]

Neupro should be stored in the original pouch. Do not store outside of pouch.

Apply the transdermal system immediately upon removal from the pouch. Discard used systems in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

17.1 Sulfite Sensitivity

Advise patients about potential for sulfite sensitivity. Neupro contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. An allergy to sulfites is not the same as an allergy to sulfa.

17.2 Falling Asleep During Activities of Daily Living and Somnolence

Advise and alert patients about the potential for sedating effects associated with Neupro, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Because somnolence can be a frequent adverse reaction with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with Neupro to gauge whether or not it affects

their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Patients should not drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of Neupro.

Because of the possible additive effects, caution should also be used when patients are taking alcohol, sedating medications, or other CNS depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with Neupro.

17.3 Hallucinations / Psychotic-Like Behavior

Inform patients that hallucinations and other psychotic-like behavior can occur while taking Neupro and that the elderly are at a higher risk than younger patients with Parkinson's disease.

17.4 Symptomatic Hypotension

Advise patients that they may develop symptomatic (or asymptomatic) hypotension while taking Neupro. Hypotension may occur more frequently during initial therapy. Accordingly, caution patients against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with Neupro.

17.5 Syncope

Advise patients about the potential for syncope in patients using dopamine agonists. For this reason, patients should be alerted to the possibility of syncope while taking Neupro.

17.6 Impulse Control / Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking one or more of the medications generally used for the treatment of Parkinson's disease, including Neupro. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Neupro. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

17.7 Elevation of Blood Pressure and Heart Rate

Advise patients that Neupro can increase blood pressure and heart rate,

17.8 Weight Gain and Fluid Retention

Advise patients that Neupro can cause increased weight and fluid retention manifesting itself as peripheral edema.

17.9 Dyskinesias

Inform patients that Neupro may cause and/or exacerbate pre-existing dyskinesias.

17.10 Application Site Reactions

Inform patients that application site reactions can occur and that the Neupro transdermal system application site should be rotated on a daily basis. Neupro should not be applied to the same application site more than once every 14 days. Patients should report persistent application site reaction (of more than a few days), increases in severity, or skin reactions that spread outside the application site

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

17.11 Melanoma

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to monitor for melanomas frequently and on a regular basis when using Neupro for *any* indication.

17.12 Augmentation and Rebound in RLS

Inform patients that Neupro may cause RLS symptoms to have an earlier onset during the day or become worse.

17.13 Magnetic Resonance Imaging and Cardioversion

Inform patients to remove Neupro before undergoing magnetic resonance imaging (MRI) or cardioversion. These procedures could cause a burn to the site where Neupro is applied.

17.14 Heat Application

Advise patients about the potential for heat application to increase drug absorption. Because applying external heat (e.g., a heating pad, sauna, or hot bath) to the transdermal system may increase the amount of drug absorbed, patients should be instructed not to apply heating pads or other sources of heat to the area of the transdermal system. Direct sun exposure of the transdermal system should be avoided.

17.15 Nausea, Vomiting, and Dyspepsia

Inform patients that Neupro causes nausea, vomiting, and general gastrointestinal distress (i.e., dyspepsia/abdominal discomfort). Nausea and vomiting may occur more frequently during initial therapy and may require dose adjustment.

17.16 Instructions for Use

Instruct patients to wear Neupro continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately. Patients can choose the most convenient time of day or night to apply Neupro but should be advised to apply the patch at approximately the same time each day. If a patient forgets to change a patch, a new patch should be applied as soon as possible and replaced at the usual time the following day.

The application site for Neupro should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days.

Neupro should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 30 seconds, making sure there is good contact, especially around the edges.

Neupro should be applied once daily to clean, dry, and intact skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Shave hairy areas at least 3 days prior to applying the patch. Do not apply to areas that could be rubbed by tight clothing, or under a waistband, to skin folds, or to skin that is red or irritated. Creams, lotions, ointments, oils, and powders should not be applied to the skin area where Neupro will be placed. Patients should wash their hands to remove any drug and should be careful not to touch their eyes or any objects.

Instruct patients not to cut or damage Neupro.

Care should be used to avoid dislodging the patch while showering, bathing or during physical activity. If the edges of the patch lift, Neupro may be taped down with bandage tape. If the patch detaches, a new one may be applied immediately to a different site. The patient should then change the patch according to their regular schedule.

Removal of the patch: Neupro should always be removed slowly and carefully to avoid irritation. After removal the patch should be folded over so that it sticks to itself and should be discarded so that children and pets cannot reach it. Wash the site with soap and water to remove any drug or adhesive. Baby or mineral oil may be used to remove any excess residue. Alcohol and other solvents (such as nail polish remover) may cause skin irritation and should not be used.

Manufactured for:
UCB, Inc.
Smyrna, GA 30080
Made in Germany
1E

PATIENT INFORMATION
NEUPRO® [NU pro]
(Rotigotine Transdermal System)

If you have Parkinson's disease, read this side. If you have Restless Legs Syndrome (also known as Willis-Ekbom disease), read the other side.

Rx Only

IMPORTANT: NEUPRO is for use on the skin only.

Read this Patient Information leaflet before you start using NEUPRO and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is NEUPRO?

NEUPRO is a prescription medicine used to treat signs and symptoms of idiopathic Parkinson's disease (PD). Neupro is a patch worn on the skin.

It is not known if NEUPRO is safe and effective in children.

Who should not use NEUPRO?

Do not use NEUPRO if you are allergic to rotigotine or any of the ingredients in NEUPRO. See the end of this leaflet for a complete list of ingredients in NEUPRO.

What should I tell my doctor before using NEUPRO?

Before you start using NEUPRO, tell your doctor if you:

- have breathing problems including asthma.
- have daytime sleepiness from a sleep disorder or have unexpected or unpredictable sleepiness or periods of sleep.
- have mental problems such as schizophrenia, bipolar disorder or psychosis.
- feel dizzy, nauseated, sweaty, or faint when you stand up from sitting or lying down.
- drink alcoholic beverages. This may increase your chances of becoming drowsy or sleepy while using NEUPRO.
- have high or low blood pressure.
- have or have had heart problems.
- are pregnant or plan to become pregnant. It is not known if NEUPRO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if NEUPRO passes into your breastmilk. You and your doctor should decide if you will use NEUPRO or breast feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

NEUPRO and other medicines may affect each other causing side effects. NEUPRO may affect the way other medicines work, and other medicines may affect how NEUPRO works.

Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use NEUPRO for Parkinson's disease?

- Use NEUPRO exactly as your doctor tells you to use it.
- NEUPRO comes in 4 different size (dose) patches for Parkinson's disease. Your doctor should start you on a low dose of NEUPRO. Your doctor will change the dose weekly until you are taking the right amount of medicine to control your symptoms. It may take several weeks before you reach the dose that controls your symptoms best.
- Apply NEUPRO 1 time each day at the same time each day.
- You may bathe, shower, or swim while wearing a NEUPRO patch. Water may loosen your NEUPRO patch.
- If the edges of the patch lift, you may tape them down with bandaging tape.
- If your NEUPRO patch falls off, apply a new NEUPRO patch for the rest of the day. The next day, apply a new patch at your regular time.
- If you miss a dose or forget to change your NEUPRO patch, apply a new NEUPRO patch as soon as you remember. Replace the NEUPRO patch at your normal time the next day.
- Talk to your doctor often about your condition. **Do not** stop or change your treatment with NEUPRO without talking to your doctor.
- Read the Instructions for Use at the end of this leaflet for specific information about the right way to apply the NEUPRO patch.

What should I avoid while using NEUPRO?

- **Do not** drive, operate machinery, or do other dangerous activities until you know how NEUPRO affects you.
- Avoid exposing the site where you have applied your NEUPRO patch to heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, and direct sunlight. Too much medicine could be absorbed into your body.
- **Do not** use NEUPRO during certain procedures called magnetic resonance imaging (MRI) or cardioversion. Using NEUPRO during these procedures could cause a burn to the site where you applied your NEUPRO patch.
- Avoid direct sunlight if you get a skin rash or irritation from NEUPRO until your skin heals. Sun exposure could lead to skin color changes.

What are the possible side effects of NEUPRO?

NEUPRO can cause serious side effects, including:

- **severe allergic reactions.** NEUPRO contains a sulfite called sodium metabisulfite. Sulfites can cause severe allergic reactions that are life threatening to some people who are sensitive to sulfites. An allergy to sulfites is not the same as an allergy to sulfa. People with asthma are more likely to be allergic to sulfites. Remove your NEUPRO patch right away and call your doctor if you have swelling of the lips or tongue, chest pain, trouble breathing or swallowing.
- **falling asleep during normal activities.** You may fall asleep while doing normal activities such as driving a car, doing physical tasks, or using hazardous machinery while taking NEUPRO. You may suddenly fall asleep without being drowsy or without warning. This may result in having accidents. Your chances of falling asleep while doing normal activities while using NEUPRO are greater if you take other medicines that cause drowsiness. Tell your doctor right away if this happens. Before starting NEUPRO, be sure to tell your doctor if you take any medicines that make you drowsy.
- **hallucinations and other psychotic-like behavior.** NEUPRO can cause or worsen psychotic-like behavior including hallucinations (seeing or hearing things that are not real), confusion, excessive suspicion, aggressive behavior, agitation, delusional beliefs (believing things that are not real), and disorganized thinking. The chances of having hallucinations or these other psychotic-like changes are higher in people with Parkinson's disease who are elderly, taking NEUPRO, or taking higher does of NEUPRO. If you have hallucinations or any of these other psychotic-like changes, talk with your doctor.
- **changes in blood pressure.** NEUPRO can decrease or increase your blood pressure. Lowering of your blood pressure is of special concern. If you faint or feel dizzy, nauseated, or sweaty when you stand up from sitting or lying down, this may mean that your blood pressure is decreased. If you notice this, you should contact your doctor. Also, when changing position from lying down or sitting to standing up, you should do it carefully and slowly. Lowering of your blood pressure can happen, especially when you start taking NEUPRO or when your dose is increased.
- **fainting.** Fainting can occur, and sometimes your heart rate may be decreased. This can happen especially when you start using NEUPRO or your dose is increased. Tell your doctor if you faint or feel dizzy.
- **unusual urges.** Some patients using NEUPRO get urges to behave in a way unusual for them. Examples of this are an unusual urge to gamble or increased sexual urges and behaviors. If you notice or your family notices that you are developing any unusual behaviors, talk to your doctor.
- **changes in heart rate**. NEUPRO can increase your heart rate.

- **increased weight and fluid retention** can occur in patients using NEUPRO. NEUPRO can cause your body to keep extra fluid which leads to swelling and weight gain. Tell your doctor if you have swelling or fluid retention, especially in the ankles or legs or have an unusually fast increase in weight.
- **uncontrolled sudden movements.** NEUPRO may cause uncontrolled sudden movements or make such movements you already have worse or more frequent. Tell your doctor if this happens. The doses of your anti-Parkinson's medicine may need to be changed.
- **skin site reactions.** Skin reactions may occur at the site where you apply NEUPRO. Tell your doctor if you get a rash, redness, swelling, or itching that will not go away at the skin site where you have applied NEUPRO.
- **skin cancer.** Some people with Parkinson's disease may have an increased chance of getting a skin cancer called melanoma. People with Parkinson's disease should have a doctor check their skin for skin cancer regularly.

The most common side effects of NEUPRO for Parkinson's disease are application site reactions, nausea, vomiting, sleepiness, dizziness, loss of appetite, increased sweating, difficulty sleeping, leg swelling, and uncontrolled, sudden movements of arms or legs.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NEUPRO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NEUPRO?

- Store NEUPRO at 68°F to 77°F (20°C to 25°C).
- Store NEUPRO in its original sealed pouch until use. **Do not** store NEUPRO outside of the pouch.

Keep NEUPRO and all medicines out of reach of children and away from pets.

General information about the safe and effective use of NEUPRO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NEUPRO for a condition for which it was not prescribed. Do not give NEUPRO to other people even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about NEUPRO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about NEUPRO that was written for healthcare professionals.

For more information, go to www.neupro.com or call 1-866-822-0068.

What are the ingredients in NEUPRO?

Active ingredient: rotigotine

Inactive ingredients: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.

INSTRUCTIONS FOR USE
NEUPRO® [NU pro]
(Rotigotine Transdermal System)

Read the Instructions for Use that come with your NEUPRO before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

When to apply NEUPRO:

Each NEUPRO patch is sealed in a pouch that protects it until you are ready to apply it. **See Figure A.**

Figure A

- NEUPRO should be applied right away after removing it from the protective pouch. **Do not** damage or cut your NEUPRO patch into smaller pieces.

- Choose the time of day or night that works best for you to apply your NEUPRO patch. Apply your NEUPRO patch at the same time each day.

- Wear your NEUPRO patch for 24 hours.
- After 24 hours, remove your NEUPRO patch and apply a new one right away to a different area of your skin.

Where to apply NEUPRO:

- Choose an area of clean, dry, and healthy skin on the stomach, thigh, hip, side of the body between the ribs and the pelvis (flank), shoulder, or upper arm. **See Figure B.**

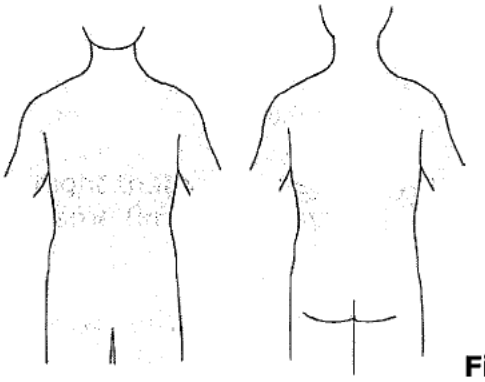


Figure B

- Apply your NEUPRO patch to a different place on your skin each day, for example, from the right side to the left side and from the upper body to the lower body. Your NEUPRO patch should not be applied to the same area of your skin more than 1 time every 14 days. Apply

NEUPRO to a different area of skin *(only one of the shaded areas in Figure B)* each day to reduce the chance of getting skin irritation.

- If you need to apply your NEUPRO patch to a hairy area, the area should be shaved at least 3 days before applying the patch.
- Avoid applying your NEUPRO patch to areas where it could be rubbed by tight clothing or under a waistband.
- Avoid applying your NEUPRO patch on skin folds.
- **Do not** apply your NEUPRO patch to skin that is red, irritated, or injured.
- Avoid applying creams, lotions, ointments, oils, and powders to the skin area where your NEUPRO patch will be placed.

How to apply NEUPRO:

Step 1. Grasp the two sides of the pouch and pull apart. **See Figures C and D.**

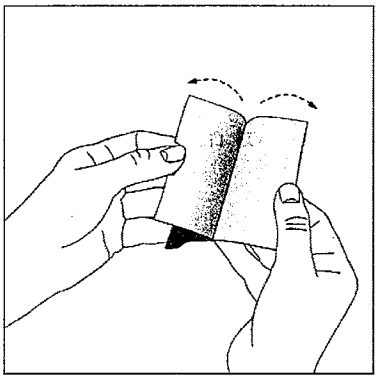


Figure C

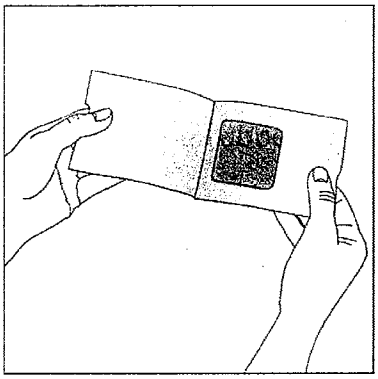


Figure D

Step 2. Remove your NEUPRO patch from the pouch. **See Figure E.**

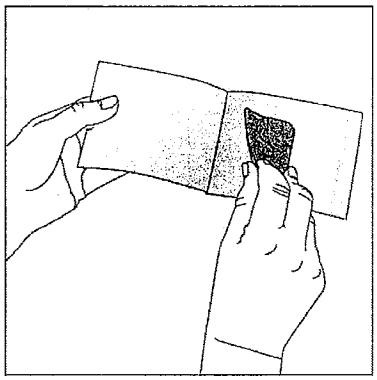


Figure E

Step 3. Hold your NEUPRO patch with both hands, with the protective liner on top. **See Figure F.**

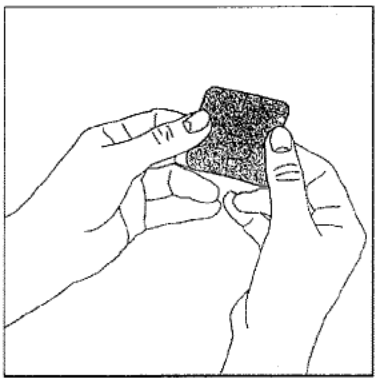


Figure F

Step 4. Bend the edges of your NEUPRO patch away from you so that the S-shaped cut in the liner opens up. **See Figure G.**

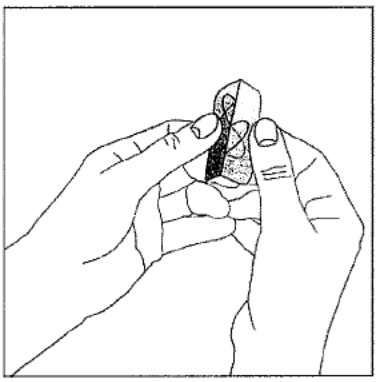


Figure G

Step 5. Peel off one half of the protective liner. **Do not** touch the sticky surface of your NEUPRO patch because the medicine could come off on your fingers. **See Figure H.**

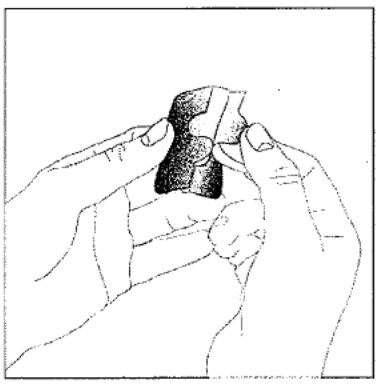


Figure H

Step 6. Apply the sticky half of your NEUPRO patch to a clean area of your skin and remove the remaining liner. **See Figures I and J**.

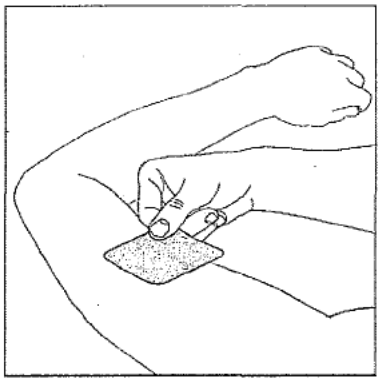


Figure I

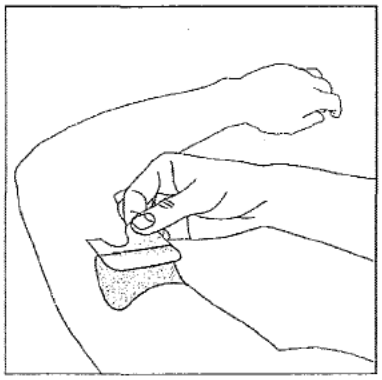


Figure J

Step 7. Press your NEUPRO patch firmly with the palm of your hand for **30** seconds to make sure there is good contact with your skin, especially around the edges. The warmth of your hand helps the adhesive on the patch to stick to your skin. Make sure that your NEUPRO patch is flat against your skin. There should be no bumps or folds in your NEUPRO patch. **See Figure K.**

Figure K

Step 8. Wash your hands with soap and water right after handling your NEUPRO patch to remove any medicine that may have gotten on them. **Do not** touch your eyes until after you have washed your hands.

How to Remove NEUPRO:

- Slowly and carefully peel off your used NEUPRO patch. Carefully fold it in half (sticky sides together) and throw away the folded patch so that children and pets cannot reach it. Your NEUPRO patch still contains some medicine and could harm a child or pet.
- Gently wash the area with warm water and mild soap to remove any sticky material (adhesive) that stays on your skin.
- Baby or mineral oil may also be used to remove any adhesive. Avoid using alcohol or other solvents, such as nail polish remover. They may cause your skin to become irritated.
- Wash your hands with soap and water.
- You may see mild redness at the site when a patch is removed like when you remove an adhesive bandage. This redness should go away over time. If irritation or itchiness continues, tell your doctor.

This Patient Package Insert and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:

UCB, Inc.
Smyrna, GA 30080

Rev. 1E 04/2012

PATIENT INFORMATION
NEUPRO® [NU pro]
(Rotigotine Transdermal System)

If you have Restless Legs Syndrome (also known as Willis-Ekbom disease), read this side. If you have Parkinson's disease, read the other side.

Rx Only

IMPORTANT: NEUPRO is for use on the skin only.

Read this Patient Information leaflet before you start using NEUPRO and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is NEUPRO?

NEUPRO is a prescription medicine used to treat moderate to severe primary Restless Legs Syndrome (RLS). Neupro is a patch worn on the skin.

It is not known if NEUPRO is safe and effective in children.

Who should not use NEUPRO?

Do not use NEUPRO if you are allergic to rotigotine or any of the ingredients in NEUPRO. See the end of this leaflet for a complete list of ingredients in NEUPRO.

What should I tell my doctor before using NEUPRO?

Before you start using NEUPRO tell your doctor if you:

- have breathing problems including asthma.
- have daytime sleepiness from a sleep disorder or have unexpected or unpredictable sleepiness or periods of sleep.
- have mental problems such as schizophrenia, bipolar disorder or psychosis.
- feel dizzy, nauseated, sweaty or faint when you stand up from sitting or lying down.
- drink alcoholic beverages. This may increase your chances of becoming drowsy or sleepy while using NEUPRO.
- have high or low blood pressure.
- have or have had heart problems.
- are pregnant or plan to become pregnant. It is not known if NEUPRO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if NEUPRO passes into your breastmilk. You and your doctor should decide if you will use NEUPRO or breast feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

NEUPRO and other medicines may affect each other causing side effects. NEUPRO may affect the way other medicines work, and other medicines may affect how NEUPRO works.

Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use NEUPRO for RLS?

- Use NEUPRO exactly as your doctor tells you to use it.
- NEUPRO comes in 3 different size (dose) patches for RLS. Your doctor should start you on the lowest dose of NEUPRO. Your doctor may change the dose weekly until you are taking the right amount of medicine to control your symptoms. It may take several weeks before you reach the dose that controls your symptoms best.
- Apply NEUPRO 1 time each day at the same time each day.
- You may bathe, shower, or swim while wearing a NEUPRO patch. Water may loosen your NEUPRO patch.
- If the edges of the patch lift, you may tape them down with bandaging tape.
- If your NEUPRO patch falls off, apply a new NEUPRO patch for the rest of the day. The next day, apply a new patch at your regular time.
- If you miss a dose or forget to change your NEUPRO patch, apply a new NEUPRO patch as soon as you remember. Replace the NEUPRO patch at your normal time the next day.
- Talk to your doctor often about your condition. **Do not** stop or change your treatment with NEUPRO without talking to your doctor.
- Read the Instructions for Use at the end of this leaflet for specific information about the right way to apply the NEUPRO patch.

What should I avoid while using NEUPRO?

- **Do not** drive, operate machinery, or do other dangerous activities until you know how NEUPRO affects you.
- Avoid exposing the site where you have applied your NEUPRO patch to heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, and direct sunlight. Too much medicine could be absorbed into your body.
- **Do not** use NEUPRO during certain medical procedures called magnetic resonance imaging (MRI) or cardioversion. Using NEUPRO during these procedures could cause a burn to the site where you applied your NEUPRO patch.
- Avoid direct sunlight if you get a skin rash or irritation from NEUPRO until your skin heals. Sun exposure could lead to skin color changes.

What are the possible side effects of NEUPRO?

NEUPRO can cause serious side effects including:

- **severe allergic reactions.** NEUPRO contains a sulfite called sodium metabisulfite. Sulfites can cause severe allergic reactions that are life threatening to some people who are sensitive to sulfites. An allergy to sulfites is not the same as an allergy to sulfa. People with asthma are more likely to be allergic to sulfites. Remove your NEUPRO patch right away and call your doctor if you have swelling of the lips or tongue, chest pain, trouble breathing or swallowing.
- **falling asleep during normal activities.** You may fall asleep while doing normal activities such as driving a car, doing physical tasks, or using hazardous machinery while taking

NEUPRO. You may suddenly fall asleep without being drowsy or without warning. This may result in having accidents. Your chances of falling asleep while doing normal activities while using NEUPRO are greater if you take other medicines that cause drowsiness. Tell your doctor right away if this happens. Before starting NEUPRO, be sure to tell your doctor if you take any medicines that make you drowsy.

- **changes in blood pressure.** NEUPRO can decrease or increase your blood pressure. Lowering of your blood pressure is of special concern. If you faint or feel dizzy, nauseated, or sweaty when you stand up from sitting or lying down, this may mean that your blood pressure is decreased. If you notice this, you should contact your doctor. Also, when changing position from lying down or sitting to standing up, you should do it carefully and slowly. Lowering of your blood pressure can happen, especially when you start taking NEUPRO or when your dose is increased.
- **fainting.** Fainting can occur, and sometimes your heart rate may be decreased. This can happen especially when you start using NEUPRO or your dose is increased. Tell your doctor if you faint or feel dizzy.
- **changes in heart rate.** NEUPRO can increase your heart rate.
- **skin site reactions.** Skin reactions may occur at the site where you apply NEUPRO. Tell your doctor if you get a rash, redness, swelling, or itching that will not go away at the skin site where you have applied NEUPRO.
- **changes in Restless Legs Syndrome symptoms**. NEUPRO may cause Restless Legs Syndrome symptoms to come back (rebound), or become worse or start earlier in the day.

The most common side effects of NEUPRO for Restless Legs Syndrome (RLS) are application site reactions, nausea, sleepiness, and headache.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NEUPRO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NEUPRO?

- Store NEUPRO at 68°F to 77°F (20°C to 25°C).
- Store NEUPRO in its original sealed pouch until use. **Do not** store NEUPRO outside of the pouch.

Keep NEUPRO and all medicines out of reach of children and away from pets.

General information about the safe and effective use of NEUPRO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NEUPRO for a condition for which it was not prescribed. Do not give NEUPRO to other people even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about NEUPRO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about NEUPRO that was written for healthcare professionals.

For more information, go to www.neupro.com or call 1-866-822-0068.

What are the ingredients in NEUPRO?

Active ingredient: rotigotine

Inactive ingredients: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.

INSTRUCTIONS FOR USE
NEUPRO® [NU pro]
(Rotigotine Transdermal System)

Read the Instructions for Use that come with your NEUPRO before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

When to apply NEUPRO:

Each NEUPRO patch is sealed in a pouch that protects it until you are ready to apply it. **See Figure A.**

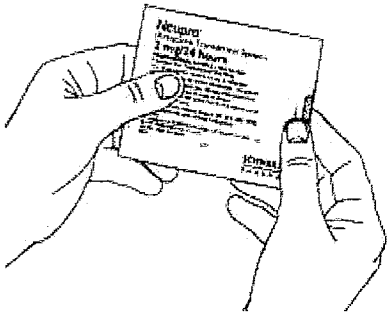


Figure A

- NEUPRO should be applied right away after removing it from the protective pouch. **Do not** damage or cut your Neupro patch into smaller pieces.
- Choose the time of day or night that works best for you to apply your NEUPRO patch. Apply your NEUPRO patch at the same time each day.
- Wear your NEUPRO patch for 24 hours.
- After 24 hours, remove your NEUPRO patch and apply a new one right away to a different area of your skin.

Where to Apply NEUPRO:

- Choose an area of clean, dry, and healthy skin on the stomach, thigh, hip, side of the body between the ribs and the pelvis (flank), shoulder, or upper arm. **See Figure B.**

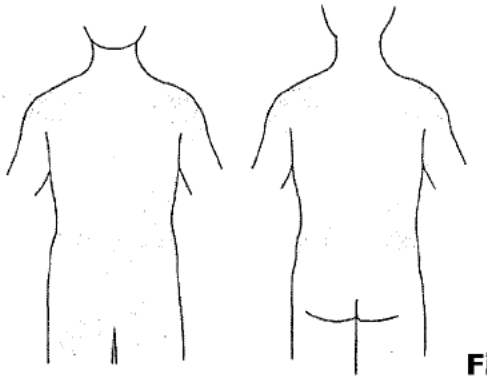


Figure B

- Apply your NEUPRO patch to a different place on your skin each day, for example, from the right side to the left side and from the upper body to the lower body. Your NEUPRO patch should not be applied to the same area of your skin more than 1 time every 14 days. Apply NEUPRO to a different area of skin *(only one of the shaded areas in Figure B)* each day to reduce the chance of getting skin irritation.
- If you need to apply your NEUPRO patch to a hairy area, the area should be shaved at least 3 days before applying the patch.
- Avoid applying your NEUPRO patch to areas where it could be rubbed by tight clothing or under a waistband.
- Avoid applying your NEUPRO patch on skin folds.
- **Do not** apply your NEUPRO patch to skin that is red, irritated, or injured.
- Avoid applying creams, lotions, ointments, oils, and powders to the skin area where your NEUPRO patch will be placed.

How to apply NEUPRO:

Step 1. Grasp the two sides of the pouch and pull apart. **See Figures C and D.**

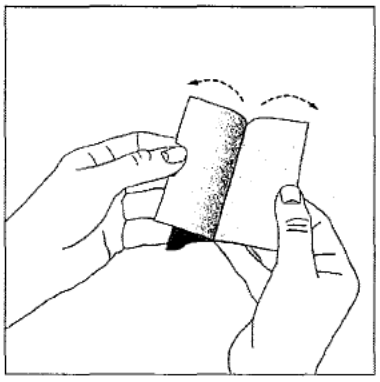


Figure C

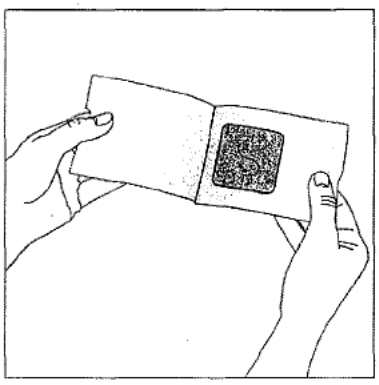


Figure D

Step 2. Remove your NEUPRO patch from the pouch. **See Figure E.**

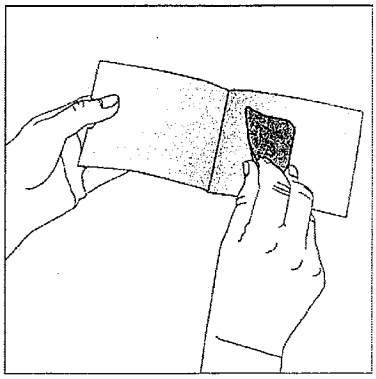


Figure E

Step 3. Hold your NEUPRO patch with both hands, with the protective liner on top. **See Figure F.**

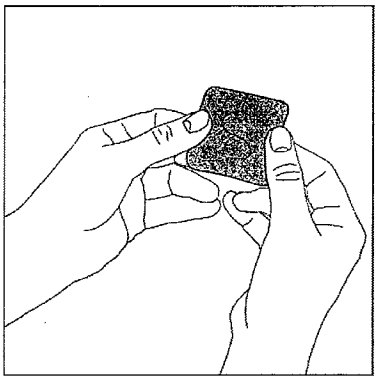


Figure F

Step 4. Bend the edges of your NEUPRO patch away from you so that the S-shaped cut in the liner opens up. **See Figure G.**

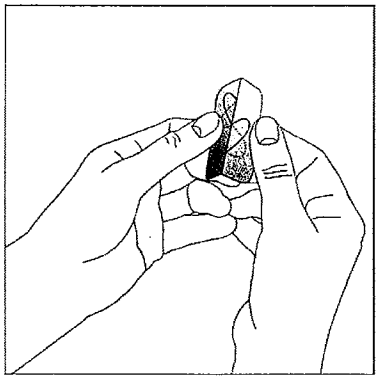


Figure G

Step 5. Peel off one half of the protective liner. **Do not** touch the sticky surface of your NEUPRO patch because the medicine could come off on your fingers. **See Figure H.**

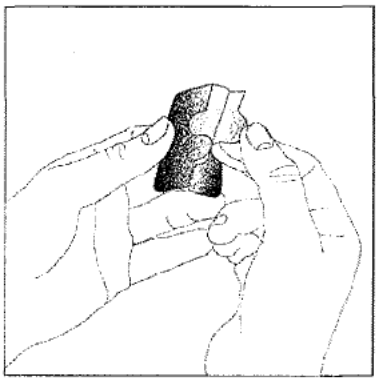


Figure H

Step 6. Apply the sticky half of your NEUPRO patch to a clean area of your skin and remove the remaining liner. **See Figures I and J.**

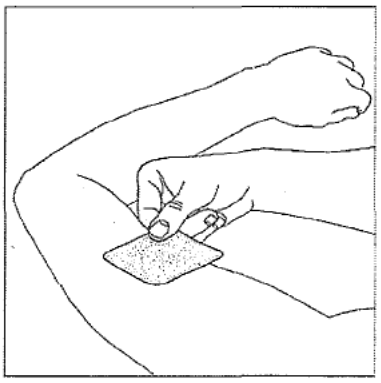


Figure I

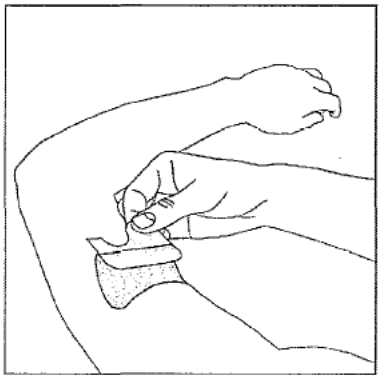


Figure J

Step 7. Press your NEUPRO patch firmly with the palm of your hand for **30** seconds to make sure there is good contact with your skin, especially around the edges. The warmth of your hand helps the adhesive on the patch to stick to your skin. Make sure that your NEUPRO patch is flat against your skin. There should be no bumps or folds in your NEUPRO patch. **See Figure K**

Figure K

Step 8. Wash your hands with soap and water right after handling your NEUPRO patch to remove any medicine that may have gotten on them. **Do not** touch your eyes until after you have washed your hands.

How to Remove NEUPRO:

- Slowly and carefully peel off your used NEUPRO patch. Carefully fold it in half (sticky sides together) and throw away the folded patch so that children and pets cannot reach it. Your NEUPRO patch still contains some medicine and could harm a child or pet.
- Gently wash the area with warm water and mild soap to remove any sticky material (adhesive) that stays on your skin.
- Baby or mineral oil may also be used to remove any adhesive. Avoid using alcohol or other solvents, such as nail polish remover. They may cause your skin to become irritated.
- Wash your hands with soap and water.
- You may see mild redness at the site when a patch is removed like when you remove an adhesive bandage. This redness should go away over time. If irritation or itchiness continues, tell your doctor.

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Distributed by:
UCB, Inc.
Smyrna, GA 30080

Rev. 1E 04/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 21-829/S-001 and S-002

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Brar, Satjit
Brodsky, Eric
Chang, Ted
Dimova, Hristina
Dorantes, Angelica
Ghosh, Tapash
Heimann, Martha
Hulett, Melissa
Kapcala, Leonard
McKinney, Luann
Men, Angela
Metz, Stacy
Ocheltree, Terrance
Podskalny, Gerald
Strasinger, Caroline
Williams, Sharon
Yasuda, Sally

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

OFFICE DIRECTOR MEMO

MEMORANDUM

DATE: March 30, 2012

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-829/S-001; S-002; S-004

SUBJECT: Action Memo for NDA 21-829/S-001; S-002; S-004, for the use of Neupro (rotigotine transdermal system) in the treatment of Advanced Parkinson's Disease (advanced PD), Restless Legs Syndrome (RLS), and product reformulation, respectively

This memo will discuss the following three supplements to NDA 21-829 for Neupro (rotigotine transdermal system), submitted by UCB, Inc:

S-001: for the treatment of Advanced Parkinson's Disease (advanced PD), submitted 9/21/07

S-002: for the treatment of Restless Legs Syndrome (RLS), submitted 10/5/07

S-004: for reformulation of the transdermal system, submitted 12/2/11

Neupro was approved in May, 2007 for the treatment of early PD. Shortly after its marketing, in August, 2007, (b) (4) (b) (4) (b) (4) rotigotine (b) (4) (b) (4) at one of the drug product manufacturing sites (LTS, Germany). (b) (4) (b) (4) (b) (4) necessitated a reformulation of the product, (b) (4) (b) (4) However, this resulted in the formation of crystals on the patch, which resulted in unacceptable performance of the product, and, as a result, Neupro was removed from the market in March, 2008.

Before the product's removal from the market, Supplements 001 and 002 had been submitted (as noted above, both in 2007). The Division reviewed those supplements, and concluded that the sponsor had provided substantial evidence of effectiveness for both indications (an 8 mg/24 hour patch was submitted with the advanced PD supplement, and a 1 mg/24 hour patch was submitted with the RLS supplement). However, because the product was no longer marketed at the time of the completion of the reviews of these supplements, the division issued a Complete Response (CR) letter on 12/15/08. The primary reason for the CR action was the unavailability of an acceptably performing product, but the 12/15/08 CR letter did include several requests for additional safety information, listed below:

1) request for analyses of female reproductive endocrine testing
2) request for a review of Case Report Forms (CRFs) for reports of changes in libido
3) request for a review of CRFs for menstrual abnormalities
4) request for analyses for adverse events related to orthostatic hypotension
5) requests for additional analyses of adverse events in various patient subgroups

The sponsor responded to the CR letter on 7/17/09. In that response, they included responses to the clinical questions included in the 12/15/08 CR letter; the division found those responses acceptable. However, the sponsor still had not provided evidence that they could produce a stable patch. As a result, the division issued a second CR letter on 4/21/10. In that letter, again, the primary reason for the action was related to the unavailability of an acceptable product, but the division did include several clinical comments (we informed the sponsor that we might include several labeling statements related to their responses, and asked them to include a revised Pediatric Plan for RLS).

(b) (4)

The current supplement, S-004, was submitted on 12/2/11. This supplement proposes a new reformulated patch, also using (b) (4) of rotigotine. This supplement contains the requisite Chemistry and Manufacturing Controls (CMC) information (including stability data), as well as the results of a bioequivalence study designed to establish that this new formulation performs similarly to the original formulation, which was used in all of the clinical trials done in PD (both early and late) as well as in the RLS trials. Further, it contains a revised Pediatric Plan for RLS. Responses to S-001 and S-002 were also submitted on 12/2/11.

This supplement has been reviewed by Dr. Caroline Strasinger, Office of New Drug Quality Assurance (ONDQA), Dr. Tapash K. Ghosh, ONDQA (Biopharmaceutics), Dr. Hristina Dimova, Office of Clinical Pharmacology, Dr. Eric Brodsky, Study Endpoints and Labeling Development (SEALD), Dr. Sharon Williams, Division of Medical Policy Programs, Dr. Leonard Kapcala, medical reviewer, and Dr. Dave Podskalny, neurology team leader and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved.

As Dr. Strasinger notes, the reformulated patch is stable and there is no evidence of crystal formation up to 24 months for the drug substance and 18 months for the drug product at storage conditions of 20°C/60%RH (Dr. Podskalny provides a brief, comprehensive accounting of the changes made). The new patch also was stable for 6 months at accelerated conditions. For these reasons, Dr. Strasinger has concluded that an expiry of 24 months at room conditions is acceptable.

Regarding the performance of the product, Dr. Ghosh describes how the sponsor has determined that the reformulated product that is the subject of this application is considered equivalent to the product used to establish the safety and effectiveness of Neupro for all three indications.

(b) (4)

. In the current submission, the sponsor has presented the results of a bioequivalence study (comparing the 4.5 mg patches) that demonstrate that the currently proposed product and PR 2.1.1 are bioequivalent. Ideally, the sponsor would have shown direct bioequivalence between the currently proposed formulation and the original formulation. However, the original patches are no longer available. For this reason, and given the results of the two bioequivalence studies described, I believe it is reasonable to interpret the data as establishing the bioequivalence of the current proposed formulation and the original product used in the clinical trials.

Dr. Ghosh also discusses the sponsor's evaluation of the adhesiveness of the patch to the skin.

The sponsor evaluated adhesiveness in the most recent bioequivalence study, and noted a slight decrease in the frequency of applications with an Adhesiveness score of at least 90% (about 86% of patients with such a score in this study compared to a range of 90-100% in 6 other Phase 1 studies). Further, there was an increase in the incidence of patches with partial detachment greater than 10% in this study compared to these 6 other studies (range of 0-9.8%; see his table 2.7.1.3.2:1, page 21 of his review).

To further evaluate this issue, the sponsor performed a dedicated adhesiveness study in 56 PD patients (Study SP1066). This was a cross-over study comparing the two formulations used in the bioequivalence study. This study demonstrated superior adhesiveness for the new formulation (see, for example, Dr. Ghosh's Table 2.7.1.2.3:1, and his Figure 2.7.1.2.3:1).

Safety

As Dr. Kapcala describes, the sponsor has submitted updated safety data that

includes data from the last safety update (10/31/08) to the new cut-off date (5/3/11). This safety update included data from 217 new patients. This represents a small increment over the number of patients from whom safety data had been submitted in the 10/31/08 update (that update included data from 1401 patients). The sponsor submitted only mortality data with the new update; there were no deaths. Clearly, no new safety signal has emerged.

Pediatrics

As noted above, the division had previously asked the sponsor to submit a pediatric plan, as required by the Pediatric Equity and Research Act (PREA). As noted by Drs. Podskalny and Kapcala, the sponsor has proposed that they be given a complete waiver for studies in PD, a waiver for studies in patients under the age of 13 with RLS, and a deferral for older pediatric patients with RLS. We agree that these requests should be granted. For the older pediatric patients, the sponsor has proposed to perform 3 studies: a pharmacokinetic study, a controlled clinical safety and effectiveness study, and a long-term safety study. We are in agreement, in form, with this proposal.

Comments

We are now confident that the sponsor has manufactured a product that does not form crystals, and that is bioequivalent to the product used in the clinical trials. It should be noted that, among the reasons we issued CR letters in the past, was our concern that the sponsor had proposed (b) (4) Given our current view that the patches proposed in the current supplement reliably do not form crystals, (b) (4)

For these reasons, then, I will issue the attached Approval letter for all three supplements, with attach product labeling, which now includes the additional two new indications, and which also has a Patient Package Insert (PPI) and Instructions for Use (IFU). We have discussed all labeling documents with the sponsor, and we agree with the contents.

Russell Katz, M.D.

Reference ID: 3110365
Reference ID: 3135144

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/s/

RUSSELL G KATZ
04/02/2012

MEMORANDUM

DATE: April 20, 2010

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-829/ (b) (4) 001, and 002

SUBJECT: Action Memo for NDA 21-829/ (b) (4) , 001, and 002, for Neupro (rotigotine) Patch

NDA 21-829, for Neupro (rotigotine) Patch was approved on 5/9/07 for use in the treatment of early Parkinson's Disease (PD). However, shortly after approval, the sponsor noted the formation of crystals (b) (4) (b) (4) of rotigotine (b) (4). Over time, extensive crystallization occurred, and, as a result, the sponsor removed the product from the market on 4/30/08.

Before the occurrence of crystals had been noted (the sponsor first notified the Agency of the appearance of crystals in 12/07), the sponsor submitted Supplements 001 and 002 for the use of Neupro Patches in the treatment of primary Restless Legs Syndrome (RLS) and advanced PD, respectively, on 9/21/07. Although the withdrawal of the product from the market occurred in April, 2008, the sponsor did not withdraw these supplements. The Agency issued Complete Response (CR) letters for these supplements on 12/15/08, citing the unresolved product issues (we had determined that the sponsor had established the effectiveness for these two indications). The CR letter also asked the sponsor to further evaluate several safety issues.

(b) (4)

(b) (4)

The sponsor responded to the CR letters for Supplements 001 and 002 on 7/17/09, (b) (4) (b) (4) Supplements 001 and 002 have been reviewed by Dr. Leonard Kapcala, medical officer and Dr. Dave Podskalny. All reviewers recommend that the division issue CR letters for all supplements.

Dr. Pinto has found that the sponsor's responses to our concerns are, for the most part, inadequate.

The sponsor has submitted data that they believe establish the stability of the patches under the proposed storage conditions (b) (4); Further, they believe that they have validated the (b) (4) for quantitating crystallization.

Regarding this latter issue, the sponsor has submitted data from 50, 10 cm^2 and 50, 40 cm^2 patches from analytic batches (smaller than stability batches, which are produced under scaled-up conditions) that were inspected by two independent company analysts. According to the sponsor, the degree of crystallization ranged from (b) (4) and there was agreement on these estimates between the two analysts. At the time of these determinations, the product was 12 months post manufacture.

The Agency requested that the sponsor send patch samples to the FDA office in St. Louis, where the FDA laboratory would attempt to independently validate the (b) (4) The sponsor submitted (b) (4); from the same batch described above that yielded estimates of crystallization of between (b) (4). The patches sent to St. Louis were, at the time of inspection, about 18 months post production.

FDA staff at the St. Louis lab inspected the patches (b) (4), and also examined the patches microscopically. Although crystals were observable, in all cases the percent of the total area affected by crystals was (b) (4) It is unclear why patches that were 12 months old were noted (by the sponsor) to have up to (b) (4) of the area affected by crystals, but 18 month old patches ***from the same batch*** were noted to have (b) (4) of the area affected by crystals by FDA staff.

According to Dr. Pinto, the sponsor has demonstrated that the patch is adequately adherent when up to (b) (4) of the area is affected by crystals.

Dr. Pinto has also concluded that the data provided from the stability batches supports the conclusion that (b) (4) of the area is affected by crystals when the product is stored at (b) (4). However, she has also concluded that the patches form crystals (b) (4) after only 1 week at room temperature, and up to (b) (4) crystallization after 11 weeks at room temperature and humidity (b) (4). Presumably, temperature excursions beyond room temperature were not assessed.

Dr. Kapcala has found that the sponsor has addressed the clinical questions included in the CR letters for Supplements 001 and 002, and recommends that several statements be added to labeling to describe an increased incidence of several adverse events. He finds nothing that would preclude approval.

Comments

The sponsor has responded to our concerns as expressed in our CR letter for supplement 001 (and to the clinical questions in the CR letter for Supplements 002 (b) (4); the latter responses may require the addition of several statements to labeling).

However, Dr. Pinto has concluded that the responses to our concerns regarding crystal formation are inadequate.

I agree.

My primary concern is that, although the results of the stability testing revealed that patches had (b) (4) (the sponsor's proposed specifications), data from the sponsor's observations of patches from the analytic batches suggested that some patches kept under these storage conditions had crystallization up to (b) (4). This suggests that even if patches meet the proposed release specifications (b) (4) crystallization at release), some batches will produce significant crystallization at (b) (4), (even greater than the proposed (b) (4). Although the sponsor asserts that their proposed (b) (4) is reproducible (by virtue of the fact that their two analysts agreed on the estimates of the degree of crystallization), FDA analysts, examining patches from the same batch, found that the degree of crystallization was (b) (4) For this reason, FDA observers could not validate that the (b) (4) can reliably or reproducibly detect crystallization at any amount (b) (4)

Throughout the course of review of this problem of crystallization, the question of whether or not (b) (4)

(b) (4)

But, if I believed that the sponsor could reliably produce a patch that at (b) (4), I would find that to be an approvable product, ***even if crystals were observable*** (b) (4)

(b) (4)

However, the data suggest that the sponsor cannot reliably produce a patch that will have (b) (4), based on the data described above. Further, we have not been able to validate the (b) (4) of crystal quantitation adequately, so that we cannot even be sure that a product has truly met any proposed specification set for (b) (4). That is, even if we were to accept the sponsor's proposed specification of (b) (4), we have not been convinced that the sponsor can reliably quantitate this degree of crystallization, so we cannot know that any given patch did or did not have more (or less) than (b) (4) crystallization. And, of course, if we cannot reliably determine if a given patch has more or less than (b) (4) crystallization, it is then possible that it may have substantially more than (b) (4) crystallization, and may be approaching a degree of crystallization that could impact on the performance of the product.

For these reasons, Dr. Pinto has concluded that, at this time, the most appropriate way forward is for the sponsor to reformulate the product to insure that (b) (4) stays in solution, and I agree. Although it is possible that the sponsor might ultimately demonstrate that their currently proposed product is adequate and stable, (b) (4). I agree that we should strongly recommend that the sponsor reformulate the product to produce a patch that is crystal-free for the entire expiry.

For the reasons described above, then, I will issue the attached CR letters (b) (4) for Supplements 001 and 002). Because of the significant outstanding manufacturing issues, we will not include draft labeling.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS
NDA-21829	SUPPL-2	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS

(b) (4)

[redacted]

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/s/

RUSSELL G KATZ
04/21/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	04/02/2012
From	Gerald D. Podskalny, D.O.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21829 S-001, 002, 004
Applicant	UCB, Inc.
Date of Submission	12/02/2011
PDUFA Goal Date	S-004-(04/02/2012) S-001, S-002-(06/02/2012)
Proprietary Name / Established (USAN) names	Neupro/Rotigotine Transdermal Patch
Dosage forms / Strength	Transdermal Patch
Proposed Indication(s)	1. Advanced Parkinson's disease (S-002) 2. Moderate to severe primary restless legs syndrome (S-001)
Recommended:	***APPROVAL***

Cross Discipline Team Leader Review

1. Introduction

Rotigotine transdermal patches were approved on May 9, 2007 for the treatment of patients with early Parkinson's disease (PD). On March 21, 2008, UCB voluntarily decided to withdraw Neupro from the U.S. Market because of crystal formation on Neupro (b) (4) patches. Ownership of the Neupro NDA was transferred From Schwarz biosciences to UCB, Inc. on November 5, 2010. UCB (Sponsor) has submitted a new CMC supplement for a reformulated Neupro (rotigotine transdermal) patch made by a new process (2.2.1) designed for room temperature storage conditions. The Sponsor has also resubmitted efficacy supplement to support approval of two new indications:

1) treatment of patients with moderate to severe primary Restless Legs Syndrome (RLS)
2) patients with advanced Parkinson's disease (PD) adding to the existing approval for patients with early PD.

2. Background

Rotigotine transdermal patch (Neupro) was approved in the U.S. on May 9, 2007 for the treatment of patients with early Parkinson's disease (PD). On March 21, 2008, UCB voluntarily decided to withdraw Neupro from the U.S. Market because of crystal formation on Neupro (b) (4) patches. Crystallization formation (b) (4)

The Sponsor had submitted 2 NDA efficacy supplement seeking approval of Neupro for the treatment of moderate to severe primary Restless legs Syndrome (RLS) and patients with advanced PD. A "Complete Response" action was taken by the Agency on 11/11/2008 for both supplements primarily because Neupro 1.0 was withdrawn from U.S market.

The Agency's review of both supplemental NDA applications found that there was substantial evidence that Neupro was effective in the treatment of patients with advanced PD and patients with moderate to severe primary RLS. The reviews did not identify any new major safety concerns.

(b) (4)

On December 2, 2011, UCB submitted CMC supplement four for the reformulated 2.2.1 Neupro patches (b) (4) (b) (4). In addition, UCB resubmitted supplements for advanced Parkinson's disease (S-002) and Restless Legs Syndrome (S001).

3. CMC/Device

General product quality considerations

UCB submitted information supporting reformulated Neupro transdermal patches made using (b) (4) (b) (4) . (b) (4) Subsequentl (b) (4) Recently, UCB has reformulated Neupro (b) (4) (b) (4) that reportedly does not from crystals when stored at room temperature. The synthesis of the (b) (4) patches is largely similar to the (b) (4) (b) (4) (b) (4) patches except that the patch starts with (b) (4) and additional changes to the manufacturing process of the (b) (4) patches.

Manufacturing Changes in The (b) (4) Patches

(b) (4)

[redacted]

A new patch strength, 8 mg/24 hrs was submitted with the advanced PD supplement. The new 1 mg/24 hrs and 3 mg/24 hrs strengths were submitted to the RLS supplement.

Overview of rotigotine patch strengths

Patch size	Total rotigotine content	Rotigotine delivered per 24hours	Release per unit area
5cm^2	2.25mg	1mg	0.2mg/cm^2
10cm^2	4.5mg	2mg	0.2mg/cm^2
15cm^2	6.75mg	3mg	0.2mg/cm^2
20cm^2	9.0mg	4mg	0.2mg/cm^2
30cm^2	13.5mg	6mg	0.2mg/cm^2
40cm^2	18.0mg	8mg	0.2mg/cm^2

(b) (4)

[redacted]

Changes in the Drug Product Release Acceptance Criteria (from FDA ONDQA CMC Review)

Test	Acceptance Criteria
(b) (4)	

The drug substance and drug product quality review was performed by ONDQA, Branch 3 reviewers Dr. Huai T. (Ted) Chang (DS) and Dr. Caroline Strasinger (DP). Portions of this CDTL review reference or reproduce information and tables from the ONDQA reviews.

Conclusions of the ONDQA Quality Review

The changes proposed in this supplement regarding drug product are for the use of Process 2.2.1, a reformulation of Neupro®, that is stable at room temperature and crystal-free through out shelf life. Multiple sections throughout module 3.2.P have been updated to support this manufacturing change. The Applicant has provided (b) (4) of stability data for (b) (4) primary stability batches supporting Process 2.2.1.

The provided stability data, supportive formulation development work, and data from (b) (4) demonstrate that the system manufactured under Process 2.2.1 remains crystal-free throughout shelf life. The proposed changes in the manufacturing of the drug product using Process 2.2.1 do not adversely impact the identity, strength, purity and quality of the drug products.

Key CMC/Quality Issues

Product Stability

ONDQA CMC reviewed data from UCB for up to (b) (4) under long-term stability storage conditions and (b) (4) stability data under accelerated storage conditions. UCB also provided data for selected batches subjected to (b) (4). Supportive data for 24 months under long-term storage condition was provided for one pilot scale batch without the new (b) (4) and with slightly different ratio of silicone adhesives.

UCB concluded that the reformulated transdermal system manufactured according to process 2.2.1 demonstrate sufficient stability of the drug product to date. They based their conclusions on real time data available up to (b) (4) under long-term storage conditions and (b) (4) data under accelerated test conditions.

No crystallization was reported in any of the reformulated patches tested. The proposed shelf life of 24 months for process 2.2.1 Neupro Transdermal Patches under controlled room temperature conditions of 20-25°C (68 -77°F) with excursions permitted to 15-30°C (59-86°F).

UCB also committed to continue annual post-approval stability testing for one batch of each strength of Neupro. The Sponsor submitted a protocol and submitted a protocol.

ONDQA Reviewer Comment: A shelf life of 24 months is granted.

Crystal Formation

UCB reported there were no crystals found in any of the patches placed on long-term or accelerated storage conditions. (b) (4)

A factor that played a role in the Agency's decision to issue a Complete Response Action for (b) (4) The method for detecting crystals in the Process 2.2.1 patches is also by (b) (4). The Sponsor evaluated several automated methods to detect crystals formation in the drug product, however the results of the (b) (4) found that (b) (4) was the most reliable method to detect crystal formation.

From UCB CMC Supplement (S-004)

(b) (4)

(b) (4)

CDTL Comment:

(b) (4) would not be expected to impact the performance (drug delivery) of the Neupro (b) (4) patch. UCB had previously proposed criteria based on (b) (4). The Sponsor was not able to validate the proposed method of measuring differences in the areas of crystallization (b) (4) to distinguish patches that were just within of the proposed specification limit from those that just exceeded the limit (b) (4)

(b) (4)

(b) (4)

Sponsor Revised Specifications

"In comparison to the test method described in the background package sent electronically to FDA on 17 February 2012, some slight revisions were implemented in order to improve method precision.

(b) (4)

(b) (4)

(b) (4) (b) (4)

ONDQA CMC Reviewer

The revised analytical procedure was applied during validation of the method and the suitability in terms of reasonably low variability and good method precision could be demonstrated. The results obtained during validation experiments clearly met the predefined acceptance criteria. The Applicant states risk mitigation strategies have been put in place to further reduce the frequency of this occurrence (b) (4) and they will continue to monitor the phenomenon in stability studies.

CDTL Reviewer Comment

(b) (4)

Drug Release Specifications

ONDQA Biopharmaceutics Review Drug Release Specifications

***Drug Release Criteria for New 2.2.1 Formulation (S 04)*:**

Based on the release and stability data presented above, the Sponsor proposed the three time points to control the *in vitro* drug release of the patch. The specification is set as follows for each time point (% of nominal content):

(b) (4)

(b) (4)

Therefore, the applicant's proposed methodology as a routinely test for batch-to-batch uniformity is acceptable. However, the Biopharmaceutical reviewer believed the drug release specifications proposed by UCB should be tightened. ONDQA proposed the following *in*

vitro drug release criteria at release and during stability and sent they revised specifications via e-mail on March 20, 2012:

UCB Submitted the following change to the in vitro drug release specifications that reflect data from the most recent batches presented in the application that were manufactured with tightened specifications for the silicone adhesives in response to the Agency's request.

ONDQA believes the revised release specifications comply with continuous improvement procedures and found them to be acceptable. The Agency will monitor the release and stability results for all assays on a routine basis and notify the Agency of any changes accordingly.

Facilities review/inspection

The drug substance manufacturer remains unchanged at:

Manufacturer	Responsibility
LTS Lohmann Therapie-Systeme AG Lohmannstraße 2 D-56626 Andernach Germany Drug Establishment Registration Number: #3003387535	• Manufacturing of bulk product (primary packaged transdermal patch in pouch) • Secondary Packaging • Process controls • Control of intermediates • Quality control of excipients and container closure system • Testing for adhesive properties, residual solvents and tightness of pouches
(b) (4)	• Quality control of drug product • Stability testing of drug product • Secondary packaging
	• Testing of microbiological purity

The ONDQA reviewer noted that there was a change in the name of a testing facility to (b) (4) has occurred without any changes to operations. Additionally, secondary packaging has been added as a function of this approved site. (b) (4) sites have been removed as secondary packaging facilities. An updated manufacturer(s) table has been provided for reference:

Container Closure System

(b) (4)

4. Nonclinical Pharmacology/Toxicology

Supplements 001, 002, 004 did not contain new Pharmacology/Toxicology data. Pharmacology and Toxicology provided comments and edits to the relevant sections of the new product labeling.

5. Clinical Pharmacology/Biopharmaceutics

Bioequivalence

The route to establishing bioequivalence (BE) for the process 2.2.1 patches was BE a comparison of the Process 2.1.1 patches with the reformulated Process 2.2.1 patches SP0987. The Sponsor previously demonstrated that the Process 1.0 patches were bioequivalent to the Process 2.1.1 patches in study SP951.

Review and conclusions from ONDQA Biopharmaceutics Review of BE Study SP951 Entered into DARRTS on 10/27/09 (Dr. Ghosh).

Test products dose and mode of administration, batch number:

Treatment A: Rotigotine transdermal patch (4.5mg/10cm^2) from modified manufacturing process using polymorphic (b) (4) as drug substance for patch production (*Test*; drug product PR2.1.1); single application of 1 patch for 24 hours; batch number 0808250002

Treatment B: Rotigotine transdermal patch (4.5mg/10cm^2) from originally approved manufacturing process using polymorphic (b) (4) as drug substance for patch production (*Reference*; drug product PR1.0); single application of 1 patch for 24 hours; batch number 0707200001

Point estimates and 90% confidence intervals (CIs) for the treatment ratio "A/B" for the primary PK parameters $AUC_{(0-tz)}$ and Cmax and the PK parameter $AUC_{(0-8)}$ are summarized in the table below:

ANOVA of PK parameters of unconjugated rotigotine (PKS in SP951)

Parameter	n	Treatment A (test)	Treatment B (reference)	Point estimate for ratio A/B	90% CI	ANOVA CV (%)
		LSMeans				
$AUC_{(0-tz)}$ (ng/mL*h)	44	2.67	2.71	0.9864	0.9103, 1.0688	22.6
$AUC_{(0-\infty)}$ (ng/mL*h)	44	2.80	2.83	0.9896	0.9179,1.0671	21.2
C_{max} (ng/mL)	44	0.130	0.136	0.9584	0.8861, 1.0367	22.1

A=single application of one 4.5mg/10cm^2 rotigotine patch from modified manufacturing process (drug product PR2.1.1); ANOVA=analysis of variance; B=single application of one 4.5mg/10cm^2 rotigotine patch from originally approved manufacturing process (drug product PR1.0); $AUC_{(0-tz)}$=area under the plasma concentration time curve from time point zero to the last analytically quantifiable concentration; $AUC_{(0-\infty)}$=area under the plasma concentration time curve from time point zero to infinity; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; LSMeans=least squares means; n=number of subjects who provided data for the parametric analysis; PK=pharmacokinetic; PKS=Pharmacokinetic Set

Thus, bioequivalence of rotigotine transdermal patch (4.5mg/10cm2) from the modified manufacturing process using (b) (4) as drug substance for patch production (drug product PR2.1.1) and from the originally approved manufacturing process using (b) (4) as drug substance for patch production (drug product PR1.0) was established.

New Bioequivalence Data from Study (SP0987) Contained in CMC Supplement 004

The study was a phase 1, open label randomized crossover trial designed to evaluate BE between the process 2.1.1 and 2.2.1 Neupro patches. A single patch size (4.5mg/10cm^2) of each formulation was compared side by side in health male subjects (n=50). Treatment A was the Process 2.2.1 patch and Treatment B was the 2.1.1 patch. Each patch was worn for 24 hours, all subjects received both treatment in one of two sequences (A-B or B-A). Analysis of the data was performed in three populations Safety set (SS) (n=50), Completer Set (CS) (N=48) and the Pharmacokinetic set (PKS) (N=40). Subjects in the PKS met predefined criteria for patch adhesiveness. If patch detachment occurred, over-taping or replacement was not permitted.

ONDQA Biopharmaceutics-Pharmacokinetic Conclusions Study SP0987

The mean plasma concentrations and PK parameters were similar between the 4.5mg/10cm^2 rotigotine patch manufactured according to process 2.2.1 (test drug product PR2.2.1; Treatment A) and manufactured according to process 2.1.1 (reference drug product PR2.1.1; Treatment B). The 90% CIs for the ratio of geometric means for $AUC_{(0-tz)}$, $AUC_{(0-8)}$, and C_{max} were fully included in the acceptance range for BE of 0.8 to 1.25. Results were very similar for the secondary analyses corrected for measured drug content.

Thus, the BE of rotigotine transdermal patch (4.5mg/10cm^2) manufactured according to process 2.2.1 (test drug product PR2.2.1; Treatment A) and manufactured according to process 2.1.1 (reference drug product PR2.1.1; Treatment B) was established.

The results of additional analyses based on the CS, comprising all randomized subjects who completed the study (including those subjects who were excluded from the PKS due to predefined patch adhesiveness criteria), support the BE conclusion.

ONDQA Biopharmaceutics Reviewer's Comments:
The reviewer's analysis of the data using WINNONLIN v. 5.2.1 confirms the applicant's conclusion of BE of rotigotine transdermal patches (4.5mg/10cm^2) manufactured according to process 2.2.1 (test drug product PR2.2.1; Treatment A) and manufactured according to process 2.1.1 (reference drug product PR2.1.1; Treatment B)

- Neupro (rotigotine transdermal) patches (4.5mg/10cm^2) manufactured according to process 2.2.1 (test drug product PR2.2.1) and manufactured according to process 2.1.1 (reference drug product PR2.1.1) are bioequivalent.

Figure 8:1. Arithmetic mean (+/-SD) plasma concentration (ng/mL) vs time profiles of unconjugated rotigotine (PKS)

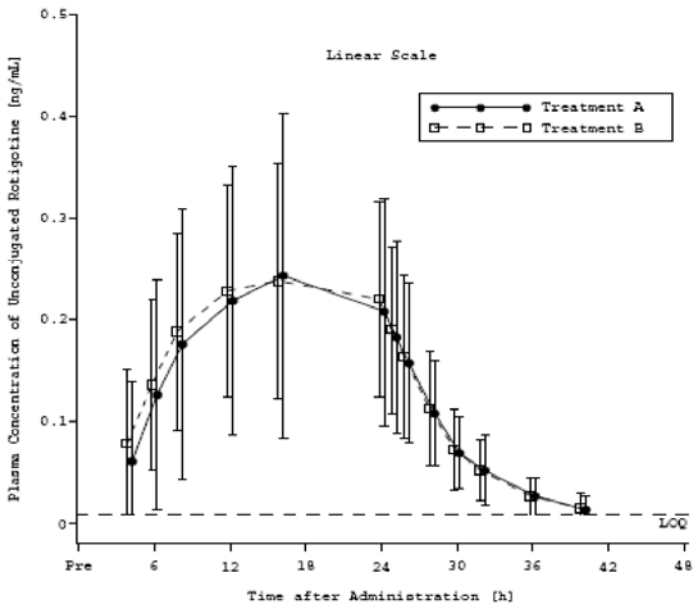


Table 8:1. Pharmacokinetic parameters of unconjugated rotigotine by treatment (PKS)

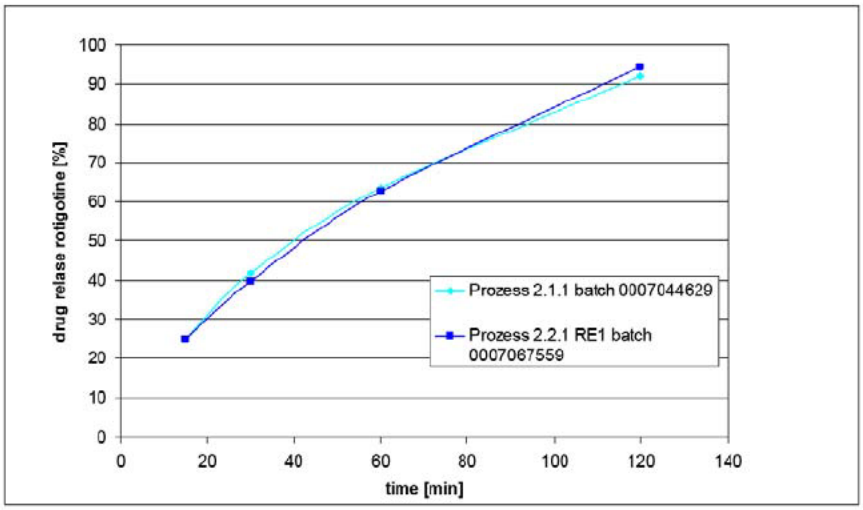
Parameter (unit)	Treatment A (test) n=40	Treatment B (reference) n=40
	Geometric mean (geometric CV [%])	
$AUC_{(0-tz)}$ (ng/mL*h)	4.5079 (61.0)	4.8658 (56.1)
$AUC_{(0-tz)\ norm\ (BW)}$ (ng*h*kg/mL)	354.733 (60.6)	382.899 (57.9)
$AUC_{(0-tz)\ norm\ (apparent\ dose)}$ (ng/mL*h/mg)	2.41996 (36.5)	2.50512 (35.4)
$AUC_{(0-\infty)}$ (ng/mL*h)	4.61392 (59.7)	4.97260 (54.6)
$AUC_{(0-\infty)\ norm\ (BW)}$ (ng*h*kg/mL)	363.080 (59.4)	391.305 (56.4)
$AUC_{(0-\infty)\ norm\ (apparent\ dose)}$ (ng/mL*h/mg)	2.47690 (35.7)	2.56012 (34.7)
C_{max} (ng/mL)	0.22607 (57.4)	0.23226 (51.6)
$C_{max,norm\ (BW)}$ (ng/mL*kg)	17.7896 (56.7)	18.2773 (53.6)
$C_{max,norm\ (apparent\ dose)}$ (ng/mL/mg)	0.121360 (36.5)	0.119580 (32.8)
MRT (h)	18.376 (10.4)	18.084 (10.6)
CL/f (L/h)	975.31 (59.7)	904.96 (54.6)
	Arithmetic mean (SD)	
$t_{1/2}$ (h)	4.4523 (0.9701)	4.3752 (0.9677)
λ_z (1/h)	0.162587 (0.033663)	0.165400 (0.033405)
	Median (range)	
t_{max} (h)	16.00 (8.0-25.0)	16.00 (8.0-28.0)

Biowaivers Granted

ONDQA Biopharmaceutics Reviewer's Comments:

UCB demonstrated bioequivalence in study (SP0987) between the 10 cm^2 patches with increased amount of 4% PVP (process 2.2.1) to patches manufactured with 2% PVP (process 2.1.1). Based on the similarities in the in-vitro release profiles (with associated F2 values for all other strengths, Biowaiver are granted for the remaining sized (1, 2, 3, 30 and 40 cm^2) patches.

Figure 2:4 Release profiles 2.1.1 vs 2.2.1 (10cm^2 batches)



f2 values of 2.2.1 batches are compared with 2.2.1 batches

Size	Batch 2.1.1	Batch 2.2.1	F2 value
5cm²	0808180004	0007067509	67
10cm²	0007044629	0007067559	86
15cm²	0808180005	0007067519	68
20cm²	0808260004	0007005000	77
30cm²	0808180007	0007067539	63
40cm²	0808250003	0007067549	66

Adhesiveness

ONDQA Biopharmaceutics Reviewer's Comments:

(b) (4)

Summary of adhesiveness data

Adhesiveness data have been collected in 5 Phase 1 studies, 1 Phase 1 adhesiveness study, and 3 Phase 3b studies using the same scoring system.

In SP0987, a Phase 1 BE study, partial or complete detachment of the patch occurred more often with drug product PR2.2.1 compared to drug product PR2.1.1. Accordingly, a dedicated adhesiveness study, SP1066, was conducted to further evaluate the adhesive properties of PR2.2.1 patches.

In-vivo Adhesiveness Study SP1066

An exploratory adhesiveness study (SP1066) was conducted in order to demonstrate at least equivalent adhesive behavior of reformulated patches with 4% PVP (process 2.2.1) compared to patches of process 2.1.1 with 2% povidone. As agreed with FDA, only the largest patch size ($40cm^2$) was investigated. Patches of process 2.2.1 used for this study were made according to the optimized conditions regarding their viscoelastic properties, as described earlier. According to the applicant, the outcome of the study demonstrated equivalent adhesiveness between the two formulations.

Study Design SP1066

This was a multicenter, randomized, outpatient, double-blind, 2-way, crossover study in subjects with idiopathic Parkinson's disease, assessing patch adhesiveness of the room temperature-stable patch (PR2.2.1) by comparing adhesiveness with the modified manufacturing process patch (PR2.1.1).

Patients (N=56) received Treatment A (rotigotine transdermal patch, 8mg/24h, test product PR2.2.1, single application in multiple day treatment) and Treatment B (rotigotine transdermal patch, 8mg/24h, reference product PR2.1.1, single application in multiple day treatment) for 2 consecutive days (either A then B [A-B], or B then A [B-A]). Assignment to 1 of the 2 treatment sequences was randomized. Thereafter, subjects were allowed to resume use of commercially available rotigotine transdermal patch as prescribed by their physician.

For each patch applied, patch adhesiveness was to be measured within 5 minutes of application (to check for correct application) and 24h later (i.e., before removal of the patch).

Safety and tolerability were assessed throughout the study by monitoring adverse events and evaluation of the skin of the application area.

Patch adhesiveness

At each PK sampling time point during the patch-on period, patch adhesiveness was assessed according to the international adhesion score described below.

0 = 90% or greater adhered (essentially no lift off of the skin)
1 = 75 - < 90% adhered (some edges only lifting off of the skin)
2 = 50 - < 75% adhered (less than half the system lifting off of the skin)
3 = < 50% adhered (more than half the system lifting off of the skin without falling off)
4 = patch detached (patch completely off the skin)

Duration of patch wear:
For Treatment A and Treatment B, the average duration of patch wear over 2 days was 22.72 hours/day and 23.25 hours/day, respectively. For Treatment A, 4 patches applied on the first day completely detached after a range of 3.5h to 6.9h, and 4 patches applied on the second day completely detached after a range of 1.4h to 20.8h. For Treatment B, 3 patches applied on the

first day completely detached after a range of 4.0h to 20.9h, and 3 patches applied on the second day completely detached after a range of 4.5h to 22.0h.

UCB Reported Results and Conclusions

For each subject, average 2-day adhesiveness scores for Treatments A and B were calculated and the difference determined by subtracting the average for Treatment A from the average for Treatment B. Using the method of Hodges-Lehmann, the point estimate for the location parameter and 2-sided 90% CI for the differences for all subjects in the Per-Protocol Set (PPS) were determined to be 0.5 [0.00, 0.75]. Since this CI includes 0.00, average adhesion of Treatment A and Treatment B is comparable. The positive point estimate indicates a trend towards better adhesiveness of Treatment A.

ONDQA Biopharmaceutics Reviewer's Comments:

The applicant's conclusion that the adhesiveness data from the study SP1066 show that the proposed PR 2.2.1 patches have an adhesiveness comparable to (b) (4) ***(PR2.1.1) and in line with established and historical ranges based on comparison to the Phase 3b data (PR1.0) is generally based on better scores in the categories 0 (≥ 90% adherence) and 1-3 (partial detachment) categories. However, in the worst-case scenario for category 4 (complete detachment), PR 2.2.1 patches are worse than PR 2.1.1 patches. Also lumping categories 1, 2 and 3 is not the best way to present adhesive scorings. Appropriate labeling language is needed to address the patch adhesiveness.***

CDTL Comment

I agree with the ONDQA Biopharmaceutics reviewer's conclusions regarding bioequivalence and adhesiveness. The label already provides instructions to prescribers and patients regarding what to do if the patch partially or fully detaches. (see below). I believe these labeling instructions adequately address the concerns regarding patch detachment. The ONDQA review team agreed that the current labeling language (below) is adequate to address these concerns.

17.16 Instructions for Use

"Care should be used to avoid dislodging the patch while showering, bathing or during physical activity. If the edges of the patch lift, Neupro may be taped down with bandage tape. If the patch detaches, a new one may be applied immediately to a different site. The patient should then change the patch according to their regular schedule".

PATIENT INFORMATION

How should I use NEUPRO for Parkinson's disease?

If the edges of the patch lift, you may tape them down with bandaging tape.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Brief Review of Efficacy
The Agency completed their review efficacy data from the clinical trials program supporting the additional indications in advanced PD and RLS in November 2008. The Agency concluded that rotigotine transdermal was effect for treating patients with advanced PD and moderate to severe primary RLS.

Restless Legs Syndrome
The clinical development program for rotigotine included 8 clinical trials that evaluated efficacy, safety, and tolerability of rotigotine in subjects with RLS. This includes 2 pivotal double- blind, trials SP790 and SP792 that were performed to assess the efficacy, safety, and tolerability of rotigotine for the treatment of idiopathic RLS. SP790 and SP792 were similar in that each followed a multicenter, randomized, double blind, and parallel-group design. The primary differences between these trials were geographic regions (SP790 was conducted in Europe, SP792 in the US) and an additional treatment arm in SP792 that included a 0.5mg/24h dose of rotigotine. The 0.5mg/24h dose was included in this trial at the request of the FDA to explore the lowest effective dose.

Two primary efficacy variables, the IRLS and CGI Item 1 (severity of illness), were chosen as Co-Primary Endpoints for this trial.

The effect of rotigotine on the pre-specified co-primary endpoints observed in clinical trials SP-790 and 792 supported a conclusion that rotigotine is effective for treating the symptoms of moderate to severe RLS. The results of study SP792 demonstrate replication of results observed in study SP790 supporting the efficacy claim for the 6.75 mg/day (3 mg/24 hours delivered) and 4.5 mg/day (2 mg/24 hours delivered) doses. However, study SP792 failed to replicate the statistically significant difference from placebo treated subjects for the primary endpoint analysis at the 2.25 mg/day dose (1 mg/24 hours delivered), demonstrated in SP790 study. The 1.125 mg/day (0.5 mg/24 hours delivered) dose was only studies in the SP-792 study the results of the analysis of the primary and most secondary endpoints failed to demonstrate a statistically significant difference from placebo treated subjects.

Advanced Parkinson's Disease
The advanced PD clinical development program consisted of two pivotal trials (SP650 and SP515), and a phase 2 study SP511. All three trials were randomized, placebo-controlled, multi-center parallel group studies with rotigotine dose ranging from 9 mg to 36 mg per day in subjects with advanced PD who were not well controlled on L-dopa.
SP650 had three treatment arms: rotigotine 18mg, rotigotine 27mg and placebo. The trial, which was conducted in North America, consisted of a titration period of up to 5 weeks followed by a maintenance period of 24 weeks. SP515 was conducted in Europe and South Africa. It was a flexible dose trial with per-day dose of rotigotine ranging from 9 mg to 36

mg. The duration of SP515 consisted of up to 7 weeks titration and 16 weeks of maintenance period. Additionally, SP511 was a dose finding study with 4 treatment groups: 9 mg, 18 mg, and 27 mg of rotigotine, and placebo. The trial was conducted in Europe and South Africa.

The common primary efficacy endpoint for the three studies was the reduction from baseline in absolute time spent "off".

The primary reviewer (Dr. Kapcala) concluded that rotigotine is effective for the treatment of advanced PD at doses ≥ 18 mg/day patch content (i.e., 8 mg delivered dose) based upon results of studies 650 and 515. The only recommended dose of rotigotine at this time is 18 mg /day because the dose-response study (650) showed that there was no additional clinical benefit of a higher dose (i.e., 27 mg/day). More specifically, reduced efficacy for the primary efficacy endpoint with the 27 mg/day dose (vs. the 18 mg/day dose) was observed and there was increased toxicity at the 27 mg/day dose.

8. Safety

The safety of rotigotine transdermal in patients with early PD was established with the approval of Neupro Process 1.0. The safety in patients with advanced PD and in patients with moderate to severe primary RLS was reviewed in detail in November 2008 prior to the Agency's initial complete response action. The initial complete response action for the advanced PD and RLS supplements were not approved following the Sponsor's voluntary withdrawal of Neupro (process 1.0)

There were several minor issues in the safety review of the initial application for the two efficacy supplements in 2008. Additional analyses to clarify the effect of potential association of rotigotine with changes in postural hypotension, visual disturbance and the potential changes in reproductive hormone levels in pre and post-menopausal women. (b) (4) The additional analyses of the safety data that adequately addressed the Agency's questions posed to the Sponsor. Dr. Kapcala concluded that the additional information did not affect the safety profile of rotigotine transdermal. I concur with Dr. Kapcala's conclusion.

UCB submitted a Final Safety Update (FSU2) in the advanced PD (002) supplement that includes safety data from 10/31/08 (FSU1) until the cut-off (5/31/11). The Sponsor's Safety Update focused on presenting mortality data. Dr. Kapcala reviewed the relatively small amount of additional mortality data and concluded the following:

Dr. Kapcala's Conclusions regarding the Final Safety Report FSU2

- The exposure/treatment of patients (advanced PD and RLS) comprised a relatively small percentage of the total number of patients treated and total number of patient-years of treatment in the total clinical development programs for both indications.

- There were no new deaths during the period of this FSU2 for advanced PD or RLS. Thus, mortality rates only decreased.

- There was no new, significant, safety information presented from the postmarketing experience nor from publications that impact on the safety profile of rotigotine/Neupro.

- My perspective on the safety profile for rotigotine remains unchanged since the time of my last clinical review

Safety Information Submitted for Restless Legs Syndrome

The Sponsor submitted the results of an "Augmentation Report" that was comprised of a retrospective analysis of data from open label trials data (SP 791 and SP 793) and a separate retrospective review of 6-month controlled clinical trials data from (SP790 and SP792).

The retrospective, post hoc nature of these analyses does not meet the Agency's standard for substantial evidence and it greatly limits the conclusions that can be drawn from these s analyses regarding the incidence of Augmentation or Rebound. The retrospective analysis of uncontrolled data poses event greater limits on the reliability of such data. The relatively low number of cases SP790 (N=5) and SP 792 (N=7) is complicated by a relative large number of "Not Evaluable" cases ((N=16 (11%)) or cases judged to meet criteria for augmentation but they were classified as "not clinically relevant augmentation" (N=32) that outnumbered the patients with "No Augmentation" (N=37). Similar findings were reported in the retrospective analysis of the augmentation data for SP792.

Classification of subjects of study SP790 according to experts' evalution of potential augmentation (N=146 evaluated subjects)

Category	Subcategory	n (%)
Non-responders	Not applicable	56 (38.3)
Responders[a]	Not applicable	90 (61.7)
No augmentation	Not applicable	37 (25.3)
Augmentation	Clinically relevant augmentation	5 (3.4)
	4-hour criterion present but not clinically relevant	22 (15.1)
	2-hour criterion plus additional signs for augmentation present but not clinically relevant	10 (6.8)
Not evaluable	Not applicable	16 (11.0)

a. A responder was defined as a subject who improved by at least 50% of the baseline IRLS total score on two consecutive visits at any time before the event of potential augmentation.

Classification of subjects of study SP792 according to experts' evalution of potential augmentation (N=161 evaluated subjects)

Category	Subcategory	n (%)
Non-responders	Not applicable	55 (34.1)
Responders[a]	Not applicable	106 (66.0)
No augmentation	Not applicable	51 (31.7)
Augmentation	Clinically relevant augmentation	7 (4.3)
	4-hour criterion present but not clinically relevant	30 (18.6)
	2-hour criterion plus additional signs for augmentation present but not clinically relevant	5 (3.1)
Not evaluable	Not applicable	13 (8.1)

a. A responder was defined as a subject who improved by at least 50% of the baseline IRLS total score on two consecutive visits at any time before the event of potential augmentation

CDTL Conclusions Regarding Augmentation:
The analyses of the clinical trials information are insufficient to permit conclusions to regarding the possible association or lack of association of Neupro with augmentation beyond what is already communicated in the product label. The information does not represent data from a systematic evaluation of augmentation in trials that were designed prospectively to evaluate the incidence of augmentation over a sufficient period of follow-up. It is believed that Augmentation requires a minimum of 6-24 months on dopaminergic before symptoms of Augmentation begin to emerge.

Final Report of Trial SP 710
Trial SP710 was an open-label trial with a 60-month maintenance period that enrolled (N=295) patients with a ≥ +50% overall change in IRLS total score were enrolled in SP710 within 7 days after completing trial SP709 if their severity of RLS worsened and the medical condition required further therapy. Patients could re be treated with Neupro doses as high as 9 mg/24 hours as tolerated.

One hundred and twenty six patients completed the maintenance phase of the trial and 93 patients (32%) withdrew from the trial prematurely. The most common reason for withdrawal was insomnia ((N-56 (19%)). A single death was reported in a 59-year-old patient who suffered a "Severe M.I." while on therapy with Neupro. The patients suffered a second M.I. during the recovery and experienced sudden death. Seventy-nine subjects reported experiencing at least 1 nonfatal SAE. Osteoarthritis was the most commonly reported SAE. Four patients suffered an M.I. and 2 had SAEs related to nausea. .

A single pregnancy was reported (subject 10311), had a positive serum pregnancy test at her Termination Visit (b) (6) while taking Neupro. The patient was at the time, a 30-year old female. She underwent a planned termination of pregnancy (abortion) on (b) (6) after the first dose of trial medication, and 17 days after her last dose.

Application site reactions were the most commonly reported AE (172 (58% of total N), nausea (11%), fatigue (10%), erythema (6%), and pruritus (5%).

CDTL Conclusion
The results of trial SP710 do not suggest a change in the safety profile of transdermal rotigotine. The flexible dose, open-label trial design of SP 710 limits conclusions regarding the tolerability of high doses of rotigotine in patients treated for RLS. There is little information regarding the incidence of rebound and Augmentation with dopamine agonist medications. The majority of publish reports describe the association of Augmentation and Rebound with treatment of RLS with levodopa. The current labeling describing Augmentation and Rebound is sufficient to alert prescribers that both complications are possible.

5.12 Augmentation and Rebound in RLS

Augmentation is a worsening of RLS symptoms during treatment, leading to an increase in overall symptom severity or earlier time of symptom onset each day compared to before initiation of treatment. Dopaminergic medicinal products, including rotigotine, may result in augmentation.

Rebound, an exacerbation of RLS symptoms, is considered to be an end of dose effect, related to the half-life of the therapeutic agent. Reports in the published literature indicate discontinuation or wearing off of dopaminergic medications can result in rebound.

9. Advisory Committee Meeting

N/A

10. Pediatrics

UCB submitted their initial version of the Pediatric Plan with the resubmitted supplements for advanced PD and RLS. The Sponsor requested a Full Waiver for advanced PD (10/18/2007), a Partial Waiver for RLS in children below the age of 13 (12/2/2011) and deferral for children with RLS ages 13-17 years. The Sponsor revised the Pediatric Plan at the Agency's request on 3/19/2012.

The Division of Neurology Products review team presented the proposed Pediatric Plan to PeRC on March 27, 2012. PeRC recommended granting the pediatric partial waiver for children from 0-12 years 11 months because studies in this pediatric age group were not feasible due to the low prevalence of children 0-12 years requiring treatment for RLS making clinical trials in this age group impractical.

PeRC also recommended deferral for children ages 13-17 years. The Pediatric Plan submitted by the Sponsor that included a Pediatric PK study, a controlled clinical efficacy and safety trial and a long-term safety trial. PeRC recommended deferral of studies in children ages 13-17 years with RLS and agreed with the types of trials requested and the Sponsor's proposed timeline. The relatively (compared to adults with) prevalence of adolescent patients with symptoms of moderate to severe primary RLS that occurs with sufficient frequency to require

treatment is expected to be prolong recruitment resulting in the extended trial completion dates.

Trials Required Under The pediatric Plan to Satisfy PREA Requirements

1. Phase 2 PK study
A multicenter, open-label, 2-group dose-escalation, Phase 2 study with multiple administrations of the rotigotine transdermal. The study will be conducted in adolescent subjects, 13 to 17 years of age, with moderate to severe primary RLS.

2. **Efficacy and Safety study (12-week maintenance period**)
A randomized, multi-center, double-blind, parallel group, placebo-controlled, fixed dose efficacy and safety study of monotherapy administration of rotigotine transdermal patch in adolescent subjects, 13 to 17 years of age, with moderate to severe primary RLS.

3. Long-term (up to 2-years on drug) Safety (including cognitive and behavioral) study
A multicenter, open-label, single-arm, dose-escalation study of monotherapy administration of rotigotine transdermal system. This study will gather data on the long-term tolerability, safety, and efficacy of rotigotine transdermal system in adolescents with idiopathic RLS, allowing subjects from SP1004 and SP1006 to continue to receive rotigotine.

Milestone Dates

Study 1: PK Study
Protocol submission to FDA: June 2012 (Sponsor initiated a trial in October 2011)
First Patient First Visit: December 2011
Last Patient Last Visit: April 2014
Study submission date: November 2014

Study 2: Efficacy and Safety
Protocol submission to FDA: September 2015
First Patient First Visit: March 2016
Last Patient Last Visit: July 2024
Study submission date: February 2025

Study 3: Long-term Safety
Protocol submission to FDA: June 2012 (Sponsor initiated a trial in October 2011)
First Patient First Visit: January 2012
Last Patient Last Visit: September 2026
Study submission date: April 2027

The studies for children ages 13-17 are required under PREA and the Sponsor agreed to conduct the PK study clinical efficacy and safety as postmarketing commitments. The Sponsor agreed to the postmarketing requirement to complete the long-term clinical safety study. The PMR and two PMC were cleared through the acting deputy director for safety in DNP (Dr. Yasuda) and the PMR and PMC templates were entered into DARRTS on 3/26/2012.

11. Other Relevant Regulatory Issues

None

12. Labeling

The Sponsor will use the currently approved carton and container labels without changes. They plan to submit minor changes to the carton and container labels as a CBE-30 following an approval action.

The Revised product label included a PLR conversion because of the two efficacy supplements. Eric Brodsky in SEALD reviewed the revised product label and Sharon Williams, patient labeling reviewer in the Division of Medical Policy reviewed the Patient Labeling and Instructions for Use,

The Division is nearing the close of labeling negotiations with the Sponsor but the label is not final at the time of this review.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval for The CMC supplement (S-004) for the reformulated product and for both efficacy supplement S-001 for the treatment of moderate to severe primary RLS and for S-002 for advanced PD.

Risk Benefit Assessment

The review team members from ONDQA Biopharmaceutics, CMC/Quality, Clinical and Clinical Pharmacology are all in agreement with the approval action. The action did not require alignment of professional opinions prior to the action. Neupro Process 2.2.1 is bioequivalent to the Process 1.0 original product. The Process 2.2.1 Neupro patch performs in an acceptable manor over the proposed shelf-live. The problem of crystal formation in the final drug product has been resolved with the Process 2.2.1 product without requiring special storage conditions. The appearance of (b) (4) do not affect drug delivery however, the requirement for limits and continued monitoring for (b) (4) will continue. The clinical trials development program provided substantial evidence of Neupro's effectiveness for the treatment of patients with advanced PD and moderate to severe primary RLS.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Commitments

Protocol development for the PK, clinical efficacy and safety and the long-term safety studies required under PREA will discussed with the Sponsor after the approval action to meet the PREA milestone dates.

Gerald D. Podskalny, D.O.
CDTL
FDA/CDER/OND-1/DNP

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/s/

GERALD D PODSKALNY
04/02/2012

Cross-Discipline Team Leader Review

Date	4/21/10
From	Gerald D. Podskalny, D.O.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21892 (001, 002 (b) (4)
Applicant	UCB Pharma
Date of Submission	7/22/09 (001, 002), (b) (4)
PDUFA Goal Date	4/21/10
Proprietary Name / Established (USAN) names	Neupro (Rotigotine)
Dosage forms / Strength	Transdermal Patches/1mg, 2mg, 3mg, 4mg, 6mg, 8mg/24 hrs
Proposed Indication(s)	1. Advanced Parkinson's disease (001) 2. Restless legs Syndrome (002) (b) (4)
Recommended:	***Complete Response***

Cross Discipline Team Leader Review Template

1. Introduction

UCB submitted efficacy supplements to the Neupro (Rotigotine) Patch NDA seeking approval for the new indications to treat patients with advanced Parkinson's disease (PD) and for the signs and symptoms of moderate to severe restless legs Syndrome (RLS). After the initial review of both efficacy supplements, the agency concluded that Neupro was effective for the treatment of advance PD and moderate to severe RLS. There were no new safety concerns raised during the review of these two supplements. However, the agency issued a complete response for both efficacy supplements because the product was voluntarily withdrawn from the market due to crystal formation on Neupro patches. At the time of the initial Complete Response action, the agency requested a limited amount of additional information and analyses. The requests for additional information included in the CR letter did not represent issues that would preclude approval of Neupro for advance PD and RLS for clinical reasons.

2. Background

Neupro was approved on May 9, 2007 for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease. On December 6, 2007, Schwarz/UCB reported crystal formation was observed on Neupro patches. Crystal formation was observed as soon as (b) (4) after manufacture using the (b) (4) in process starting with (b) (4) of the drug substance. The sponsor informed the Agency of their intention to withdraw the product from the market effective April 30, 2008. The problem with crystal formation was traced to the

presence of a (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

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(b) (4)

4. Safety

As part of the original complete response of the RLS and Advanced PD efficacy supplements the agency's reviewers asked for additional data and analysis. The additional information was not expected to alter the clinical reviewer's conclusions that Neupro was safe and effective for the treatment of patients with Advanced PD and RLS.

DNP Complete Response Letter Question No. 2:

"Please conduct analyses of female reproductive endocrine testing (e.g., serum/plasma LH, FSH, estradiol, progesterone) of all patients in RS1 pool (i.e., all RLS patients in Double-blind phase of studies SP790 and SP792) according to whether the patients are considered pre-

menopausal or post-menopausal at the time of screening/randomization. It is not clear if you have applied the same reproductive endocrine testing reference range for patients with the same reproductive status (i.e., pre-menopausal or post-menopausal) considering that we believe that you have utilized a central laboratory for all these tests. If a central laboratory was utilized for all RS1 pool patients, the same reference range should be applied to each individual patient based upon their pre-menopausal or post-menopausal status.

Initially, please categorize all patients in the RS1 pool as to whether they are pre-menopausal or post-menopausal. After this categorization, please conduct and present all the various, central tendency and outlier analyses of pool RS1 for the different perspectives (e.g., mean absolute values over time, mean change from baseline over time, shift analysis over time, incidence of "low" or "increased" value at any time during the study, and similar respective analyses for "markedly abnormal" values). Please show results for these analyses for placebo, each specific rotigotine dose, and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted.

If we do not have a correct understanding about the apparent deficiencies in these analyses, it may be helpful to contact us for clarification about what is needed and what should be done in your resubmission of your Complete Response."

UCB Response

UCB provided information that described the method used to categorize female patients enrolled in the pivotal RLS efficacy trials as pre- or post-menopausal. A different set of lab values were used to establish a normal range for reproductive hormones in both pre and post-menopausal female participants. A central lab analyzed all trial related serum reproductive hormone levels.

CDTL Conclusion

In his primary review, Dr. Kapcala, found the sponsor's criteria for classifying women as pre- or post-menopausal acceptable. I agree Dr. Kapcala, key points from his review are summarized below.

- There did not appear to be any clear dose-related shifts produced by rotigotine in either population of women with one exception. The sole exception appeared to be a possible-dose-related shift in serum prolactin from normal at baseline to subnormal at the end of the 6 month MP and at the final visit in post-menopausal females.

- The magnitude of the shift in women completing the trials was small.

- The data was limited by the clinical history that did not report menstrual cycle phase in women who were premenopausal.

- There was no TEAE related to changes in fertility despite the suppression of Prolactin levels associated with dopamine agonists.

DNP Complete Response Letter Question No. 3:
"Please review all Case Report Forms (CRFs) for TEAEs (in RS1 pool for RLS) that suggest any change in libido and have not been characterized as either essentially increased or decreased. Most likely, a change in libido would either reflect a change such as increased or decreased libido. Please consider recharacterizing any TEAE suggesting a change/alteration in libido that is not specific (e.g., libido abnormal or libido altered) to a more specific characterization such as libido increased or decreased.

Once all libido-related TEAEs have been reviewed and possibly recharacterized, present the incidence of all similar AE terms suggesting either increased or decreased libido for the RS1 pool according to randomized treatment (i.e., for placebo and each specific rotigotine dose and also for "any" dose) for these TEAEs occurring at any time during the double-blind phase. If these various AE terms can be considered as reflecting either increased or decreased libido, please present the incidence of all these similarly related AE terms suggesting the possibility of increased or decreased libido.

Please show results for these analyses for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted."

TEAEs suggestive of a change in libido by randomized dose (Pool RS1)

TEAEs based on re-characterized events	Placebo N=217 n (%)	Rotigotine dose (mg/24h) 0.5 N=99 n (%)	1 N=215 n (%)	2 N=211 n (%)	3 N=220 n (%)	Any Rotigotine N=745 n (%)
Any decreased libido TEAE	4 (1.8)	3 (3.0)	8 (3.7)	3 (1.4)	4 (1.8)	18 (2.4)
Any increased libido TEAE	2 (0.9)	4 (4.0)	2 (0.9)	5 (2.4)	6 (2.7)	17 (2.3)

TEAE=treatment-emergent adverse event
Data source: Table 3.2

Dr. Kapcala's Comments

- Following the sponsor's recharacterization when possible of adverse events as reflecting decreased libido, there was no clear dose-related effect of rotigotine nor a clear effect of "any" dose of rotigotine compared to that of placebo. The incidence of decreased libido was 1.8 % for placebo and the highest dose of rotigotine (6.75 mg). The incidence of decreased libido for "any" rotigotine treatment was 2.4 % (~ 2 %), similar to that for placebo (~ 2 %).

- This increased risk for increased libido should be described in the label.

CDTL Comment

There are several published reports of ICDs that occurred in RLS patients treated with other approved dopamine agonists (DAs) in addition to patients treated for PD. The sponsor conducted a study looking for ICDs reported as TEAEs in their clinical trials development program. A total of 21 RLS patients reported ICD related TEAEs 19 occurred in patients receiving rotigotine and 2 were reported in RLS patients taking placebo. The product label will be revised to reflect the recent revision to class label language regarding the potential for impulse control disorders (ICD) associated with dopamine agonist use. The Division recently decided to revise and elevate class language regarding the potential for ICDs to the Warnings and Precautions section of the label for all drugs that increase dopaminergic tone. The current Neupro label contains the old class label language in the information for patients section of the label.

DNP Complete Response Letter Question No. 4:
"Please have your clinicians review all Case Report Forms (CRFs) for TEAEs (in RS1 pool for RLS) that suggest any change in menses (e.g., non-specific characterizations such as menstrual disorder, menses abnormal, menstruation irregular or other such non-specific characterizations) that have not been characterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea, menstruation delayed). Once these CRF reviews have been completed, have your clinicians determine whether these various menstrual TEAEs can be recharacterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea). Typically, a significant change in menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea) suggests that there is anovluation. After all menstrual TEAEs have been reviewed and possibly recharacterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea), present the incidence of all similar AE terms suggesting that menses are anovulatory according to randomized treatment (i.e. for placebo and each specific rotigotine dose and also for "any" dose) for these TEAEs occurring at any time during the double-blind phase.

Please show results for these analyses for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted."

Dr. Kapcala's Review
The sponsor was asked to recharacterize adverse event terms to examine the potential association of rotigotine with anovulatory menses. After review of the sponsors data, Dr. Kapcala concluded "there was no suggestion of an increased risk for anovulatory menses for either the highest dose of rotigotine (6.75 mg) or "any" rotigotine dose compared to that for

placebo. The incidence of a TEAE suggestive of anovulatory menses as related to "menstruation delayed" was 3.6 %, 4.3 %, and 3.2 % for placebo, 6.75 mg rotigotine, and "any" rotigotine dose, respectively".

CDTL Comment
I concur with Dr. Kapcala's opinion that there was no suggestion of an increased risk for anovulatory menses associated with rotigotine.

DNP Complete Response Letter Question No. 5:
"Please conduct and submit analyses of TEAEs that might possibly reflect events (regardless of level of severity) suggestive of the occurrence of hypotension/orthostatic hypotension/postural dizziness for Pool AS1 (double-blind phase of studies SP511 and SP650) for advanced Parkinson's disease and for Pool RS1 (double-blind phase of studies SP790 and SP792). Search for a variety of AE terms that might be suggestive of orthostatic hypotension/postural dizziness despite the fact that the AE may not have been coded as such. You have used the following AE search terms for searching for possible "severe" hypotension or orthostatic hypotension (i.e., blood pressure orthostatic, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, dizziness postural, and orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension). Please add the following AE search terms including: dizziness, vertigo, light-headedness, postural light-headedness, impaired balance, and feeling drunk

Analyses should be conducted according to randomized treatment (i.e., for placebo and each specific rotigotine dose and also for "any" dose) for TEAEs occurring at any time during the double-blind phase, for SAEs occurring at any time during the double-blind phase, and for TEAEs causing study discontinuation at any time during the double-blind phase."

Primary Clinical Reviewer

- This approach of evaluating the risk of several TEAEs that might suggest orthostatic hypotension is a common one for drugs that increase dopaminergic tone and particularly for patients with Parkinson's disease and RLS who are treated with drugs that increase dopaminergic tone.

- There was a mildly increased risk for TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness in patients with advanced Parkinson's disease treated with rotigotine. Whereas the incidence of this adverse reaction was 14.2 % for placebo, there was a mildly increased dose-related risk for the highest doses of rotigotine (18.3 % and 16.8 % for 8 and 12 mg/delivered, respectively). The incidence of this TEAE for "any" rotigotine dose (16.3 %) was also increased compared to placebo (16.3 %).

- This increased risk should be described in the label.

- There was a borderline increased incidence of TEAEs possibly suggesting orthostatic hypotension as a cause of study discontinuation in Parkinson's disease patients treated with rotigotine. Although there was no dose-related increased risk for rotigotine, the incidence for TEAEs possibly suggesting orthostatic hypotension as a cause of study discontinuation was 1.7 % (~ 2 %) for "any" rotigotine dose compared to 1 % for placebo.

- There was a mildly increased risk for TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness in patients with RLS treated with rotigotine. Whereas the incidence of this adverse reaction was 6.9 % for placebo, the incidence of this TEAE for "any" rotigotine dose (9.3 %). There was no clear dose-relationship for rotigotine for this risk.

- This risk should be described in the label.

CDTL Comment

Section 5.4 of the proposed product label incorporating the advanced PD and RLS indications describes a slight increase in reporting of AE terms related to orthostatic hypotension (OH) in patients (both PD and RLS) treated with Neupro compared to placebo. The actual numbers differ from the frequency of OH reported in Dr. Kapcala's review. The representation of this issue in labeling will be resolved in discussions with UCB when a final label for an approved product take place.

DNP Complete Response Letter Question No. 6:
"Please conduct and submit subgroup analyses of treatment-emergent adverse vents (TEAEs) occurring in certain subgroups (i.e., age, gender, concomitant medication such as vasodilator/hypotensive agents) for Pool AS1 (double-blind phase of studies SP511 and SP650) or advanced Parkinson's disease and for Pool RS1 (double-blind phase of studies SP790 and P792). Your subgroup analyses of TEAEs only considered the frequency of TEAEs for rotigotine treatment relative to each subgroup comparison and did not consider the frequency for placebo treatment in each subgroup analysis.

To conduct these analyses, please present a summary analysis of the incidence of the treatment effect (e.g., % for specific rotigotine dose - % for placebo) for each TEAE according to various level terms (e.g., system organ class [SOC], high level and high level group terms, and preferred term as presented previously) in each requested subgroup. Please show results for each subgroup immediately below the other subgroup for each AE term for each specific rotigotine dose and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted."

CDTL Review

The primary reviewer did not find a new safety signal in the subgroup analysis of the safety data by age, gender or concomitant medication use. The were disproportionate reporting of dizziness in patients with advanced PD taking a beta-blocker and rotigotine but dizziness was not broken down further to distinguish between feeling of being off balance, faint or vertiginous. Although, patients taking several dose strengths of rotigotine reported dizziness more frequently than patients treated with placebo there was no relationship to increasing doses of rotigotine.

Safety Update

Primary Review of Deaths Reported in the Safety Update

Deaths

Advanced Parkinson's Disease

As of the clinical cutoff (31 Oct 2008) for this final safety update, 50 deaths have been reported in the advanced-stage Parkinson's disease program among the 1407 subjects treated with rotigotine. Of these 50 deaths, 20 occurred since filing the sNDA.

In the cumulative analysis, the most common events that led to death were cerebrovascular accident (5 subjects), myocardial infarction (4 subjects), Parkinson's disease (6 subjects), death/cardiac death (3 subjects), pneumonia aspiration (3 subjects), and sepsis/septic shock (3 subjects). Of the 50 deaths that occurred in Pool AS3, 19 deaths occurred 2 to 75 days after last dose of trial medication (FSU APD Table 81.1). The mortality rate per 100 patient exposure years was 2.08 (FSU APD Table 81.2). In the sNDA, the mortality rate was 1.67 (ISS APD Table 81.2).

RLS

As of the clinical cutoff (31 Oct 2008) for this final safety update, 3 deaths have been reported in the RLS program among the 1309 subjects treated with rotigotine. Of these deaths, 2 occurred since filing the sNDA. Subject 516/108008 died of myocardial infarction on (b) (6) The investigator assessed both of these deaths as possibly related to trial medication. The remaining death was assessed by the investigator as unlikely or not related to trial medication.

Primary Reviewers Conclusion

- My review of the sponsor's Safety Update does not suggest any substantial or notable change in the safety profile for the label for rotigotine treatment of early Parkinson's Disease nor for the safety profile characterized for advanced Parkinson's Disease and RLS based upon our safety review of the sponsor's original NDA submission for these indications.

CDTL Conclusion

The frequency and best determined cause of death for clinical trial participants reported in the safety update are consistent with the published literature reports of mortality in patients with PD and RLS. The primary review also covered non-fatal SAEs, non-serious AEs and postmarketing events reported in the safety update. I agree with Dr. Kapcala's conclusion that there are no new safety concerns raised by the contents of the sponsor's safety update.

5. Pediatrics

The sponsor must update their pediatric plan at the time they resubmit the application for approval for the RLS indication.

6. Labeling

Carton and container labeling for the New Strengths of Neupro must be submitted and reviewed by agency prior to approval.

7. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Complete Response

Risk Benefit Assessment

The sponsor should reformulated product to be: crystal free throughout shelf-life, well controlled with validated analytical methods, bioequivalent to the approved formulation, and adequately adherent.

Recommended Comments to Applicant

Please update the pediatric submitted to the RLS supplement (002) with you resubmission.

Update carton and container labeling for the 1mg/24 hours, 3mg/24 hours and 8mg/24 hours strengths.

Gerald D. Podskalny, DO
CDTL Medical Reviewer
Division Of Neurology Products
ODE I/CDER/FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS
NDA-21829	SUPPL-2	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS

(b) (4)

[redacted]

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

/s/

GERALD D PODSKALNY
04/21/2010

Cross-Discipline Team Leader Review

Date	12/16/08
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21829 (1 and 2)
Applicant	UCB Pharma/Schwarz Pharma
Date of Submission	10/11/07
PDUFA Goal Date	11/11/08
Proprietary Name / Established (USAN) names	Neupro/ Rotigotine
Dosage forms / Strength	Transdermal Patches
Proposed Indication(s)	1. Advanced Parkinson's Disease 2. Restless Leg Syndrome
Recommended:	Complete Response

Introduction

Rotigotine is a dopaminergic agonist, available as a patch, which was approved for the treatment of early Parkinson's disease in 2/06. It was available until 2008 when it was removed from the US market because of the demonstration of the formation crystals (b) (4) (b) (4). In vitro evidence indicted that significant crystallization may impede this drugs bioequivalence. The drug is still marketed in the countries of the European Union and Hong Kong (b) (4). The Sponsor is presently reformulating the product to prevent crystal formulation.

The present application is submitted to expand the indication to two groups: 1) advanced Parkinson's disease, 2) of moderate-to-severe primary Restless Legs Syndrome (RLS).

Rotigotine dosage can be noted as either complete contents of each patch or total dose delivered over a 24 hour period. For this review the reference will be made to the 24 hour dose when described as mg/day units or total patch content when described as mg/5cm^2 units.

CMC

Two new dosages (2.25mg/5cm^2 and 6.75mg/15cm^2 patches) are proposed by the Sponsor, which are to be used in the treatment of RLS. The CMC reviwer notes that the data is supported by the informtion provided. As noted in the introduction the patches have been

removed form the market [redacted] (b) (4)] of rotigotine that results in crystallization and probable altered systemic absorption. This is the predominant reason for issuing a "CR" response. The Sponsor will be requested to provide a new formulation, where crystallization is not problematic. The CMC reviewer requests the following be provided with the new formulation:

Drug Substance
1) Physical and chemical characterization of the [redacted] (b) (4) used,
2) Data to support any revisions to the manufacturing process and in process controls,
3) Specifications with justification for any new specifications proposed,
4) Batch release data, and
5) Stability data from three production scale batches, stored under long term (marketed) conditions through retest period and six months under accelerated conditions.

Drug Product
1) Components and composition,
2) Unit and batch formula,
3) Batch release data,
4) Data to support any revisions to the manufacturing process, in process controls,
5) Specifications with justification for any new specifications proposed, and
6) Stability data from three production scale batches, stored under long term (marketed) conditions through the shelf life and six months under accelerated conditions.

Once the new formulation is established the Sponsor will have to produce a pharmacokinetic bridge between new and old formulations. If such a bridge is not possible some form of efficacy study will be required.

Pharmacology/Toxicology

New additional maternal toxicity studies were submitted. Fetal effects were determined, but these were attributed to secondarily to dam toxicity and no action is recommended.

Clinical Pharmacology

The submission contained a single bioavailability study to support the RLS indication. The Clinical Pharmacology reviewer found this study to be adequate. However, becasue of the CMC issue noted above such a study may be considered mote. The drug product will require e reformulation with PK bridging studies for approval as noted above.

A formal double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400mg IV, single dose) parallel group trial with an overall treatment period of 52 days in male and

female patients with advanced-stage Parkinson's disease QT study was submitted. According to the Clinical Pharmacology reviewer there was no indication of a QT/QTc prolonging effect of Neupro in doses up to 24 mg/24 hours. This study had not been sent to the TQT team fro review, but will be.

Clinical Review

Efficacy

Advanced Parkinson's disease

Dr. Kapcala reviewed this indication and considered 3 submitted studies as "pivotal" trials. Two of these were phase 3 studies (SP650 and SP515) and one phase 2 (SP511) . All three trials were randomized, placebo-controlled, multi-center parallel group studies with rotigotine dose ranging from 9 mg to 36 mg per day in subjects with advanced PD who were not well controlled on L-dopa. All studies included a titration period of up to 7 weeks and varying maintenance of 7 to 24 weeks. Study SP515 used a flexible dosing design, comparing placebo with rotigotine (9 to 36 mg/day) and pramipexole (n was 100, 201 and 200 respectively). Study SP650 compared placebo to two dosage arms of 18 and 27 mg/day (with an n of 100, 201 and 200, respectively) and SP511 compared placebo to 9, 18 and 27 mg/day (with an n of 81, 77, 75 and 77, respectively). Upon entry into the study, patients in SP650 and SP515 were not to be taking dopaminergic agonists, but were to be only on L-dopa. Upon entry into the study patients in SP511 could be on other dopaminergic agonists, but if so the patient required a pretreatment period during which the agonist would be withdrawn and compensated with an increase in L-dopa dosage. L-dopa dosage could only be reduced, not increased, and this could generally occur during defined periods.

The primary efficacy endpoint was change from baseline in total "off" time (e.g., hours) in all pivotal studies. This endpoint is a commonly used primary endpoint in studies in advanced Parkinson's disease. Statistical analysis generally used a $p \leq 0.05$ with a hierarchical analysis of dosage arms (High to low) to correct for multiple comparisons.

Both phase 3 studies (i.e. SP 650 and SP 515) demonstrated a statistically significant increase in off time in drug when compared to placebo. The treatment effect[1] observed in SP650 was 1.8 and 1.1 hours in the 18 and 27 mg/day dose groups, respectively. The treatment effect observed in SP515 was 1.6 and 1.9 hours for the rotigotine and pramipexole group, respectively (both statistically significant). While a large range of rotigotine dosages were

1 Treatment effect = (mean decrease in drug off time from baseline) – (mean decrease in placebo off time from baseline).

examined in study SP515, Dr Kapcala notes that little can be said regarding efficacy lower dosages as a majority of patients were receiving 18 mg/day. None of the dosage groups in study SP511 exhibited a statistically significant reduction over placebo, although there was a slight trending toward a decreased off period in the highest dose group, of 27 mg/day with a treatment effect of 0.52 hours. Other doses where essentially unchanged from baseline when compared to placebo. While the sponsor did not provide nominal p-values for the secondary efficacy endpoint, numerical changes were consistent with potential clinical benefit. Dr Kapcala believes that a potential reason for the failure of SP511 in demonstrating a benefit may be its unusually large placebo effect. Dr Kapcala conclude that a therapeutic benefit is observed, but the additional dose response data is needed, as the 27 mg/day dose shows no additional benefit over 27 mg/day in study SP650, but shows additional toxicity. Moreover, lower dosages have not been carefully examined. Dr Kapcala recommends this as a phase 4 commitment to examine dose dependency of the therapeutic effect. At the present the recommended dose should be to start patients on a dose of 2 mg/day and to increase, if tolerated, to an efficacious dose. This reviwer agrees with all of Dr. Kapcala's recommendations.

The statistical reviewer, Dr Yan, confirmed all of the Sponsor's primary endpoint analyses.

Moderate-to-Severe Primary Restless Legs Syndrome

Dr Podskalny reviewed two six months, multi-centered, double blind placebo controlled clinical trials which he considered as pivotal trials. They were both of similar design. Studies consisted of a 3 to 4 week titration period followed by a 6 month maintenance period. Study SP790 compared Placebo to 1, 2 and 3 mg/day in separate arms (with an n of 114, 112, 109 and 112, respectively) and SP792 compared placebo to 0.5, 1, 2 and 3 mg/day in separate arms (with an n of 99, 98, 99, 95 and 103, respectively).

Two co-primary endpoints were used, the International Restless Leg Scale (IRLS) and the CGI item 1 (severity of illness). These have been typically used for evaluation of therapeutic actions in other RLS applications. Dr Podskalny's notes in his review initial that a $p \leq 0.05$ is used to correct for multiple comparison. This is not correct, a two sided $p<0.05$ (or one sided < 0.025) is used with hierarchal (high to low dosage) analysis is performed to correct for multiple dosing. He has placed an addendum into the record.

Primary analysis of study SP-790 revealed significant differnce with the placebo for all dosages (1, 2 and 3 mg/day) for both co-primary endpoint. Study SP792 won on co-primary endpoints at the 2 and 3 mg/day dosages but lost on the o.5 and 1 mg dosage. The 1 mg/day dosage p value was borderline for the IRLS ($p=0.54$) but 0.086 for the CGI.

The statistical reviwer, Dr Yan, confirmed the Sponsor's statistical analysis.

A number of secondary endpoints were examined. In general these endpoints trended in the direction of a therapeutic effect with a number showing statistical significance. Dr Podskalny, in his review, notes that two secondary endpoints were not examined through inferential statistical analysis. This included the CGI-3 and the RLS-6. The use of only central analysis of these endpoints was protocol driven. My examination suggested a trend for the RLS-6 and mixed results for the CGI-3. These endpoints have not been typically used as primary endpoints in FDA studies. This reviwer feels that the results observed here are consistent with a therapeutic effect. There is no need to obtain additional informtion on inferential analysis of these endpoints, as requested by Dr. Podskalny, short of providing correlative informtion on these with more validated endpoints.

This reviwer concludes efficacy for dosages of 1, 2 and 3 mg/day, (b) (4). While the dose of 2 and 3 demonstrated efficacy in both pivotal trials, 1 mg/day only exhibited a statically significant therapeutic effect in one study. In the study where statistical significance was not observed the effect trended in a therapeutic direction with one of the coprimary endpoints near statistical significance. Becasue of the potential dose depnedent adverse events exhibited by this class of agents, this reviwer feels it is best to initiate treatment at low and potentially effective dosage and titrate up to a therapeutic effect Therefore 1 mg/day should be labeled. Response was generally observed to be dose dependent for the full range of these 3 dosages and should be libeled. Dr Podskalny has posited the same dosage recommendation.

Safety

Both Drs. Podskalny and Kapcala conclude that there were adequate exposures in the present new populations. They also conclude that no new safety issues were identified other then that already described for this drugs use in the treatment of early-stage Parkinson's disease.

Dr Kapcala, however, notes that reproductive endocrine testing was not provided with pre- and post-menopausal patients segregated and separately examined. Such an analysis is important because of the well described influence of dopamine on the hypothalamic pituitary axis. This will be requested. This reviewer agrees. To compliment this, Dr Kapcala also requests that an analysis be carried out on endocrine adverse events related to abnormal menses. This reviwer concurs. Also requested by the medical reviewers is a more in depth analysis of adverse events associated with hypotension in the new populations. While some informtion is provided in the present labeling for early onset Parkinson's disease, this new informtion will be useful, particularly the informtion in the RLS population, who consist of an otherwise healthy group. Lastly the medical reviewers ask for a more in depth examination of alterations in libido, based upon a CRF reviews. This relates to the present class labeling for drugs that increase dopaminergic tone that notes such drugs will result in reduced impulse control with hyper-sexuality and gabling. . The label presently provides this informtion in the "Precautions" and "Informtion for Patients," but becasue this informtion is predominately gleaned from reports of post marketing data the labeling notes it is "not proven that the medication caused these events." This additional information should help to increase data quality and contribute to the attribution of causality.

Action

A Complete Response letter will be sent. The deficiency principally surrounds the issue of crystallization of the present formulation. The Sponsor will also be requested to provide additional safety informtion, as described above.

Labeling

Labeling has been deferred as the requested informtion may require a major modification of the present label (e.g. Additonal PK and efficacy studies may be required).

Comments to Sponsor

Please see letter.

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/s/

Norman Hershkowitz
12/16/2008 01:29:57 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21829
Submission Code	Supplements S1 and S2
Letter Date	12/2/11
Stamp Date	12/2/11
PDUFA Goal Date	6/2/12
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	3/30/12
Established Name	rotigotine
(Proposed) Trade Name	Neupro
Therapeutic Class	Dopaminergic agonist
Applicant	UCB Pharma/Schwarz Pharma
Priority Designation	S
Formulation	Patch
Dosing Regimen	Once daily
Indication	Adjunctive Treatment of Advanced Parkinson's Disease Treatment of Restless Leg Syndrome
Intended Population	Advanced Parkinson's Disease Restless Leg Syndrome

TABLE OF CONTENTS

1. 1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approving this most recent supplement for rotigotine/Neupro for treatment of advanced Parkinson's Disease and Restless Legs Syndrome (RLS) in adults.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

Under PREA, the sponsor needs to conduct three separate studies in adolescent (13-17 years) patients with Restless Legs Syndrome (RLS) to determine : 1) the pharmacokinetic parameters of rotigotine/Neupro; 2) clinical efficacy and safety of rotigotine/Neupro, presumably in a randomized, double-blinded, placebo-controlled trial investigating several fixed doses of rotigotine/Neupro; and 3) a long-term safety. The sponsor has committed to milestone dates for submission of a final study report for each study.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

Neupro (rotigotine) treatment was judged to be effective and safe for the treatment of advanced Parkinson's Disease and Restless Legs Syndrome. Details about efficacy and safety findings are included in previous clinical reviews (Efficacy for advanced Parkinson's Disease – Dr. Leonard P. Kapcala, 11/26/08; Efficacy for RLS – Dr. Gerald D. Podskalny – 1/16/09; Joint Safety Review for advanced Parkinson's Disease and RLS – Dr. Leonard P. Kapcala and Dr. Gerald D. Podskalny; Complete Response - Dr. Leonard P. Kapcala – 4/21/10).

2. INTRODUCTION AND BACKGROUND

This NDA 21829 supplement for advanced Parkinson's Disease and RLS was submitted. previously and Complete Response letters were issued on 12/15/08 and 4/21/10. The last Complete Response letter was issued on 4/21/10 because the sponsor did not have an approved product available for marketing. The sponsor had withdrawn Neupro from the market because of problems with crystal formation on the Neupro patch. Thus, the DNP did not approve Neupro for new indications of treating advanced Parkinson's Disease and RLS because a suitable product was not available at the time and the sponsor was working on developing a new formulation that did not have problems with crystal formation. The sponsor has developed a new formulation that does not have crystal formation and submitted a separate chemistry (CMC) supplement for approval of this new formulation. This new formulation has been reviewed by the Agency in a separate CMC supplement and has been judged to be adequate for approval and marketing. .

In the last Complete Response letter, the sponsor was asked to focus on presenting new safety data about deaths in the Safety Update. The sponsor was also asked to submit a pediatric clinical development plan to study rotigotine/Neupro for adolescent patients (13-17 years).

3. SAFETY UPDATE : FINAL SAFETY UPDATE 2 (FSU2)

This FSU2 includes safety data from 10/31/08 (FSU1) until the cut-off (5/3111. The sponsor’s Safety Update focused on presenting mortality data.

The following tables present information (exposure and mortality) on patients treated with Parkinson's Disease

Summary of duration of exposure and subject-years of exposure (Pool AS3)

Duration of exposure	Statistic	All rotigotine-treated subjects		
		FSU1 cumulative N=1401	FSU2 new N=217	FSU2 cumulative N=1507
>0 months	n (%)	1401 (100)	217 (100)	1507 (100)
	Subject-years of exposure	2404.0	93.6	2449.7
>6 months	n (%)	778 (55.5)	64 (29.5)	781 (51.8)
	Subject-years of exposure	2291.5	68.1	2314.7
>12 months	n (%)	647 (46.2)	40 (18.4)	686 (45.5)
	Subject-years of exposure	2194.4	46.6	2241.5
>24 months	n (%)	540 (38.5)	0	540 (35.8)
	Subject-years of exposure	2037.0	0	2038.5

Data source: FSU2 APD Table 2

Summary of duration of exposure and subject-years of exposure (Pool RS3)

Duration of exposure	Statistic	All rotigotine-treated subjects		
		FSU1 cumulative N=1309	FSU2 new N=85	FSU2 cumulative N=1309
>0 months	n (%)	1309 (100)	85 (100)	1309 (100)
	Subject-years of exposure	1812.1	12.7	1824.9
>6 months	n (%)	908 (69.4)	0	908 (69.4)
	Subject-years of exposure	1739.1	0	1751.9
>12 months	n (%)	710 (54.2)	0	710 (54.2)
	Subject-years of exposure	1600.2	0	1613.0
>24 months	n (%)	192 (14.7)	0	192 (14.7)
	Subject-years of exposure	846.6	0	859.4

Data source: FSU2 RLS Table 1

Mortality rate for all-cause mortality (Pool AS3)

	FSU1 cumulative	FSU2 new	FSU2 cumulative
Number of subjects	1401	217	1507
Number of deaths	50	0	50
Crude mortality[a]	0.036	0	0.033
Subject exposure (years)	2404.03	93.61	2449.75
Mortality per 100 PEY	2.08	0	2.04

PEY=patient exposure years

Note: FSU1 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 Oct 2008. FSU2 new includes all advanced Parkinson's disease subjects who received rotigotine at least once since 31 Oct 2008 and before 31 May 2011. FSU2 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 May 2011.

[a] Crude mortality is the number of deaths divided by the number of subjects exposed.

.Data source: FSU2 APD Table 10

Mortality rate for cardiac-related deaths (Pool AS3)

	FSU1 cumulative	FSU2 new	FSU2 cumulative
Number of subjects	1401	217	1507
Number of deaths	9	0	8[b]
Crude mortality[a]	0.006	0	0.005
Subject exposure (years)	2404.03	93.61	2449.75
Mortality per 100 PEY	0.37	0	0.33

PEY=patient exposure years

Note: FSU1 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 Oct 2008. FSU2 new includes all advanced Parkinson's disease subjects who received rotigotine at least once since 31 Oct 2008 and before 31 May 2011. FSU2 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 May 2011.

[a] Crude mortality is the number of deaths divided by the number of subjects exposed.

[b] Because of an adverse event recoding, Subject 515107601 was no longer considered to have experienced a cardiac death.

Data source: FSU2 APD Table 10

Mortality rate for death due to MI (Pool AS3)

	FSU1 cumulative	FSU2 new	FSU2 cumulative
Number of subjects	1401	217	1507
Number of deaths	2	0	2
Crude mortality[a]	0.001	0	0.001
Subject exposure (years)	2404.03	93.61	2449.75
Mortality per 100 PEY	0.08	0	0.08

MI=myocardial infarction; PEY=patient exposure years

Note: FSU1 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 Oct 2008. FSU2 new includes all advanced Parkinson's disease subjects who received rotigotine at least once since 31 Oct 2008 and before 31 May 2011. FSU2 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 May 2011.

[a] Crude mortality is the number of deaths divided by the number of subjects exposed.

Data source: FSU2 APD Table 10

Mortality rate for non–cardiac-related death (Pool AS3)

	FSU1 cumulative	FSU2 new	FSU2 cumulative
Number of subjects	1401	217	1507
Number of deaths	41	0	42[b]
Crude mortality[a]	0.029	0	0.028
Subject exposure (years)	2404.03	93.61	2449.75
Mortality per 100 PEY	1.71	0	1.71

PEY=patient exposure years

Note: FSU1 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 Oct 2008. FSU2 new includes all advanced Parkinson's disease subjects who received rotigotine at least once since 31 Oct 2008 and before 31 May 2011. FSU2 cumulative includes all advanced Parkinson's disease subjects who received rotigotine at least once before 31 May 2011.

[a] Crude mortality is the number of deaths divided by the number of subjects exposed.

[b] Because of an adverse event recoding, Subject 515107601 was no longer considered to have experienced a cardiac death.

Data source: FSU2 APD Table 10

A total of 3 deaths occurred in the whole RLS clinical development program. However, there were no deaths that occurred during the period for this final safety update (FSU2).

Reviewer Comment

- The exposure/treatment of patients (advanced Parkinson's Disease and RLS) comprised a relatively small percentage of the total number of patients treated and total number of patient-years of treatment in the total clinical development programs for both indications.

- There were no new deaths during the period of this FSU2 for advanced Parkinson's Disease or RLS. Thus, mortality rates only decreased.

- There was no new, significant, safety information presented from the postmarketing experience nor from publications that impact on the safety profile of rotigotine/Neupro.

- My perspective on the safety profile for rotigotine remains unchanged since the time of my last clinical review

4. PEDIATRIC CLINICAL DEVELOPMENT PLAN (ATTACHED IN APPENDIX)

The sponsor submitted a pediatric clinical development plan to conduct 3 trials including a pharmacokinetic (PK) trial, an efficacy and safety trial, and a long-term, open-label extension safety trial. The last Complete Response letter had requested the sponsor to submit a plan to study adolescents 13-17 years old for RLS under PREA. The DNP was planning to give a full waiver to the sponsor for pediatric studies for Parkinson's Disease, a deferral for requiring studies from 13-17 years for RLS, and a full waiver for pediatric studies below the age of 13 years for RLS because such studies are considered not practical/feasible.

Initially, the sponsor submitted a plan to conduct an efficacy and safety study using a flexible dose titration design. Because such a trial would not provide useful information on critically desired dose-response for the efficacy and safety curves, the DNP asked the sponsor to revised the plan to conduct a trial in which adolescents are randomized to placebo or one of several fixed doses of rotigotine so that useful efficacy and safety information on dose-response could be collected.

Reviewer Comments

- Although the sponsor's most recent pediatric clinical development plan notes that it plans to conduct a fixed dose trial, it does not note that multiple fixed rotigotine doses will be investigated nor does it specify any rotigotine/Neupro doses. The sponsor wants to wait until it completes and analyzes results of its pharmacokinetic (PK) trial before it plans specific dosing to be investigated in the efficacy and safety trial.

  Whereas it is reasonable to wait until adolescent PK data have been collected and analyzed before proposing specific doses for investigation the efficacy and safety trial, I believe it is possible now to consider that at least 3 fixed doses, and ideally, 4 fixed doses should be

investigated in the adolescent trial (SP1006). The sponsor had previously investigated four fixed doses of rotigotine (0.5, 1, 2, 3 mg) vs placebo in Study 792, that provided efficacy and safety information in adults and which supports the approval of rotigotine for this indication in adults. Investigating 4 fixed doses vs placebo is likely to provide excellent dose-response information for characterizing the efficacy and safety curves of rotigotine for treating RLS in adolescents.

- Determining precise dosing information such as the lowest effective dose and the lowest maximally effective dose of rotigotine is of the utmost importance in this pediatric population (i.e., adolescents).

  It is critically important that precise/optimal dosing be characterized for treating adolescent (pediatric) patients with RLS with Neupro because : 1) Neupro would provide relatively constant dopaminergic stimulation; 2) there is no information available about the effects of any chronic dopaminergic stimulation in pediatric subjects (let alone relatively constant, sustained dopaminergic stimulation); and 3) central dopaminergic systems play a role in the onset and maturation of pubertal changes (e.g., especially those for reproductive endocrine function and growth) that occur during adolescence. If Neupro was approved for treating adolescent patients, one would want to know the lowest effective dose to minimize not only the many, recognized adverse effects of Neupro (observed in adults) but also Neupro's unknown effects on puberty. Knowing the lowest, maximally effective dose helps prevent and avoid excessive dosing. Dosing at a level above the lowest, maximally effective dose does not allow the patient to experience any additional therapeutic benefit but increases the likelihood for increased, unnecessary toxicity.

- When we negotiate the final protocol (SP1006) for the efficacy and safety trial in adolescents, my desire will be that the protocol plans to randomize patients to 4 fixed dose of rotigotine vs placebo (as was done by the sponsor in Study 792 for adults). Overall, following the study design of Study 792 (the trial in adults in which patients were randomized to placebo or one of 4 fixed doses of rotigotine – 0.5, 1, 2, 3 mg) for the adolescent trial might be an optimal study design. Thus, the sponsor has a protocol (Study 792) which could be used as a template for the adolescent efficacy and safety trial. Furthermore, a significant addition to the adolescent protocol would be to propose collecting information on the timing of the menstrual cycle in each individual at the time of reproductive hormone collection. Such information was not collected in the adult trial (792).

- My only other comment pertains to the dates for the planned protocol submission to FDA, for first and last patient enrollment date in each study, and for final study report. The sponsor's proposed dates are show below here.

  All the dates include a very, long time, much longer than I would personally expect to be required.

2.4 Timetable for Studies

UCB plans to follow the timelines outlined below.

2.4.1 SP1004

Protocol submission to FDA: June 2012*

First Patient First Visit: December 2011

Last Patient Last Visit: April 2014

Study submission date: November 2014

*Protocol originally submitted in October 2011 will be amended and resubmitted

2.4.2 SP1005

Protocol submission to FDA: June 2012*

First Patient First Visit: January 2012

Last Patient Last Visit: September 2026

Study submission date: April 2027

*Protocol originally submitted in October 2011 will be amended and resubmitted

2.4.3 SP1006

Protocol submission to FDA: September 2015

First Patient First Visit: March 2016

Last Patient Last Visit: July 2024

Study submission date: February 2025

The sponsor has proposed taking about 2 years to conduct the PK study, 11 years for the efficacy and safety study, and 14 years for the long-term, open-label safety study. Final study reports are not planned until 2014 for the PK study, 2025 for the efficacy and safety study, and 2027 for the long-term, open-label safety study. I believe that these dates are so long because similar long periods were given to another sponsor to conduct similar trials for another drug, gabapentin enacarbil (Horizant; NDA 22399). Such long dates were considered required because of difficulty in patients recruitment. However, I think that patient recruitment might be able to occur much faster than currently planned and that all three studies could be completed in a much shorted period. In particular, if the sponsor expanded enrollment to a global scale, many additional patients could be recruited to speed up the rate of study enrollment and study completion.

I believe that approximately 250,000 adolescents in the U.S. could potentially be candidates for these trial. If enrollment was expanded to a global scale, many more patients, perhaps as much as a million adolescents could potentially be enrolled.

APPENDIX : Sponsor's Pediatric Clinical Development Plan

1 INTRODUCTION

NDA 021829 Supplement S-001 submitted in support of Neupro for the treatment of the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS) included a waiver for development in patients under 8 years of age and a deferral for development in patients 8-17 years of age (Sequence No. 0035, submitted 21 September 2007). In FDA's Complete Response (CR) letter for the RLS supplement dated 21 April 2010, the Agency requested that UCB provide a revised pediatric plan for RLS, including a proposal for studies in pediatric patients aged 13 years and older. Based on the Agency's request and the fact that the diagnosis of RLS and evaluation of symptoms relies on the subjective reporting of the patients, the waiver request is amended to include patients up to 12 years of age. The pediatric population to be studied with Neupro will be 13 to 17 years of age.

2 BRIEF DESCRIPTION OF THE PLANNED PEDIATRIC STUDIES

The pediatric clinical program is comprised of 3 clinical studies to assess symptoms of moderate to severe primary RLS. Two of the studies are open-label studies: a pharmacokinetic study with the primary objective to assess pharmacokinetics following multiple doses (SP1004) and an open-label extension study with the primary objective to collect long-term tolerability and safety data (SP1005). The third study (SP1006) is a double-blind, placebo-controlled study to assess efficacy and safety.

Details of the individual studies are provided in the following sections.

2.1 SP1004

2.1.1 Study Design

SP1004 is an ongoing, open-label, dose-escalation, Phase 2 study with multiple administrations of the rotigotine transdermal system. The study will be conducted in adolescent subjects, 13 to 17 years of age, with moderate to severe primary RLS.

The Screening Period will last a minimum of 7 days prior to the baseline visit so RLS data can be collected and homogeneous baseline conditions can be established for all subjects. After completing a Screening Period, subjects will receive their first dose of rotigotine at Baseline. The rotigotine dose will be increased weekly up to a maximum dose of 3mg/24h as detailed in Table 2:1, unless safety and tolerability assessments do not allow for further dose titration.

Table 2:1. Dosing Schedule

Day	Dose
Day 1	0.5mg/24h (2.5cm^2)
Day 8	1mg/24h (5cm^2)
Day 15	2mg/24h (10cm^2)
Day 22	3mg/24h (15cm^2)

At Day 29, subjects will begin dose de-escalation by 1 dose step every 2 days until they reach the lowest dose for their dosing schedule for medication withdrawal.

2.1.2 Population

Subjects will be aged 13 to 17 years and meet the diagnosis of RLS based on specified features of the proposed 2011 Revised International Restless Legs Syndrome Group Diagnostic Criteria.

2.1.3 Objectives

The primary objective of this study is to determine the steady-state pharmacokinetics of rotigotine in adolescents with idiopathic RLS after multiple patch administration with weekly escalating doses. Secondary objectives are assessment of the safety, tolerability, and efficacy of rotigotine treatment in adolescents with idiopathic RLS.

2.1.4 Dosing

The doses demonstrated to be effective for RLS in adults are 1, 2 and 3mg/24h. These doses correspond to rotigotine AUC values of approximately 3ng/mL*h, 6ng/mL*h, and 9ng/mL*h, respectively in adults (SP871). The target AUC for the first dose applied to adolescents will be 3ng/mL*h, in accordance to the corresponding AUC for the lowest effective dose in adults. The doses needed to reach the respective exposure were adjusted for age-related differences in body weight through calculations based on allometric scaling of the rotigotine clearance in adults and included consideration of the following:

- Rotigotine is absorbed from the patch via the skin, following zero order kinetics. The absorption rate over 24h of patch application provides on average 45% of the total drug content of the patch (0.2mg/cm^2/24h). As the skin of children is considered to be comparable to adults at the age of 2 years and older, it can be assumed that the absorption rate in children will not differ significantly from the absorption rate in adults (Kearns et al 2003). However, as the study will be the first in the adolescent population, UCB prefers to take a conservative approach and assume 100% absorption from the patch for starting dose estimation in adolescents.
- Rotigotine is primarily cleared by metabolism, including conjugation (sulfation and glucuronidation) as major metabolic pathway, and oxidative desalkylation via cytochrome P450 enzymes with subsequent conjugation. All enzymes known to be involved in the metabolism show expression in the liver at 13 years of age close to the adult level (Johnson et al 2006, Vietri et al 2001). Hence, no change in intrinsic clearance of rotigotine is expected for children of ≥13 years of age compared to adults.
- Rotigotine is a rather lipophilic compound that is more likely to distribute into fatty tissue. The body composition of children is different at very low ages, i.e. in newborns and infants. However, at the starting age for this study, 13 years, body composition is similar to that of adults (Kearns et al 2003, Friis-Hansen 1983). As the body weight is lower in children compared with adults, an adaptation needed to be performed by dosing per kg body weight.
- As less than 1% of the total drug absorbed is eliminated renally (Cawello et al 2009) and no difference is expected in renal elimination in the proposed age range of 13 to 17 years when compared to adults (Hines 2008), no adaptation for renal elimination was considered necessary.

- Rotigotine shows a relatively high protein binding of about 92%. A decrease in protein binding due to a lower capacity would increase the active amount of drug. However, a reduced amount of plasma protein is present only in neonates and infants. In children and adolescents, the amount of plasma protein is equivalent to adults (Ehrnebo et al 1971, Kurz et al 1977).

Based on the results of the allometric scaling, the doses given in Table 2.1 are considered to be adequate in terms of exposure to be used in SP1004.

2.1.5 Pharmacokinetics

Plasma concentrations will be measured based on samples taken at pre-determined time points throughout the study after subjects have reached steady-state at each dose level. The pharmacokinetic data will be analyzed in an exploratory manner for predefined datasets. Unconjugated rotigotine concentrations will be analyzed using standard non-compartmental analysis, leading to a reduced PK profile due to sparse sampling in this study. In addition, the concentration data will be used to build a population PK model to evaluate potential differences in the PK of rotigotine over the investigated age range. All data will be analyzed in an exploratory manner. The pharmacokinetic sampling timepoints are listed in Table 2.2.

Table 2:2. Plasma and Urine Collection Schedule

Assessments	Visit 2 to 10 and WD					
	Day 1	**Days 7, 14, 21 and 28**				**Days 8, 15, 22, 29 and WD**
	Predose[a]	Predose[a]	1h postdose[b]	2h postdose[b]	7h-12h postdose	22h-24h postdose[c]
Plasma sampling	X	X	X	X	X	X
Urine collection		X[d]				

WD=withdrawal; h=hour

[a] Predose sample to be collected within 1 hour prior to patch application.

[b] Plasma samples to be collected within a ±15 minute window. A minimum of 45 minutes is required between the 1h and 2h postdose sample collections.

[c] Samples to be collected prior to removal of the previous day's patch.

[d] Urine sample to be collected at any time during the visit.

The study will be powered with 80% to target a 95% confidence interval within 60 and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution.

2.1.6 Efficacy Analyses

Descriptive statistics will be provided for IRLS, RLS-6, CGI Item 1, 2 and 3 by dose step. Periodic limb movements will be measured at baseline and at end of each dose step via actimetry and will be summarized by dose step. A potential correlation of efficacy and pharmacokinetic variables will be investigated. A model-based approach may be used for this purpose.

2.1.7 Safety and Tolerability Analyses

Descriptive statistics will be provided for adverse events, ECG, vital signs, neurological examination, skin tolerability, hormone status, safety laboratory data, menstrual and sexual function, mMIDI, Tanner Stage, CGI-Item 4, C-SSRS and global subject rating of tolerability.

2.2 SP1005

2.2.1 Study Design

SP1005 is an ongoing multicenter, open-label, single-arm, dose-escalation study of monotherapy administration of rotigotine transdermal system. This study will gather data on the long-term tolerability, safety, and efficacy of rotigotine transdermal system in adolescents with idiopathic RLS, allowing subjects from SP1004 and SP1006 to continue to receive rotigotine.

Subjects may remain in the study for 2 years after study entry or until approval of rotigotine has been obtained for subjects in their age range or until the investigational product development is discontinued.

2.2.2 Population

Subjects will have participated in SP1004 and SP1006 and met the enrollment criteria.

2.2.3 Objectives

The primary objective of this study is to assess the long-term tolerability and safety of rotigotine treatment in adolescents with idiopathic RLS. The secondary objective of this study is to assess the long-term efficacy of rotigotine treatment in adolescents with idiopathic RLS.

2.2.4 Dosing

The study will begin with a Titration Period of up to 4 weeks (at maximum) with the aim of achieving the individually optimized dosage (with a maximum dose of 3mg/24h). Titration will be followed by a Maintenance Period of up to 2 years, a 1-week Taper Period, and a 30-day Safety Follow-Up. Once a subject's dose has been optimized by the investigator, the subject should be maintained on that dose throughout the Maintenance Period. If necessary from a medical perspective, dose adjustments may be performed at the investigator's discretion at later timepoints.

2.2.5 Safety and Tolerability Analyses

Safety variables will be analyzed in a descriptive way. Summary statistics will be provided for the adverse events, laboratory data, Tanner stage, menstrual and sexual function, mMIDI, vital signs, body weight, height, BMI, ECG, neurological examination findings, CGI Item 4, Global Subject Rating of Tolerability, skin tolerability data and the potential risk for increased suicidality (C-SSRS). Cognitive and neuropsychiatric (including behavioral) effects will also be assessed.

2.2.6 Efficacy Analyses

Summary statistics will be provided for the efficacy variables (CGI, IRLS, PLMs, RLS-6) by dose.

2.3 SP1006

2.3.1 Study design

SP1006 will be a randomized, multi-center, double-blind, parallel group, placebo-controlled, fixed-dose efficacy and safety study of monotherapy administration of rotigotine transdermal patch in adolescent subjects, 13 to 17 years of age, with moderate to severe primary RLS.

After completing a Screening Period, subjects will be randomized to either placebo or one of the active doses. Subjects will receive their first dose of rotigotine at Baseline. Dose levels for the active arms will be defined based on the results of SP1004. Subjects must be able to tolerate the lowest dose.

2.3.2 Population

The number of subjects to be enrolled will be dependent on the final study design. Subjects will be aged 13 to 17 years and meet the diagnosis of RLS based on specified features of the proposed 2011 Revised International Restless Legs Syndrome Group Diagnostic Criteria.

2.3.3 Objectives

The primary objective of this study will be to assess the efficacy of rotigotine treatment in adolescents with moderate to severe primary RLS. The secondary objective of this study will be to assess the safety and tolerability of rotigotine treatment.

2.3.4 Dosing

The dose range will be determined based on results from the initial PK and safety study SP1004. Subjects will be titrated to their randomized dose and undergo a 12-week Maintenance Period. After completing the Maintenance Period (or prematurely discontinuing the study), subjects will enter a De-escalation Period during which the dose will be decreased every other day as in the adult population. In order to follow the long-term efficacy and safety of rotigotine in the pediatric population, subjects completing SP1006 will be allowed to enter the open-label extension trial, SP1005.

2.3.5 Efficacy Analyses

The co-primary efficacy variables will be the change from Baseline to the end of the Maintenance Period in the sum score of the IRLS rating scale and in the sum score of CGI-Item 1. For the primary analysis, an analysis of covariance (ANCOVA) will be performed for the changes from Baseline to end of the Maintenance Period with Baseline as a covariate and center (if applicable) as a factor. From this ANCOVA, treatment least-square (LS) means (with 95% confidence intervals [CI]) will be calculated and one-sided two-sample t-test will be performed (significance level 0.025) to demonstrate superiority of rotigotine versus placebo. Both co-primary endpoints must demonstrate significant results (at significance level 0.025) to demonstrate superiority of this dose level of rotigotine over placebo.

2.3.6 Population PK Analysis

Plasma concentrations of unconjugated rotigotine will be collected in SP1006. A population PK model will be developed to further describe the influence of age on the pharmacokinetics of rotigotine to support the results of SP1004.

2.3.7 Safety and Tolerability Analyses

Safety variables will be analyzed in a descriptive way. Summary statistics will be provided for the adverse events, laboratory data, Tanner stage, menstrual and sexual function, mMIDI, vital signs, body weight, height, BMI, ECG, neurological examination findings, CGI Item 4, Global Subject Rating of Tolerability, skin tolerability data, and both cognitive and neuropsychiatric (including behavioral) effects. The C-SSRS will be performed to assess the potential risk for increased suicidality.

2.3.8 Exposure-response analyses

The data from SP1004, SP1005, and SP1006 will be combined to develop exposure-response for safety and efficacy endpoints. The goals of these analyses are a) to provide supportive evidence of effectiveness and b) to support the dosing recommendations.

2.4 Timetable for Studies

UCB plans to follow the timelines outlined below.

2.4.1 SP1004

Protocol submission to FDA: June 2012*

First Patient First Visit: December 2011

Last Patient Last Visit: April 2014

Study submission date: November 2014

*Protocol originally submitted in October 2011 will be amended and resubmitted

2.4.2 SP1005

Protocol submission to FDA: June 2012*

First Patient First Visit: January 2012

Last Patient Last Visit: September 2026

Study submission date: April 2027

*Protocol originally submitted in October 2011 will be amended and resubmitted

2.4.3 SP1006

Protocol submission to FDA: September 2015

First Patient First Visit: March 2016

Last Patient Last Visit: July 2024

Study submission date: February 2025

3 PEDIATRIC FORMULATION

The excipients and components of the marketed product are considered safe for humans and present no additional risks to the intended pediatric population. The composition per unit area is identical for all patch sizes, allowing dose delivery to be determined by the size of the patch applied to the skin. A 0.5mg/24h [2.5cm^2] patch size previously tested will be used along with the existing doses demonstrated to be effective in adults (1mg/24h [5cm^2],

2mg/24h [10cm^2] and 3mg/24h [15cm^2]) to enable titration and dosing over the intended therapeutic range.

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/s/

LEONARD P KAPCALA
04/02/2012
Ready for your signature, Dave

GERALD D PODSKALNY
04/02/2012

CLINICAL REVIEW OF COMPLETE RESPONSE

Application Type	NDA 21829
Submission Number	Supplements 001 and 002 (Resubmission Class 2)
Submission Code	BZ (Sequence 94 and 95)
Letter Date	7/17/09
Stamp Date	7/22/09
PDUFA Goal Date	4/21/10 (after 3 month extension)
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	4/19/10
Established Name	Rotigotine
(Proposed) Trade Name	Neupro
Therapeutic Class	Dopaminergic agonist
Applicant	UCB Pharma
Priority Designation	S
Formulation	Patch
Dosing Regimen	Once daily
Indication	Adjunctive Treatment of Advanced Parkinson's Disease and Treatment of Restless Leg Syndrome
Intended Population	Adults with advanced Parkinson's Disease and Restless Leg Syndrome

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- I recommend a Complete Response action because the sponsor has not adequately addressed the Agency's CMC concerns that a safe and effective patch product (NEUPRO, rotigotine) can be manufactured and marketed in the U.S. with regard to crystal formation on the patch, despite the sponsor's proposal for a new manufacturing process.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

- I have no recommendations.

1.2.2 Required Phase 4 Commitments

- I have no recommendations.

1.2.3 Other Phase 4 Requests

- I have no recommendations.

1.3 Brief Summary of Sponsor's Complete Response

The sponsor submitted a Complete Response to the Agency's Complete Response letter of 12/15/08. In this response, the sponsor attempted to address the Agency's concerns about crystal formation with the NEUPRO/rotigotine patch, but the sponsor's response was determined to be adequate based upon the review of the CMC team (see CMC reviews by Dr.s Julia Pinto, James Vidra, Nallaperum Chidambaram, Eric Duffy) and discussion with clinical and clinical pharmacology colleagues on the whole review team.

The sponsor addressed the 5 clinical issues in the Complete Response letter that primarily dealt with characterizing the safety of the product in the label.

2 INTRODUCTION AND BACKGROUND

General Background

Rotigotine is a dopaminergic agonist that has been developed as a once daily patch for the treatment of early and advanced Parkinson's Disease and restless leg syndrome (RLS).

Presubmission Regulatory Activity

The sponsor had a Pre-NDA meeting with the DNP on 11/9/06 to plan this NDA submission for advanced Parkinson's Disease and RLS. All relevant issues were considered for all review disciplines. Many clinical recommendations were made with regard to the content and format for efficacy and safety analyses for both indications. It is worthy of note that this reviewed attended this Pre-NDA meeting and provide recommendations for many of the analyses.

Other Relevant Background Information

Rotigotine has been approved in Europe for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy and as adjunctive therapy with levodopa for advanced-stage Parkinson's disease.

The Agency approved NDA 21829 for rotigotine (NEUPRO) for treatment of early Parkinson's Disease on 5/9/07.

On 9/21/07 and 10/5/07, Supplements 001 and 002 were submitted to support the use of NEUPRO in the treatment of patients with advanced Parkinson's Disease and RLS, respectively. On 12/15/08 (following an extension of the PDUFA date because of submissions late in the review cycle), the Agency issued a Complete Response letter for both these supplements. This letter outlined the DNP's concerns about the new development of crystallization on the rotigotine/NEUPRO patches which prevented approval and marketing of NEUPRO for these new indications. The letter also outlined questions/concerns about 5 additional clinical issues.

Although the rotigotine product continues to be marketed outside the U.S. with the sponsor's revised manufacturing process because of crystallization on patches, the sponsor has voluntarily withdrawn NEUPRO from marketing in the U.S. because of the problems with patch crystallization.

On 3/23/09, the DNP held a Type C meeting with the sponsor to discuss the [redacted] (b) (4)

[redacted] (b) (4) (b) (4) plans to address the Complete Response letter of 12/15/08.

On 7/22/09, the sponsor submitted a Complete Response to the 12/15/08 letter for advanced Parkinson's Disease and RLS. [redacted] (b) (4)

This clinical review evaluates the sponsor's Complete Response of 7/22/09.

3 SPONSOR COMPLETE RESPONSE SUBMISSION

All individual trials included in this response to questions expressed the rotigotine dose as the total drug load per patch (mg/day) while the proposed marketed doses will be expressed as the dose delivered per 24 hours (nominal dose; mg/24h). Text and in-text tables in this response to questions express the dose as mg/24h, but the supporting statistical tables use the previous format of mg/day. The table below provides the equivalence between these 2 dosing conventions. The dosing conventions will be used jointly as needed for clarity. Doses were converted using the following formula: dose in mg/24h=dose in mg/day divided by 2.25.

Rotigotine nominal dose/24h (Summary documents)	Rotigotine content per transdermal system (CTRs)	Patch surface area (cm^2)
0.5mg	1.125mg	2.5
1mg	2.25mg	5
2mg	4.5mg	10
3mg	6.75mg	15
4mg	9mg	20
6mg	13.5mg	30
8mg	18mg	40
10mg	22.5mg	50
12mg	27mg	60
14mg	31.5mg	70
16mg	36mg	80
18mg	40.5mg	90
20mg	45mg	100
22mg	49.5mg	110
24mg	54mg	120

CTR=clinical trial report
Note: Doses >8mg/24h require a combination of patches.

3.1 Question 2 : Central Tendency and Outlier Analyses for Reproductive Endocrine Hormones in Pre-menopausal and Post-menopausal Women with RLS

DNP Complete Response Letter Question No. 2 :

"Please conduct analyses of female reproductive endocrine testing (eg, serum/plasma LH, FSH, estradiol, progesterone) of all patients in RS1 pool (i.e., all RLS patients in Double-blind phase of studies SP790 and SP792) according to whether the patients are considered pre-menopausal or post-menopausal at the time of screening/randomization. It is not clear if you have applied the same reproductive endocrine testing reference range for patients with the same reproductive status (i.e., pre-menopausal or post-menopausal) considering that we believe that you have utilized a central laboratory for all these tests. If a central laboratory was utilized for all RS1 pool patients, the same reference range should be applied to each individual patient based upon their pre-menopausal or post-menopausal status.

Initially, please categorize all patients in the RS1 pool as to whether they are pre-menopausal or post-menopausal. After this categorization, please conduct and present all the various, central tendency and outlier analyses of pool RS1 for the different perspectives (e.g., mean absolute values over time, mean change from baseline over time, shift analysis over time, incidence of "low" or "increased" value at any time during the study, and similar respective analyses for "markedly abnormal" values). Please show results for these analyses for placebo, each specific rotigotine dose, and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted.

If we do not have a correct understanding about the apparent deficiencies in these analyses, it may be helpful to contact us for clarification about what is needed and what should be done in your resubmission of your Complete Response."

Sponsor Response :
Pool RS1 (primary safety pool) consists of subjects from 2 Phase 3 double-blind trials (SP790 and SP792). Both SP790 and SP792 were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials to investigate the efficacy and safety of transdermal rotigotine. Subjects in SP790 were randomized to receive placebo, 1, 2, or 3mg/24h (2.25, 4.5, or 6.75mg/day) of rotigotine; subjects in SP792 were randomized to receive placebo, 0.5, 1, 2, or 3mg/24h rotigotine (1.125, 2.25, 4.5, or 6.75mg/day). The maximum duration of both trials was approximately 8 months (consisting of a 3-week [SP790] or a 4-week [SP792] Titration Period, a 6-month Maintenance Period, a 7-day Taper Period, and a 30-day Safety Follow-Up Period). SCHWARZ BIOSCIENCES has conducted a comprehensive analysis of reproductive status (pre-menopausal and post-menopausal) in females in Pool RS1 for the following endocrine parameters: 17-beta-estradiol, follicle-stimulating hormone (FSH), luteinising hormone (LH), progesterone, and prolactin.

Pre-menopausal and post-menopausal status was determined as follows, based on the

Gynecologic History and Demographics pages of the CRF:
1st (based on gynecologic history page)

- If an age entry for "age at menopause" is present, then the subject was considered post-menopausal
- If "age at menopause" is NA or missing, then the next step in the evaluation process was Performed

2nd (based on demography)

- If question "is subject 2 years post menopausal?" is answered with "Yes", then the subject was considered post-menopausal
- If the answer is "No" or missing, then the next step in the evaluation process was performed

3rd (based on gynecologic history page)

- If the "first day of last menstruation" (date) is more than 1 year before start of trial, then the subjects was considered post-menopausal
- If missing, then the next step in the evaluation process was performed

4th (based on demography page)

- If age ≥55 years, then the subject was considered post-menopausal.

Different reference ranges have been applied based on the subjects' menopausal status. For each analyte, a central laboratory was used.

The sponsor provided the normal reference range for these reproductive hormones.

Endocrine Reference Ranges for Females

Parameter	Reference Range	Unit of Measure
17-beta-estradiol	Pre-menopausal: 45.9 to 1828.2 Post-menopausal: 18.4 to 200.8	pmol/L
Follicle-stimulating hormone (FSH)	Pre-menopausal: 1.7 to 21.5* Post-menopausal: 25.8 to 134.8	U/L
Luteinising hormone (LH)	Pre-menopausal: 1.0 to 95.6* Post-menopausal: 7.7 to 58.5	U/L
Progesterone	Pre-menopausal: 0.2 to 27* Post-menopausal: 0.1 to 0.8	U/L
Prolactin	Pre- and post-menopausal: 6.0 to 29.9	ng/mL

*Applied ranges from SP790 central laboratory

1 ENDOCRINE VALUES OVER TIME

Timepoint values and change from Baseline by visit and randomized dose are presented for endocrine parameters in Table 2.1 (sponsor table submitted). Timepoint values and change from Baseline by visit and dose at the time of measurement are presented in Table 2.2 (sponsor table submitted)..

Mean and mean change from Baseline to the end of the Maintenance Period (MP) for the selected endocrine parameters by randomized dose are summarized in the following table.

Mean and mean change from Baseline to end of MP in endocrine parameters (Pool RS1 [Female])

Parameter (unit)	Placebo	Randomized dose (mg/24h)				
		0.5	1	2	3	Any
	Mean (SD) at end of MP					
	Mean change (SD) from Baseline to end of MP					
17-beta-estradiol (pmol/L)						
Pre-menopausal	n=23	n=16	n=34	n=41	n=39	n=130
	305.81 (427.96)	401.16 (473.01)	285.37 (331.92)	409.23 (484.08)	314.52 (231.64)	347.43 (381.55)
	n=23	n=16	n=34	n=41	n=39	n=130
	23.12 (433.97)	57.12 (595.89)	72.21 (350.95)	46.74 (793.07)	-127.16 (581.64)	2.51 (612.24)
Post-menopausal	n=89	n=38	n=89	n=93	n=93	n=313
	87.51 (123.12)	84.93 (100.24)	119.00 (131.55)	83.49 (111.95)	113.90 (192.14)	102.80 (144.62)
	n=88	n=37	n=88	n=93	n=92	n=310
	-4.08 (82.67)	-42.83 (152.65)	-28.34 (369.35)	-17.63 (97.59)	-18.94 (219.74)	-24.07 (241.35)
FSH (U/L)						
Pre-menopausal	n=23	n=16	n=34	n=41	n=39	n=130
	20.97 (28.25)	8.85 (15.16)	19.31 (24.86)	14.41 (21.56)	16.00 (21.59)	15.48 (21.82)
	n=23	n=16	n=34	n=41	n=39	n=130
	5.57 (16.53)	-1.58 (4.87)	5.93 (17.00)	2.82 (18.90)	-0.34 (13.22)	2.15 (15.70)
Post-menopausal	n=89	n=38	n=89	n=93	n=93	n=313
	68.99 (30.20)	62.51 (31.95)	64.76 (29.24)	59.71 (27.46)	57.56 (26.64)	60.84 (28.32)
	n=89	n=37	n=88	n=93	n=92	n=310
	-4.74 (13.44)	1.76 (14.46)	-4.33 (18.75)	-5.05 (11.52)	-3.77 (15.31)	-3.65 (15.36)

Mean and mean change from Baseline to end of MP in endocrine parameters (Pool RS1 [Female])

Parameter (unit)	Placebo	Randomized dose (mg/24h)				
		0.5	1	2	3	Any
	Mean (SD) at end of MP					
	Mean change (SD) from Baseline to end of MP					
Luteinising hormone (U/L)						
Pre-menopausal	n=23	n=16	n=34	n=41	n=39	n=130
	12.82 (14.40)	6.02 (8.29)	16.57 (19.17)	14.52 (19.00)	13.34 (14.76)	13.66 (16.97)
	n=23	n=16	n=34	n=41	n=39	n=130
	2.46 (13.91)	-2.23 (4.71)	5.57 (17.90)	5.99 (19.41)	-1.69 (12.95)	2.56 (16.29)
Post-menopausal	n=89	n=38	n=89	n=93	n=93	n=313
	32.73 (12.58)	30.83 (15.21)	34.94 (16.34)	31.40 (13.35)	29.57 (12.41)	31.79 (14.32)
	n=89	n=37	n=88	n=93	n=92	n=310
	-1.19 (7.28)	-0.89 (8.06)	1.67 (13.14)	-0.47 (5.96)	-0.96 (8.86)	-0.06 (9.55)
Progesterone (nmol/L)						
Pre-menopausal	n=23	n=16	n=34	n=41	n=39	n=130
	4.42 (7.83)	10.31 (19.05)	9.29 (15.64)	8.00 (13.04)	8.09 (13.72)	8.65 (14.62)
	n=23	n=16	n=34	n=41	n=39	n=130
	-5.64 (21.30)	2.43 (24.88)	3.91 (18.01)	-1.22 (16.06)	-2.40 (24.11)	0.22 (20.32)
Post-menopausal	n=89	n=38	n=89	n=93	n=93	n=313
	0.74 (0.47)	1.31 (3.66)	0.81 (0.57)	1.23 (2.96)	0.76 (0.54)	0.98 (2.10)
	n=88	n=37	n=89	n=93	n=92	n=311
	0.03 (0.48)	-1.43 (5.80)	-0.23 (1.63)	0.38 (2.56)	-0.98 (6.23)	-0.41 (4.29)

Mean and mean change from Baseline to end of MP in endocrine parameters (Pool RS1 [Female])

Parameter (unit)	Placebo	Randomized dose (mg/24h)				
		0.5	1	2	3	Any
	Mean (SD) at end of MP					
	Mean change (SD) from Baseline to end of MP					
Prolactin (µg/L)						
Pre-menopausal	n=23	n=16	n=34	n=41	n=39	n=130
	24.03 (27.87)	16.99 (9.17)	14.06 (9.37)	15.26 (9.79)	15.42 (7.65)	15.21 (8.94)
	n=23	n=16	n=34	n=41	n=39	n=130
	-2.93 (28.39)	2.07 (6.94)	-0.44 (11.21)	-0.21 (8.19)	0.41 (9.26)	0.20 (9.19)
Post-menopausal	n=89	n=38	n=89	n=93	n=93	n=313
	12.55 (12.40)	13.01 (12.93)	10.97 (7.32)	11.48 (11.82)	14.55 (26.96)	12.43 (17.11)
	n=89	n=37	n=89	n=93	n=92	n=311
	-3.79 (24.72)	-0.17 (3.90)	-0.08 (6.41)	-0.47 (9.32)	-0.38 (22.90)	-0.30 (13.90)

MP=Maintenance Period; SD=standard deviation
Data source: Table 2.1

In the pre-menopausal group, the mean change from Baseline for 17-beta-estradiol was 2.51pmol/L in the any rotigotine group and 23.12pmol/L in the placebo group. In the post-menopausal group, the mean change from Baseline was -24.07pmol/L in the any rotigotine group and -4.08pmol/L in the placebo group. In the any rotigotine group, a mean increase in 17-beta-estradiol of 2.51pmol/L was noted in the pre-menopausal group, compared with a decrease of -24.07pmol/L in the post-menopausal group.

In the pre-menopausal group, the mean change from Baseline for FSH was 2.15U/L in the any rotigotine group and 5.57U/L in the placebo group. In the post-menopausal group, the mean change from Baseline for FSH was -3.65U/L in the any rotigotine group, compared with -4.74U/L in the placebo group. In the any rotigotine group, a mean increase from Baseline in FSH of 2.15U/L was noted in the pre-menopausal group, compared with a decrease of -3.65U/L in the post-menopausal group.

In the pre-menopausal group, the mean change from Baseline for LH was 2.56U/L in the any rotigotine group and 2.46U/L in the placebo group. In the post-menopausal group, the mean change from Baseline for LH was -0.06U/L in the any rotigotine group and -1.19U/L in the

placebo group. In the any rotigotine group, a mean increase from Baseline of 2.56U/L was noted in the pre-menopausal group, compared with a slight mean decrease of -0.06U/L in the post-menopausal group.

In the pre-menopausal group, the mean change from Baseline for progesterone was 0.22nmol/L in the any rotigotine group and -5.64nmol/L in the placebo group. In the post-menopausal group, the mean change from Baseline for progesterone was -0.41nmol/L in the any rotigotine group and 0.03nmol/L in the placebo group. In the any rotigotine group, a slight mean increase from Baseline in progesterone of 0.22nmol/L was noted in the pre-menopausal group, compared with a slight decrease of -0.41nmol/L in the post-menopausal group.

In the pre-menopausal group, the mean change from Baseline for prolactin was 0.20µg/L in the any rotigotine group and -2.93µg/L the placebo group. In the post-menopausal group, the mean change from Baseline for prolactin was -0.30µg/L in the any rotigotine group and -3.79µg/L in the placebo group. In the any rotigotine group, a mean increase from Baseline in prolactin of 0.20µg/L was noted in the pre-menopausal group, compared with a decrease of -0.30µg/L in the post-menopausal group.

It should be noted that the endocrine data are highly variable. For each of the selected endocrine parameters, the mean values at the end of the MP remained within the normal reference ranges, regardless of pre- or post-menopausal status. Standard deviations were often larger than the mean value; therefore, the results should be interpreted with caution.

The sponsor noted that there appeared to be no dose-dependent change in the selected endocrine values for either pre-menopausal or postmenopausal subjects.

Reviewer Comments

- The sponsor's approach for categorizing women as pre-menopausal or post-menopausal seemed to be reasonable.

- I agree that there does not appear to be any clear effect of rotigotine on these hormones in pre-menopausal or post-menopausal women based upon analyses of randomized treatment for mean absolute data over time and mean change from baseline over time (assessing central tendency comparisons of placebo and various rotigotine doses at different visits). However, there are methodological and analytical problems/concerns that I will discuss below here.

- Probably the most important female group in need of evaluation of potential effects of rotigotine on reproductive hormones is the pre-menopausal population. However, a major problem/flaw in the collection and analysis of these data in the pre-menopausal population is the fact that samples collected were not associated with a particular time/stage of the menstrual cycle. This is important because there are different "normal" reference ranges for these hormones depending on whether the sample was collected in the follicular phase or after ovulation in the luteal phase. This deficiency makes it difficult to establish any effect of

rotigotine on these hormones. Thus, the absence of noting any particular effect of rotigotine on these hormones in pre-menopausal women does not exclude an effect of rotigotine.

- An additional problem associated with these reproductive hormone results of is the observation and that there is a substantial proportion of missing samples in patients at the "end" of the study (e.g., "final" visit for completers or patients who discontinued prematurely) and for "completers" (patients who completed treatment at the end of the 6 months maintenance period. In the post-menopausal population, an average of nearly 10 % of patients had missing samples for the final visit and an average of approximately 33 % of patients had missing samples at the end of the scheduled 6 month maintenance period. In the pre-menopausal population, the percentages of missing samples was even larger. In this group, an average of nearly 20 % of patients had missing samples for the final visit and an average of approximately a little more than 40 % of patients had missing samples at the end of the scheduled 6 month maintenance period. The relatively large, notable percentages of missing samples further compromise the integrity of the samples collected and likelihood that these data would adequately indicate whether rotigotine did or did not alter these hormones.

Percentage of Reproductive Hormone Samples Missing (Relative to Baseline Sampling) in Pre-Menopausal and Post-Menopausal Women after Treatment for 6 Months (Maintenance Period-MP) and up to End of MP (Final Visit)

	Treatment					
		Rotigotine (Daily Dose mg; Total Patch Content)				
	Placebo	1.125	2.5	4.5	6.75	Any
Reproductive Hormones						
Pre-Menopausal						
Month 6 of MP (Completer)	**50**	**59**	**44**	**30**	**40**	**41**
End of MP/Final Visit	**18**	**27**	**17**	**11**	**17**	**17**
Post-Menopausal						
Month 6 of MP (Completer)	**34**	**26**	**36**	**28**	**37**	**33**
End of MP/Final Visit	**18**	**0**	**10**	**10**	**9**	**8**

- My focus on these central tendency analyses was on the randomized treatment rather than on the actual dose of rotigotine at the time of data collection. My focus was on the randomized treatment groups because analyses of these data are more likely to reveal true dose-dependent effects.

2 INDIVIDUAL SUBJECT CHANGES IN ENDOCRINE VALUES

Shifts for abnormal values by visit and randomized dose are presented in Table 2.3 (sponsor table submitted). Shifts for abnormal values by visit and dose at the time of measurement are presented in Table 2.4 (sponsor table submitted).

The sponsor did not think that there was any clear effect of rotigotine on producing particular abnormal shifts.

Reviewer Comments

- I reviewed the sponsor's presentation of shifts from normal at Baseline to abnormal (i.e., above or below the "normal" reference range) at various visits up to the end of the MP that occurred in subjects in each rotigotine treatment group (or "any" rotigotine dose) or placebo treatment groups for reproductive endocrine parameters. Because the data presentations are extensive and the sponsor did not provide an in-text presentation of these results according to each rotigotine dose, I have presented some results that I have considered notable for pre-menopausal females and also for post-menopausal females. In addition, my presentation of notable shifts focuses on results for completers at the end of the 6 month maintenance period (MP) or at the final visit (.i.e., end of MP).

- My focus on these shift analyses was on the randomized treatment rather than on the actual dose of rotigotine at the time of data collection. My focus was on the randomized treatment groups because analyses of these data are more likely to reveal true dose-dependent effects than analyses of actual dose.

Reviewer Notable Shifts in Reproductive Hormones in Pre-Menopausal and Post-Menopausal Women After Treatment for 6 Months (Maintenance Period-MP) and up to End of MP (Final Visit)

Shift of Hormone from Baseline to On-Treatment Timepoint	Treatment					
		Rotigotine (Daily Dose mg; Total Patch Content)				
	Placebo	1.125	2.5	4.5	6.75	Any
Serum 17-β-Estradiol Normal to Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**3.6**	**4.5**	**7.3**	**4.3**	**6.4**	**5.8**
End of MP/Final Visit	**3.6**	**4.5**	**7.3**	**6.5**	**6.4**	**6.4**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**0**	**0**	**0**	**0**
End of MP/Final Visit	**0**	**0**	**0**	**0**	**0**	**0**
Serum FSH Normal to Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**4.5**	**2.4**	**0**	**0**	**1.3**
End of MP/Final Visit	**0**	**4.5**	**2.4**	**0**	**0**	**1.3**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**2.6**	**4.0**	**2.9**	**1.0**	**2.6**
End of MP/Final Visit	**0**	**2.6**	**4.0**	**2.9**	**2.9**	**3.2**
Serum LH Normal to Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**9.1**	**2.4**	**2.2**	**0**	**2.4**
End of MP/Final Visit	**3.6**	**18.2**	**2.4**	**4.3**	**0**	**4.5**
Post-Menopausal						
Month 6 of MP (Completer)	**0.9**	**0**	**1.0**	**0**	**0**	**0.3**
End of MP/Final Visit	**0.9**	**0**	**1.0**	**0**	**0**	**0.3**
Serum Progesterone Normal to Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**3.6**	**0**	**9.8**	**6.5**	**0**	**4.5**
End of MP/Final Visit	**7.1**	**0**	**9.8**	**6.5**	**2.1**	**5.1**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**2.6**	**3.0**	**2.9**	**1.9**	**2.6**
End of MP/Final Visit	**0**	**2.6**	**4.0**	**3.9**	**2.9**	**3.5**
Serum Prolactin Normal to Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**0**	**4.3**	**2.1**	**1.9**
End of MP/Final Visit	**0**	**0**	**0**	**4.3**	**6.4**	**3.2**
Post-Menopausal						
Month 6 of MP (Completer)	**2.7**	**5.1**	**3.0**	**3.9**	**7.8**	**4.9**
End of MP/Final Visit	**3.6**	**5.1**	**5.0**	**6.8**	**7.8**	**6.4**
Serum Prolactin Normal to High						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**2.4**	**2.2**	**2.1**	**1.3**
End of MP/Final Visit	**0**	**4.5**	**4.9**	**0**	**4.3**	**3.2**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**3.0**	**1.0**	**0**	**1.2**
End of MP/Final Visit	**0**	**0**	**3.0**	**1.0**	**0**	**1.2**

Reviewer Comments

- There did not appear to be any clear dose-related shifts produced by rotigotine in either population of women with one exception. The sole exception appeared to be a possible-dose-related shift in serum prolactin from normal at baseline to subnormal at the end of the 6 month MP and at the final visit in post-menopausal females.

- The above tables shows that there appeared to be a very small shift for "any" rotigotine dose for each hormone in the incidence of patients who were normal at baseline but had a subnormal value either at the end of 6 months treatment MP (i.e., completers) and/or at the final visit in either population or both populations. This similar shift was usually observed for completers and at the final visit and in most instances for both female populations. The magnitude of the shift showed a very small treatment difference (any rotigotine % - placebo %) usually ranging from 1-3 %. The yellow highlight emphasizes my findings.

- These results are compatible with the possibility that chronic dopaminergic stimulation from rotigotine results in some suppression of reproductive hormones in a very small percentage of patients with pre-menopausal females and post-menopausal females. The reason that these samples were obtained was to attempt to serve as surrogate markers for a possible effect (especially detrimental) of rotigotine on reproductive hormone levels and ultimately reproductive function that is regulated by these hormones. **However, given the limitations of the data collection for these reproductive hormones that I previously noted, and the fact that there did not appear to be a clear signal of anovulation as manifested by an increased incidence of oligomenorrhea/amenorrhea as an adverse event in rotigotine-treated patients compared to placebo patients, it is difficult to conclude that clear effects of rotigotine on reproductive hormones were identified and characterized and are worthy of description in the label.**

- The effect of rotigotine on suppressing serum prolactin is not surprising but a well-recognized effects of dopaminergic drugs.

- Of interest, there may have been a small signal for a few patients who experienced an increased incidence of increase in serum prolactin above the "normal" reference range.

- These observations may be worthy of description in the rotigotine label in a section describing drug effects on laboratory tests.

3 ENDOCRINE ABNORMALITIES

3.1 Markedly abnormal endocrine values

Shifts for marked abnormalities in endocrine parameters by randomized dose and dose at time of measurement is presented in Table 2.5 (sponsor table submitted). and Table 2.6 (sponsor table submitted) , respectively.

Markedly abnormal endocrine values (defined as an increase or decrease of at least 10% from the upper and lower limits of the reference range) in the any rotigotine or placebo treatment groups are summarized in the following table.

The sponsor did not think that there was any clear effect of rotigotine on producing particular markedly abnormal shifts.

Reviewer Comments

- I reviewed the sponsor's presentation of shifts from not markedly abnormal at Baseline to markedly abnormal (i.e., at least 10 % above or below the "normal" reference range) at various visits up to the end of the MP that occurred in subjects in each rotigotine treatment group (or "any" rotigotine dose) or placebo treatment groups for reproductive endocrine parameters. Because the data presentations are extensive and the sponsor did not provide an in-text presentation of these results according to each rotigotine dose, I have presented some results that I have considered notable for pre-menopausal females and also for post-menopausal females. In addition, my presentation of notable shifts focuses on results for completers at the end of the 6 month maintenance period (MP) or at the final visit (.i.e., end of MP).

- My focus on these shift analyses was on the randomized treatment rather than on the actual dose of rotigotine at the time of data collection. My focus was on the randomized treatment groups because analyses of these data are more likely to reveal true dose-dependent effects than analyses of actual dose.

Reviewer Notable Markedly Abnormal Shifts in Reproductive Hormones in Pre-Menopausal and Post-Menopausal Women After Treatment for 6 Months (Maintenance Period-MP) and up to End of MP (Final Visit)

Shift of Hormone from Baseline to On-Treatment Timepoint	Treatment					
		Rotigotine (Daily Dose mg; Total Patch Content)				
	Placebo	1.125	2.5	4.5	6.75	Any
Serum 17-β-Estradiol Not Markedly Abnl to Markedly Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**4.5**	**2.4**	**6.5**	**6.4**	**5.1**
End of MP/Final Visit	**0**	**4.5**	**2.4**	**8.7**	**6.4**	**5.8**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**0**	**0**	**0**	**0**
End of MP/Final Visit	**0**	**0**	**0**	**0**	**0**	**0**
Serum FSH Not Markedly Abnl to Markedly Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**4.5**	**2.4**	**0**	**0**	**1.3**
End of MP/Final Visit	**3.6**	**4.5**	**2.4**	**0**	**0**	**1.3**
Post-Menopausal						
Month 6 of MP (Completer)	**1.8**	**0**	**4.0**	**1.0**	**0**	**1.4**
End of MP/Final Visit	**1.8**	**0**	**4.0**	**1.0**	**2.9**	**2.3**
Serum LH Not Markedly Abnl to Markedly Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**9.1**	**2.4**	**2.2**	**0**	**2.6**
End of MP/Final Visit	**3.6**	**18.2**	**2.4**	**4.3**	**0**	**4.5**
Post-Menopausal						
Month 6 of MP (Completer)	**0.9**	**0**	**1.0**	**1.0**	**0**	**0.6**
End of MP/Final Visit	**0.9**	**0**	**1.0**	**1.0**	**0**	**0.6**
Serum Progesterone Not Markedly Abnl to Markedly Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**3.6**	**0**	**9.8**	**4.3**	**0**	**3.8**
End of MP/Final Visit	**7.1**	**0**	**9.8**	**4.3**	**2.1**	**4.5**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**3.0**	**2.9**	**1.0**	**2.0**
End of MP/Final Visit	**0**	**2.6**	**4.0**	**3.9**	**1.0**	**2.9**
Serum Prolactin Not Markedly Abnl to Markedly Low						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**0**	**4.3**	**2.1**	**1.9**
End of MP/Final Visit	**0**	**0**	**0**	**4.3**	**4.3**	**2.6**
Post-Menopausal						
Month 6 of MP (Completer)	**1.8**	**2.6**	**1.0**	**4.9**	**7.8**	**4.3**
End of MP/Final Visit	**2.7**	**2.6**	**3.0**	**6.8**	**7.8**	**5.5**
Serum Prolactin Not Markedly Abnl to Markedly High						
Pre-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**2.4**	**2.2**	**2.1**	**1.3**
End of MP/Final Visit	**0**	**0**	**4.9**	**0**	**2.1**	**1.9**
Post-Menopausal						
Month 6 of MP (Completer)	**0**	**0**	**2.0**	**1.0**	**0**	**0.9**
End of MP/Final Visit	**0**	**0**	**2.0**	**1.0**	**0**	**0.9**

Reviewer Comments

- There did not appear to be any clear dose-related shifts produced by rotigotine in either population of women with one exception. The sole exception appeared to be a possible-dose-related shift in serum prolactin from not markedly abnormal at baseline to markedly low at the end of the 6 month MP and at the final visit in post-menopausal females.

- The above tables shows that there appeared to be a very small shift for "any" rotigotine dose for each hormone in the incidence of patients who were not markedly abnormal at baseline but had a markedly abnormal value either at the end of 6 months treatment MP (i.e., completers) and/or at the final visit in either population or both populations. This similar shift was usually observed for completers and at the final visit and in most instances for both female populations. The magnitude of the shift showed a relatively small treatment difference (any rotigotine % - placebo %) usually ranging from 1-6 %. The yellow highlight emphasizes my findings.

- In many instances, there results for markedly abnormal shifts were quite similar to those noted by me for simple shifts from normal at baseline to low or high (relative to the reference range).

- These results are compatible with the possibility that chronic dopaminergic stimulation from rotigotine results in some suppression of reproductive hormones in a very small percentage of patients with pre-menopausal females and post-menopausal females. The reason that these samples were obtained was to attempt to serve as surrogate markers for a possible effect (especially detrimental) of rotigotine on reproductive hormone levels and ultimately reproductive function that is regulated by these hormones. **However, given the limitations of the data collection for these reproductive hormones that I previously noted, and the fact that there did not appear to be a clear signal of anovulation as manifested by an increased incidence of oligomenorrhea/amenorrhea as an adverse event in rotigotine-treated patients compared to placebo patients, it is difficult to conclude that clear effects of rotigotine on reproductive hormones were identified and characterized and are worthy of description in the label.**

- The effect of rotigotine on suppressing serum prolactin is not surprising but a well-recognized effects of dopaminergic drugs.

- Of interest, there may have been a small signal for a few patients who experienced an increased incidence of increase in serum prolactin from not markedly abnormal to a markedly increased value.

- These observations may be worthy of description in the rotigotine label in a section describing drug effects on laboratory tests.

3.2 Question 3 : Treatment- Emergent Adverse Events Reflecting Increased or Decreased Libido)

DNP Complete Response Letter Question No. 3:
"Please review all Case Report Forms (CRFs) for TEAEs (in RS1 pool for RLS) that suggest any change in libido and have not been characterized as either essentially increased or decreased. Most likely, a change in libido would either reflect a change such as increased or decreased libido. Please consider recharacterizing any TEAE suggesting a change/alteration in libido that is not specific (e.g., libido abnormal or libido altered) to a more specific characterization such as libido increased or decreased.

Once all libido-related TEAEs have been reviewed and possibly recharacterized, present the incidence of all similar AE terms suggesting either increased or decreased libido for the RS1 pool according to randomized treatment (i.e., for placebo and each specific rotigotine dose and also for "any" dose) for these TEAEs occurring at any time during the double-blind phase. If these various AE terms can be considered as reflecting either increased or decreased libido, please present the incidence of all these similarly related AE terms suggesting the possibility of increased or decreased libido.

Please show results for these analyses for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted."

Sponsor Response:

1 POOL RS1

Pool RS1 (primary safety pool) consists of subjects from 2 Phase 3 double-blind trials (SP790 and SP792). Both SP790 and SP792 were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials to investigate the efficacy and safety of transdermal rotigotine. Subjects in SP790 were randomized to receive placebo, 1, 2, or 3mg/24h (2.25, 4.5, or 6.75mg/day) of rotigotine; subjects in SP792 were randomized to receive placebo, 0.5, 1, 2, 3mg/24h rotigotine (1.125, 2.25, 4.5, or 6.75mg/day). The maximum duration of both trials was approximately 8 months (consisting of a 3-week [SP790] or a 4-week [SP792] Titration Period, a 6-month Maintenance Period, a 7-day Taper Period, and a 30-day Safety Follow-Up Period).

1.1 Treatment-emergent adverse events suggestive of change in libido

The CRFs of subjects for whom a treatment-emergent adverse event (TEAE) was reported that indicated a change of libido (but without characterizing the change as increase or decrease) were re-evaluated.

Re-evaluation of these cases was based on physician blinded review of adverse event (AE) reports, medical history, prior and concomitant medication, menstrual and sexual function (in females only), and the Self-Rating Depression Scale (SDS). The SDS item 6 has the statement "I still enjoy sex" scored from 1 (a little of the time) to 4 (most of the time), which was used to assess if libido was increased or decreased. Details on re-chacterization were also provided.

Subjects with re-characterized TEAEs suggestive of a change in libido (increase or decrease) for Pool RS1 are presented in Table 3.1 and in the following table.

Subjects with re-characterized TEAEs suggestive of change in libido (Pool RS1)

Subject number	Randomized treatment	Reported term	Re-characterization
790015117	Rotigotine 3mg/24h	Changes in libido	Libido decreased
790018002	Rotigotine 3mg/24h	Libido change	Libido increased
792013501	Rotigotine 1mg/24h	Change in sexual function	Libido decreased
792015608	Rotigotine 2mg/24h	Change in libido	Libido increased
792015901	Rotigotine 0.5mg/24h	Libido changes	Libido increased

TEAE=treatment-emergent adverse event

Data source: Table 3.1

The reported term was re-characterized to indicate the direction of change in libido or sexual function for 5 rotigotine-treated subjects. The reported term was re-characterized to decreased libido for 2 subjects and to increased libido for 3 subjects.

1.1.1 Libido-related adverse events by randomized dose

Treatment-emergent AEs suggestive of a change in libido for Pool RS1 are summarized in Table 3.2 (sponsor submitted table) and in the following table. The table below presents the overall incidence of any decreased libido TEAEs and any increased libido TEAEs based on re-characterized TEAEs.

TEAEs suggestive of a change in libido by randomized dose (Pool RS1)

TEAEs based on re-characterized events	Placebo N=217 n (%)	Rotigotine dose (mg/24h) 0.5 N=99 n (%)	1 N=215 n (%)	2 N=211 n (%)	3 N=220 n (%)	Any Rotigotine N=745 n (%)
Any decreased libido TEAE	4 (1.8)	3 (3.0)	8 (3.7)	3 (1.4)	4 (1.8)	18 (2.4)
Any increased libido TEAE	2 (0.9)	4 (4.0)	2 (0.9)	5 (2.4)	6 (2.7)	17 (2.3)

TEAE=treatment-emergent adverse event

Data source: Table 3.2

In summary, the sponsor noted that the overall incidence of decreased or increased libido in subjects treated with rotigotine was low (2%) and the difference between rotigotine and placebo was similar for both decreased or increased libido.

Table 3.2
Libido-Related TEAEs by Randomized Dose
Pool: RS1

Libido decreased

MedDRA(Version 9.1) System Organ Class/ High Level Term/ Preferred Term	Placebo N=217 n	(%)	[AEs]	Rotigotine 1.125mg/day N=99 n	(%)	[AEs]	Rotigotine 2.25mg/day N=215 n	(%)	[AEs]	Rotigotine 4.5mg/day N=211 n	(%)	[AEs]	Rotigotine 6.75mg/day N=220 n	(%)	[AEs]	Rotigotine Total N=745 n	(%)	[AEs]
Any AE	4	(1.8)	[4]	3	(3.0)	[3]	8	(3.7)	[8]	3	(1.4)	[3]	4	(1.8)	[4]	18	(2.4)	[18]
Psychiatric disorders	4	(1.8)	[4]	3	(3.0)	[3]	7	(3.3)	[7]	3	(1.4)	[3]	4	(1.8)	[4]	17	(2.3)	[17]
SEXUAL DESIRE DISORDERS	4	(1.8)	[4]	3	(3.0)	[3]	7	(3.3)	[7]	3	(1.4)	[3]	4	(1.8)	[4]	17	(2.3)	[17]
Libido decreased	3	(1.4)	[3]	3	(3.0)	[3]	4	(1.9)	[4]	3	(1.4)	[3]	3	(1.4)	[3]	13	(1.7)	[13]
Loss of libido	1	(0.5)	[1]	0			3	(1.4)	[3]	0			0			3	(0.4)	[3]
Libido disorder	0			0			0			0			1	(0.5)	[1]	1	(0.1)	[1]
Reproductive system and breast disorders	0			0			1	(0.5)	[1]	0			0			1	(0.1)	[1]
SEXUAL FUNCTION AND FERTILITY DISORDERS NEC	0			0			1	(0.5)	[1]	0			0			1	(0.1)	[1]
Sexual dysfunction	0			0			1	(0.5)	[1]	0			0			1	(0.1)	[1]

Reviewer Comments

- Following the sponsor's recharacterization when possible of adverse events as reflecting decreased libido, there was no clear dose-related effect of rotigotine nor a clear effect of "any" dose of rotigotine compared to that of placebo. The incidence of decreased libido was 1.8 % for placebo and the highest dose of rotigotine (6.75 mg). The incidence of decreased libido for "any" rotigotine treatment was 2.4 % (~ 2 %), similar to that for placebo (~ 2 %).

Table 3.2
Libido-Related TEAEs by Randomized Dose
Pool: RS1

Libido increased

MedDRA(Version 9.1) System Organ Class/ High Level Term/ Preferred Term	Placebo N=217 n	(%)	[AEs]	Rotigotine 1.125mg/day N=99 n	(%)	[AEs]	Rotigotine 2.25mg/day N=215 n	(%)	[AEs]	Rotigotine 4.5mg/day N=211 n	(%)	[AEs]	Rotigotine 6.75mg/day N=220 n	(%)	[AEs]	Rotigotine Total N=745 n	(%)	[AEs]
Any AE	2	(0.9)	[2]	4	(4.0)	[4]	2	(0.9)	[2]	5	(2.4)	[5]	6	(2.7)	[6]	17	(2.3)	[17]
Psychiatric disorders	2	(0.9)	[2]	4	(4.0)	[4]	2	(0.9)	[2]	5	(2.4)	[5]	6	(2.7)	[6]	17	(2.3)	[17]
SEXUAL DESIRE DISORDERS	2	(0.9)	[2]	4	(4.0)	[4]	2	(0.9)	[2]	5	(2.4)	[5]	6	(2.7)	[6]	17	(2.3)	[17]
Libido increased	2	(0.9)	[2]	3	(3.0)	[3]	2	(0.9)	[2]	4	(1.9)	[4]	5	(2.3)	[5]	14	(1.9)	[14]
Libido disorder	0			1	(1.0)	[1]	0			1	(0.5)	[1]	1	(0.5)	[1]	3	(0.4)	[3]

Reviewer Comments

- Following the sponsor's recharacterization when possible of adverse events as reflecting increased libido, there was a relatively small increased incidence of increased libido associated with rotigotine treatment. The incidence of increased libido for "any" rotigotine dose was 2.3 % and that for placebo was 0.9 %. There did not appear to be a dose-relationship to rotigotine.

- This increased risk for increased libido should be described in the label.

3.3 Question 4 : Treatment-Emergent Adverse Events Reflecting Anovulatory Menses)

DNP Complete Response Letter Question No. 4:
"Please have your clinicians review all Case Report Forms (CRFs) for TEAEs (in RS1 pool for RLS) that suggest any change in menses (e.g., non-specific characterizations such as menstrual disorder, menses abnormal, menstruation irregular or other such non-specific characterizations) that have not been characterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea, menstruation delayed). Once these CRF reviews have been completed, have your clinicians determine whether these various menstrual TEAEs can be recharacterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea). Typically, a significant change in menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea) suggests that there is anovluation.
After all menstrual TEAEs have been reviewed and possibly recharacterized as either essentially "normal"/unaltered or "abnormal" suggesting anovulatory menses (e.g., increased frequency throughout the menstrual cycle or decreased/absent menses in frequency such as oligomenorrhea, hypomenorrhea, amenorrhea), present the incidence of all similar AE terms suggesting that menses are anovulatory according to randomized treatment (i.e. for placebo and each specific rotigotine dose and also for "any" dose) for these TEAEs occurring at any time during the double-blind phase.

Please show results for these analyses for placebo, each specific rotigotine dose and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted."

Sponsor Response:

1 POOL RS1

Pool RS1 (primary safety pool) consists of subjects from 2 Phase 3 double-blind trials (SP790 and SP792). Both SP790 and SP792 were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials to investigate the efficacy and safety of transdermal rotigotine.

Subjects in SP790 were randomized to receive placebo, 1, 2, or 3mg/24h (2.25, 4.5, or 6.75mg/day) of rotigotine; subjects in SP792 were randomized to receive placebo, 0.5, 1, 2, or 3mg/24h rotigotine (1.125, 2.25, 4.5, or 6.75mg/day). The maximum duration of both trials was approximately 8 months (consisting of a 3-week [SP790] or a 4-week [SP792] Titration Period, a 6-month Maintenance Period, a 7-day Taper Period, and a 30-day Safety Follow-Up Period).

1.1 Treatment-emergent adverse events suggestive of change in menses

The CRFs of subjects for whom a treatment-emergent adverse event (TEAE) was reported that indicated a change in menses (but without characterizing the change as either essentially normal/unaltered or abnormal) were re-evaluated. These cases were found under the preferred terms (PTs) menstruation disorder and menstruation irregular in the high level term (HLT) of menstruation and uterine bleeding NEC.

Re-evaluation of these cases was based on physician blinded review of the adverse event (AE) reports (with particular attention to AE duration), medical history, gynecological history, menstrual cycle, method of contraception, menstrual and sexual function, and prior and concomitant medication. Details on re-characterization were also provided.

Re-characterized TEAEs suggestive of a change in menses (normal/unaltered or abnormal) for Pool RS1 are presented in Table 4.1 (sponsor submitted table) and in the following table.

Re-characterized TEAEs suggestive of change in menses (Pool RS1)

Subject number	Randomized treatment	Reported term	Re-characterization
790010606	Rotigotine 2mg/24h	Disorder of menstruation (2 episodes)	Normal/unaltered
790011423	Rotigotine 2mg/24h	Dysmenorrhea Premature menstruation	Normal/unaltered Abnormal
790012320	Rotigotine 3mg/24h	Menstrual dysfunction	Normal/unaltered
790012806	Rotigotine 2mg/24h	Changes in menstrual functioning	Abnormal
790018201	Placebo	Abnormal menses at Baseline changed to normal menses	Normal/unaltered
790018608	Rotigotine 2mg/24h	Menstrual disorder	Abnormal
792010702	Rotigotine 2mg/24h	Menstrual cramps	Normal/unaltered
792010704	Rotigotine 0.5mg/24h	Early menstruation	Abnormal
792012710	Rotigotine 2mg/24h	Presence of menses (subject has not had menstrual cycle in 5 years)	Normal/unaltered
792013419	Rotigotine 0.5mg/24h	Peri-menopausal irregularities	Abnormal
792013902	Rotigotine 0.5mg/24h	Irregular menses	Normal/unaltered
792014311	Rotigotine 3mg/24h	Menstrual cycle came one week early	Abnormal
792014418	Rotigotine 3mg/24h	Increased dysmenorrhea	Normal/unaltered
792014601	Rotigotine 2mg/24h	Change in menstrual functioning	Normal/unaltered

TEAEs=treatment-emergent adverse events

Data source: Table 4.1

Table 4.2
TEAEs Suggestive of Anovulatory Menses by Randomized Dose
Pool: RS1 (Female, pre-menopausal)

MedDRA(Version 9.1) System Organ Class/ High Level Term/ Preferred Term	Placebo N=28			Rotigotine 1.125mg/day N=22			Rotigotine 2.25mg/day N=41			Rotigotine 4.5mg/day N=46			Rotigotine 6.75mg/day N=47			Rotigotine Total N=156		
	n	(%)	[AEs]	n	(%)	[AEs]	n	(%)	[AEs]	n	(%)	[AEs]	n	(%)	[AEs]	n	(%)	[AEs]
Any AE	3	(10.7)	[3]	3	(13.6)	[4]	2	(4.9)	[3]	7	(15.2)	[7]	4	(8.5)	[7]	16	(10.3)	[21]
Reproductive system and breast disorders	3	(10.7)	[3]	3	(13.6)	[4]	2	(4.9)	[3]	7	(15.2)	[7]	4	(8.5)	[7]	16	(10.3)	[21]
MENSTRUATION WITH INCREASED BLEEDING	2	(7.1)	[2]	0			2	(4.9)	[3]	2	(4.3)	[2]	3	(6.4)	[4]	7	(4.5)	[9]
Menorrhagia	1	(3.6)	[1]	0			1	(2.4)	[2]	0			3	(6.4)	[3]	4	(2.6)	[5]
Polymenorrhoea	0			0			0			1	(2.2)	[1]	1	(2.1)	[1]	2	(1.3)	[2]
Metrorrhagia	1	(3.6)	[1]	0			1	(2.4)	[1]	1	(2.2)	[1]	0			2	(1.3)	[2]
MENSTRUATION AND UTERINE BLEEDING NEC	0			2	(9.1)	[2]	0			3	(6.5)	[3]	1	(2.1)	[1]	6	(3.8)	[6]
Menstrual disorder	0			1	(4.5)	[1]	0			2	(4.3)	[2]	1	(2.1)	[1]	4	(2.6)	[4]
Menstruation irregular	0			1	(4.5)	[1]	0			1	(2.2)	[1]	0			2	(1.3)	[2]
MENSTRUATION WITH DECREASED BLEEDING	1	(3.6)	[1]	1	(4.5)	[2]	0			2	(4.3)	[2]	2	(4.3)	[2]	5	(3.2)	[6]
Menstruation delayed	1	(3.6)	[1]	0			0			1	(2.2)	[1]	1	(2.1)	[1]	2	(1.3)	[2]
Hypomenorrhoea	0			0			0			0			1	(2.1)	[1]	1	(0.6)	[1]
Oligomenorrhoea	0			0			0			1	(2.2)	[1]	0			1	(0.6)	[1]
Amenorrhoea	0			1	(4.5)	[2]	0			0			0			1	(0.6)	[2]

NOTE: n=number of subjects reporting at least 1 adverse event within high level group term /high level term/preferred term; (%)=percentage of subjects among total (N); [AEs]=count of individual adverse events occurring among the n subjects.

Reviewer Comments

- Following the sponsor's recharacterization when possible of adverse events as reflecting possibly, abnormal, anovulatory menses, there was no suggestion of an increased risk for anovulatory menses for either the highest dose of rotigotine (6.75 mg) or "any" rotigotine dose compared to that for placebo. The incidence of a TEAE suggestive of anovulatory menses was 10.7 %, 8.5 %, and 10.3 % for placebo, 6.75 mg rotigotine, and "any" rotigotine dose, respectively.

- Because I am not certain that the sponsor's grouping of all these TEAEs shown in the above table necessarily reflects anovulatory menses, I also evaluated the incidence of TEAEs in another grouping shown in the above table for the higher level term menstruation with decreased bleeding, including preferred terms of menstruation delayed, hypomenorrhea, oligomenorrhea, and/or amenorrhea. In this grouping, there was no suggestion of an increased risk for anovulatory menses for either the highest dose of rotigotine (6.75 mg) or "any" rotigotine dose compared to that for placebo. The incidence of a TEAE suggestive of anovulatory menses as related to "menstruation delayed" was 3.6 %, 4.3 %, and 3.2 % for placebo, 6.75 mg rotigotine, and "any" rotigotine dose, respectively.

- This analysis is important because it does not suggest that there is a risk of anovulatory menses as an adverse event associated with rotigotine treatment for RLS.

3.4 Question 5 : Treatment-Emergent Adverse Events Possibly Suggesting Orthostatic Hypotension

DNP Complete Response Letter Question No. 5:
"Please conduct and submit analyses of TEAEs that might possibly reflect events (regardless of level of severity) suggestive of the occurrence of hypotension/orthostatic hypotension/postural dizziness for Pool AS1 (double-blind phase of studies SP511 and SP650) for advanced Parkinson's disease and for Pool RS1 (double-blind phase of studies SP790 and SP792). Search for a variety of AE terms that might be suggestive of orthostatic hypotension/postural dizziness despite the fact that the AE may not have been coded as such. You have used the following AE search terms for searching for possible "severe" hypotension or orthostatic hypotension (i.e., blood pressure orthostatic, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, dizziness postural, and orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension). Please add the following AE search terms including: dizziness, vertigo, light-headedness, postural light-headedness, impaired balance, and feeling drunk.

Analyses should be conducted according to randomized treatment (i.e., for placebo and each specific rotigotine dose and also for "any" dose) for TEAEs occurring at any time during the double-blind phase, for SAEs occurring at any time during the double-blind phase, and for TEAEs causing study discontinuation at any time during the double-blind phase."

Sponsor Response:

1 ADVANCED-STAGE PARKINSON'S DISEASE

1.1 Pool AS1

Pool AS1 (primary safety pool) consists of subjects from a Phase 2b (SP511) and a Phase 3 (SP650) trial. Both SP511 and SP650 were multicenter, multinational, randomized, double-blind, parallel-group trials to investigate the efficacy and safety of transdermal rotigotine. Subjects in SP511 were randomized to receive placebo, 4, 8, or 12mg/24h (9, 18, or 27mg/day) of rotigotine; subjects in SP650 were randomized to receive placebo, 8, or 12mg/24h rotigotine (18, or 27mg/day). The maximum duration of SP511 was approximately 3.5 months (consisting of a 5-week Titration period, a 7-week Maintenance Period, and a 2-week Safety Follow-Up Period; there was no Taper Period). The maximum duration of SP650 was approximately 8.5 months (consisting of a 5-week Titration Period, a 24-week Maintenance Period, an 8-day Taper Period, and a 4-week Safety Follow-Up Period). Subjects who completed the Maintenance Period were eligible to participate in open-label extension trials.

1.1.1 Treatment-emergent adverse events suggestive of hypotension/orthostatic hypotension/postural dizziness

1.1.1.1 Treatment-emergent adverse events occurring at any time during the double-blind phase

Treatment-emergent adverse events (AEs) possibly suggestive of hypotension/orthostatic hypotension/postural dizziness that occurred in at least 1 subject are summarized for placebo and rotigotine dose groups for Pool AS1 in Table 5.1.1 (sponsor submitted table) and in the table below. This table includes both preferred terms (PTs) and high level terms (HLTs), based on Medical Dictionary for Regulatory Activities (MedDRA) Version 9.1. It should be noted that reported terms of light-headedness, postural light-headedness, and impaired balance coded to dizziness, dizziness postural, and balance disorder, respectively.

For any AE suggestive of hypotension/orthostatic hypotension, the sponsor noted that there did not appear to be a clear dose response with regard to the incidences of AEs under investigation. For the 8 and 12mg/24h rotigotine groups, the incidence of dizziness was increased compared with placebo. However, dizziness is an AE common of dopaminergic agents and is not necessarily related to orthostatic hypotension.

TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness by randomized nominal dose (Pool AS1)

MedDRA HLT/ PT	Placebo N=204 n (%)	Rotigotine dose (mg/24h)			
		4 N=80 n (%)	8 N=197 n (%)	12 N=190 n (%)	Any N=467 n (%)
Any AE of special interest	29 (14.2)	8 (10.0)	36 (18.3)	32 (16.8)	76 (16.3)
Inner ear signs and symptoms					
Vertigo	1 (0.5)	0	1 (0.5)	2 (1.1)	3 (0.6)
Vascular tests NEC (incl blood pressure)					
Blood pressure diastolic decreased	1 (0.5)	0	0	0	0
Neurological signs and symptoms NEC					
Dizziness	20 (9.8)	6 (7.5)	30 (15.2)	28 (14.7)	64 (13.7)
Dizziness postural	2 (1.0)	1 (1.3)	2 (1.0)	1 (0.5)	4 (0.9)
Vascular hypotensive disorders					
Hypotension	0	1 (1.3)	2 (1.0)	2 (1.1)	5 (1.1)
Orthostatic hypotension	10 (4.9)	0	2 (1.0)	2 (1.1)	4 (0.9)

AE=adverse event; HLT=high level term; incl=including; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the respective treatment group; n=number of subjects reporting at least 1 AE of special interest; NEC=not elsewhere classified; PT=preferred term; TEAE=treatment-emergent adverse event

Data source: Table 5.1.1

Reviewer Comments

- This approach of evaluating the risk of several TEAEs that might suggest orthostatic hypotension is a common one for drugs that increase dopaminergic tone and particularly for patients with Parkinson's Disease and RLS who are treated with drugs that increase dopaminergic tone.

- There was a mildly increased risk for TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness in patients with advanced Parkinson's Disease treated with rotigotine. Whereas the incidence of this adverse reaction was 14.2 % for placebo, there was a mildly increased dose-related risk for the highest doses of rotigotine (18.3 % and 16.8 % for 8 and 12 mg/delivered, respectively). The incidence of this TEAE for "any" rotigotine dose (16.3 %) was also increased compared to placebo (16.3 %).

- This increased risk should be described in the label.

1.1.1.2 Treatment-emergent serious adverse events occurring at any time during the double-blind phase

One serious treatment-emergent AE possibly suggestive of hypotension/orthostatic hypotension/postural dizziness occurred in Pool AS1: one AE of dizziness (MedDRA PT) was reported for 1 subject (Subject SP511/2501) included in the 12mg/24h rotigotine treatment group (Table 5.1.2).

1.1.1.3 Treatment-emergent adverse events causing study discontinuation at any time during the double-blind phase

Treatment-emergent AEs leading to study discontinuation and possibly suggestive of hypotension/orthostatic hypotension/postural dizziness for placebo and rotigotine dose groups for Pool AS1 are summarized in Table 5.1.3 (sponsor submitted table) and in the table below. This table includes both PTs and HLTs, based on MedDRA Version 9.1. **The sponsor noted that a dose-relationship was not detected.**

TEAEs leading to study discontinuation and possibly suggestive of hypotension/orthostatic hypotension/postural dizziness by randomized nominal dose (Pool AS1)

MedDRA HLT/ PT	Placebo N=204 n (%)	Rotigotine dose (mg/24h) 4 N=80 n (%)	8 N=197 n (%)	12 N=190 n (%)	Any N=467 n (%)
Any AE of special interest	2 (1.0)	1 (1.3)	5 (2.5)	2 (1.1)	8 (1.7)
Neurological signs and symptoms NEC					
Dizziness	0	1 (1.3)	5 (2.5)	2 (1.1)	8 (1.7)
Vascular hypotensive disorders					
Orthostatic hypotension	2 (1.0)	0	0	0	0

AE=adverse event; HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the respective treatment group; n=number of subjects reporting at least 1 AE of special interest; NEC=not elsewhere classified; PT=preferred term; TEAE=treatment-emergent adverse event

Data source: Table 5.1.3

Reviewer Comments

- There was a borderline increased incidence of TEAEs possibly suggesting orthostatic hypotension as a cause of study discontinuation in Parkinson's Disease patients treated with rotigotine. Although there was no dose-related increased risk for rotigotine, the incidence for TEAEs possibly suggesting orthostatic hypotension as a cause of study discontinuation was 1.7 % (~ 2 %) for "any" rotigotine dose compared to 1 % for placebo.

- We can discuss whether this borderline increased risk for study discontinuation should be described in the label.

2 RESTLESS LEGS SYNDROME

2.1 Pool RS1

Pool RS1 (primary safety Pool) consists of subjects from 2 Phase 3 trials (SP790 and SP792). Both SP790 and SP792 were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials to investigate the efficacy and safety of transdermal rotigotine. Subjects in SP790 were randomized to receive placebo, 1, 2, or 3mg/24h (2.25, 4.5, or 6.75mg/day) of rotigotine; subjects in SP792 were randomized to receive placebo, 0.5, 1, 2, or 3mg/24h rotigotine (1.125, 2.25, 4.5, or 6.75mg/day). The maximum duration of both trials was approximately 8 months (consisting of a 3-week [SP790] or a 4-week [SP792] Titration Period, a 6-month Maintenance Period, a 7-day Taper Period, and a 30-day Safety Follow-Up Period). Subjects who completed the 6-month Maintenance Period were eligible to participate in an open-label extension trial.

2.1.1 Treatment-emergent adverse events suggestive of hypotension/orthostatic hypotension/postural dizziness

2.1.1.1 Treatment-emergent adverse events occurring at any time during the double-blind phase

Treatment-emergent AEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness that occurred in at least 1 subject are summarized for placebo and rotigotine dose groups for Pool RS1 in Table 5.2.1 (sponsor submitted table) and in the table below. This table includes both PTs and HLTs, based on MedDRA Version 9.1. It should be noted that reported terms of light-headedness, postural light-headedness, and impaired balance coded to dizziness, dizziness postural, and balance disorder, respectively.

The sponsor noted that there did not appear to be a clear dose response with regard to the incidences of AEs under investigation.

TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness by randomized nominal dose (Pool RS1)

MedDRA HLT/ PT	Placebo N=217 n (%)	Rotigotine dose (mg/24h) 0.5 N=99 n (%)	1 N=215 n (%)	2 N=211 n (%)	3 N=220 n (%)	Any N=745 n (%)
Any AE of special interest	15 (6.9)	8 (8.1)	17 (7.9)	26 (12.3)	18 (8.2)	69 (9.3)
Inner ear signs and symptoms						
Vertigo	3 (1.4)	0	8 (3.7)	6 (2.8)	3 (1.4)	17 (2.3)
Neurological signs and symptoms NEC						
Dizziness	12 (5.5)	7 (7.1)	10 (4.7)	18 (8.5)	14 (6.4)	49 (6.6)
Dizziness postural	0	0	0	1 (0.5)	0	1 (0.1)
Vascular hypotensive disorders						
Orthostatic hypotension	0	1 (1.0)	0	2 (0.9)	0	3 (0.4)
Hypotension	1 (0.5)	0	0	0	2 (0.9)	2 (0.3)

AE=adverse event; HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the respective treatment group; n=number of subjects reporting at least 1 AE of special interest; NEC=not elsewhere classified; PT=preferred term; TEAE=treatment-emergent adverse event

Data source: Table 5.2.1

Reviewer Comments

- There was a mildly increased risk for TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness in patients with RLS treated with rotigotine. Whereas the incidence of this adverse reaction was 6.9 % for placebo, the incidence of this TEAE for "any" rotigotine dose (9.3 %). There was no clear dose-relationship for rotigotine for this risk.

- This risk should be described in the label.

2.1.1.2 Treatment-emergent serious adverse events occurring at any time during the double-blind phase

Two serious treatment-emergent AEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness occurred in Pool RS1: one AE of vertigo (MedDRA preferred term), was reported for 1 subject (Subject SP792/15607) included in the placebo group and for 1 subject (Subject SP790/11602) included in the 3mg/24h rotigotine treatment group (Table 5.2.2).

2.1.1.3 Treatment-emergent adverse events causing study discontinuation at any time during the double-blind phase

Treatment-emergent AEs leading to study discontinuation and possibly suggestive of hypotension/orthostatic hypotension/postural dizziness for placebo and rotigotine dose groups for Pool RS1 are summarized in Table 5.2.3 (sponsor submitted table) and in the table below.

The sponsor noted that a clear dose response was not observed, although respective discontinuations occurred only in rotigotine-treated subjects.

TEAEs leading to study discontinuation and possibly suggestive of hypotension/orthostatic hypotension/postural dizziness by randomized nominal dose (Pool RS1)

MedDRA HLT/ PT	Placebo N=217 n (%)	Rotigotine dose (mg/24h) 0.5 N=99 n (%)	1 N=215 n (%)	2 N=211 n (%)	3 N=220 n (%)	Any N=745 n (%)
Any AE of special interest	0	1 (1.0)	1 (0.5)	2 (0.9)	5 (2.3)	9 (1.2)
Inner ear signs and symptoms						
Vertigo	0	0	0	0	1 (0.5)	1 (0.1)
Neurological signs and symptoms NEC						
Dizziness	0	1 (0.1)	1 (0.5)	2 (0.9)	3 (1.4)	7 (0.9)
Vascular hypotensive disorders						
Hypotension	0	0	0	0	2 (0.9)	2 (0.3)

AE=adverse event; HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the respective treatment group; n=number of subjects reporting at least 1 AE of special interest; NEC=not elsewhere classified; PT=preferred term; TEAE=treatment-emergent adverse event

Data source: Table 5.2.3

Reviewer Comments

- There was a mildly increased risk for TEAEs possibly suggestive of hypotension/orthostatic hypotension/postural dizziness causing study discontinuation in patients with RLS treated with rotigotine. Whereas the incidence of this adverse reaction was 0 % for placebo, the incidence of this TEAE for “any” rotigotine dose (1.2 %). The highest incidence (2.3 %) for this TEAE occurred in the group treated with the highest dose of rotigotine (6.75 mg rotigotine patch content or 3 mg rotigotine delivered), suggesting a possible dose-relationship for rotigotine for this risk.

- This risk should be described in the label.

3.5 Question 6 : Subgroup Analyses (Age, Gender, Concomitant Medication) for Treatment-Emergent Adverse Events

DNP Complete Response Letter Question No. 6:
"Please conduct and submit subgroup analyses of treatment-emergent adverse events (TEAEs) occurring in certain subgroups (ie, age, gender, concomitant medication such as vasodilator/hypotensive agents) for Pool AS1 (double-blind phase of studies SP511 and SP650) for advanced Parkinson's disease and for Pool RS1 (double-blind phase of studies SP790 and SP792). Your subgroup analyses of TEAEs only considered the frequency of TEAEs for rotigotine treatment relative to each subgroup comparison and did not consider the frequency for placebo treatment in each subgroup analysis.

To conduct these analyses, please present a summary analysis of the incidence of the treatment effect (e.g., % for specific rotigotine dose - % for placebo) for each TEAE according to various level terms (e.g., system organ class [SOC], high level and high level group terms, and preferred term as presented previously) in each requested subgroup. Please show results for each subgroup immediately below the other subgroup for each AE term for each specific rotigotine dose and "any" rotigotine dose on the same page so that a comparison across treatments can be easily interpreted."

Sponsor Response:

1 POOL AS1

Pool AS1 (primary safety pool) consists of subjects from SP511, a Phase 2b trial, and SP650, a Phase 3 trial. Both SP511 and SP650 were multicenter, multinational, randomized, double-blind, parallel-group trials to investigate the efficacy and safety of transdermal rotigotine. Subjects in SP511 were randomized to receive placebo, 4, 8, or 12mg/24h (9, 18, or 27mg/day) of rotigotine; subjects in SP650 were randomized to receive placebo, 8, or 12mg/24h of rotigotine (18 or 27mg/day). The maximum duration of SP511 was approximately 3.5 months (consisting of a 5-week Titration Period, a 7-week Maintenance Period, and a 2-week Safety Follow-Up Period; there was no Taper Period). The maximum duration of SP650 was approximately 8.5 months (consisting of a 5-week Titration Period, a 24-week Maintenance Period, an 8-day Taper Period, and a 4-week Safety Follow-Up Period). Subjects who completed the Maintenance Period were eligible to participate in open-label extension trials.

Reviewer Comments

- The sponsor conducted and submitted the requested subgroup analyses for age, gender, and many groups of concomitant medications, including vasodilator/hypotensive medications for the advanced Parkinson's Disease and RLS pools.

- The age subgroups were $\geq$ 65 vs < 65 years old and also $\geq$ 75 vs < 75 years old. My focus on the age subgroups is for the standard subgroups ($\geq$ 65 vs < 65) because that is our usual focus and also because there were substantial proportions in this subgroup for each pool. For this age subgroup categorization, 43 % and 46 % of patients were in the younger age subgroup

for the placebo and "any" rotigotine dose groups for the Parkinson's Disease pool. For the RLS pool, 70 % and 77 % of patients were in the younger age subgroup the placebo and "any" rotigotine dose groups. When the older subgroup threshold (≥ 75 vs < 75) was applied, 87 % and 85 % of patients were in the placebo and "any" rotigotine dose groups for the Parkinson's Disease pool.

- The sponsor presented adverse events for the system organ class (SOC), high level term (HLT), and preferred term (PT) whenever there was a ≥ 5 % treatment difference between any rotigotine dose (including specific doses) and placebo for TEAEs by age category during treatment by randomized dose. For the Parkinson's Disease pool, treatment differences (vs placebo) were presented for 9, 18, and 27 mg daily rotigotine patch content and "any" rotigotine dose. For the RLS pool, treatment differences (vs placebo) were presented for 1.125, 2.5, 4.5, and 6.75 mg daily rotigotine patch content and "any" rotigotine dose.

- I focused my review on subgroup differences in the 18 mg dose group (patch content; 8 mg delivered dose) for Parkinson's Disease because that is the only dose that is likely to be approved based upon the current evidence, if rotigotine is approved for treatment of advanced Parkinson's Disease. I also focused my assessment of possible subgroup differences as being particularly notable when the treatment difference (rotigotine % - placebo %) between the subgroups was ≥ 5 %.

- For the RLS pool, I focused my review on assessing possible subgroup differences in the "any" rotigotine group or the highest dose group (6.75 mg patch content) for treatment differences (vs placebo).

- **Instead of presenting all of the sponsor's tables of all TEAEs in which there is a treatment difference of ≥ 5 % for any randomized treatment dose or "any" rotigotine dose (all rotigotine groups combined), I will present only data which meet my criteria of notable interest (≥ 5 % subgroup difference for the treatment difference) suggesting a noteworthy subgroup difference.**

- **I consider many of these differences that I have shown in the following tables and commented upon worthy of consideration of description in the label, especially when there are numerical differences suggesting an increased risk across all dose groups.**

Age Subgroup Differences

Advanced Parkinson's Disease

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by age category during treatment by randomized dose (Pool AS1)

SOC HLT Preferred term	Subgroup	ROT 4mg/24h - Placebo (%)	ROT 8mg/24h - Placebo (%)	ROT 12mg/24h - Placebo (%)	Any ROT - Placebo (%)
Nausea	<65	20.6	16.3	6.7	13.2
	≥65	14.0	1.6	-2.4	2.0
Somnolence	<65	-5.5	8.7	12.6	7.7
	≥65	-23.7	0.3	-5.3	-5.9

Reviewer Comments

- There was an increased risk for the incidence of nausea with all rotigotine doses in patients < 65 years old.

- There was an increased risk for the incidence of somnolence with the two highest rotigotine doses (i.e., 8 and 12 mg rotigotine delivered or 18 and 27 mg rotigotine patch content) and any rotigotine dose in patients < 65 years old.

RLS

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by age category during treatment by randomized dose (Pool RS1)

SOC HLT Preferred term	Subgroup	ROT 0.5mg/24h – Placebo (%)	ROT 1mg/24h – Placebo (%)	ROT 2mg/24h - Placebo (%)	ROT 3mg/24h - Placebo (%)	Any ROT - Placebo (%)
Application and instillation site reactions	<65	22.2	20.1	31.5	41.3	29.9
	≥65	4.4	30.6	41.3	31.1	31.6
Nervous system disorders	<65	19.1	7.2	15.6	13.9	13.2
	≥65	19.8	-2.7	4.9	-1.2	2.4
Headaches NEC	<65	13.1	4.8	6.8	6.0	6.9
	≥65	5.5	3.0	5.7	0.9	3.6
Psychiatric disorders	<65	0.8	2.2	6.1	11.6	5.9
	≥65	-4.9	-11.0	-6.0	2.9	-5.0

Reviewer Comments

- There was an increased risk for the incidence of application and instillation site reactions with the three highest rotigotine doses (i.e., 1, 2, and 3 mg rotigotine delivered or 2.25, 4.5, and 6.75 mg rotigotine patch content) in patients ≥ 65 years old.

- There was an increased risk for the incidence of nervous system disorders with the three highest rotigotine doses (i.e., 1, 2, and 3 mg rotigotine delivered or 2.25, 4.5, and 6.75 mg rotigotine patch content) and any rotigotine dose in patients < 65 years old.

- There was an increased risk for the incidence of headaches with the three rotigotine doses (i.e., 0.5, 2, and 3 mg rotigotine delivered or 1.125, 4.5, and 6.75 mg rotigotine patch content) in patients < 65 years old.

- There was an increased risk for the incidence of psychiatric disorders with the two highest rotigotine doses (i.e., 2, and 3 mg rotigotine delivered or 4.5, and 6.75 mg rotigotine patch content) and for any rotigotine doses in patients < 65 years old.

Gender Subgroup Differences

Advanced Parkinson's Disease

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by gender during treatment by randomized dose and subgroup (Pool AS1)

SOC HLT Preferred term	Subgroup	ROT 4mg/24h - Placebo (%)	ROT 8mg/24h - Placebo (%)	ROT 12mg/24h - Placebo (%)	Any ROT - Placebo (%)
Dizziness	Male	-3.4	2.8	4.7	2.6
	Female	-0.8	10.5	5.4	6.2
Nausea	Male	19.3	13.6	-0.2	8.9
	Female	13.4	-0.5	5.5	4.6

Reviewer Comments

- There was an increased risk for the incidence of dizziness with the 8 mg delivered rotigotine dose (i.e., 18 mg rotigotine patch content) in females.

- There was an increased risk for the incidence of nausea with the 4 and 8 mg delivered rotigotine doses (i.e., 9 and 18 mg rotigotine patch content) in males. However, there was an increased risk for the incidence of nausea with the 12 mg delivered rotigotine dose (i.e., 27 mg rotigotine patch content) in females

RLS

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by gender during treatment by randomized dose (Pool RS1)

SOC HLT Preferred term	Subgroup	ROT 0.5mg/24h – Placebo (%)	ROT 1mg/24h – Placebo (%)	ROT 2mg/24h - Placebo (%)	ROT 3mg/24h - Placebo (%)	Any ROT - Placebo (%)
Application and instillation site reactions	Male	22.5	19.2	26.8	20.5	22.0
	Female	17.7	24.7	37.3	48.4	34.7
Asthenic conditions	Male	-1.1	4.5	8.2	9.4	6.0
	Female	5.3	-3.7	4.7	0.6	1.2
Fatigue	Male	-1.1	4.5	6.6	9.4	5.6
	Female	6.1	-3.7	4.7	-0.0	1.1
Nervous system disorders	Male	21.8	5.3	19.4	13.7	13.8
	Female	16.5	3.7	8.8	7.9	8.0
Headache	Male	16.0	3.0	14.3	6.4	8.9
	Female	6.8	4.7	2.3	2.8	3.7

Reviewer Comments

- There was an increased risk for the incidence of application and instillation site reactions with the three highest rotigotine doses (i.e., 1, 2, and 3 mg rotigotine delivered or 2.25, 4.5, and 6.75 mg rotigotine patch content) in females. However, there was an increased risk for the incidence of application and instillation site reactions for the lowest rotigotine dose (0.5 mg delivered or 1.125 mg total patch content) in males.

- There was an increased risk for the incidence of asthenic conditions with the highest rotigotine dose (i.e., 3 mg rotigotine delivered or 6.75 mg rotigotine patch content) and any rotigotine dose in males. However, there was an increased risk for the incidence of asthenic conditions for the lowest rotigotine dose (0.5 mg delivered or 1.125 mg total patch content) in females.

- There was an increased risk for the incidence of fatigue with the highest rotigotine dose (i.e., 3 mg rotigotine delivered or 6.75 mg rotigotine patch content) and any rotigotine dose in males. However, there was an increased risk for the incidence of fatigue for the lowest rotigotine dose (0.5 mg delivered or 1.125 mg total patch content) in females.

- There was an increased risk for the incidence of nervous system disorders with three rotigotine doses (i.e., 0.5, 2, and 3 mg rotigotine delivered or 1.125, 4.5, and 6.75 mg rotigotine patch content) and any rotigotine dose in males.

- There was an increased risk for the incidence of headache with two rotigotine doses (i.e., 0.5, and w mg rotigotine delivered or 1.125, and 4.5 mg rotigotine patch content) and any rotigotine dose in males.

Concomitant Medication (Beta-Blocking Agents) Differences

Advanced Parkinson's Disease

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by concomitant medication during treatment by randomized dose: beta-blocking agents (Pool AS1)

SOC HLT Preferred term	Subgroup	ROT 4mg/24h - Placebo (%)	ROT 8mg/24h - Placebo (%)	ROT 12mg/24h - Placebo (%)	Any ROT - Placebo (%)
Dizziness	Yes	27.1	11.9	7.4	11.8
	No	-5.1	4.4	4.4	2.7

Reviewer Comments

- There was an increased risk for the incidence of dizziness with two rotigotine doses (i.e., 4 and 8 mg rotigotine delivered or 9 and 18 mg rotigotine patch content) and any rotigotine dose in patients who were treated with a concomitant beta-blocker.

Concomitant Medication (Vasodilator/Hypotensive Drug) Differences

Advanced Parkinson's Disease

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by vasodilator/hypotensive medication during treatment by randomized dose (Pool AS1)

SOC HLT Preferred term	Subgroup	ROT 4mg/24h - Placebo (%)	ROT 8mg/24h - Placebo (%)	ROT 12mg/24h - Placebo (%)	Any ROT - Placebo (%)
Application and instillation site reactions	Yes	7.0	24.1	19.0	18.9
	No	-4.7	13.7	23.4	14.5
Oedema peripheral	Yes	-1.2	11.5	15.2	10.8
	No	0.0	3.0	4.9	3.2
Perception disturbances	Yes	0.0	6.3	11.9	7.6
	No	-2.5	0.5	5.7	2.1
Dyskinesia	Yes	-1.2	9.5	10.1	7.8
	No	6.8	3.1	8.8	6.0
Somnolence	Yes	-10.9	9.4	9.4	5.8
	No	-19.0	0.4	-1.9	-3.8
Dizziness	Yes	7.0	13.0	-0.4	6.2
	No	-7.2	2.1	8.0	2.9

Reviewer Comments

- There was an increased risk for the incidence of application and instillation site reactions with two rotigotine doses (i.e., 4 and 8 mg rotigotine delivered or 9 and 18 mg rotigotine patch content) in patients who were treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of peripheral edema with the two highest rotigotine doses (i.e., 8, and 12 mg rotigotine delivered or 18, and 27 mg rotigotine patch content) and any rotigotine dose in patients who were treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of perception disturbances with the two highest rotigotine doses (i.e., 8, and 12 mg rotigotine delivered or 18, and 27 mg rotigotine patch

content) and any rotigotine dose in patients who were treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of dyskinesia with the 8 rotigotine dose (i.e.,18 mg rotigotine patch content) and any rotigotine dose in males. However, there was an increased risk for the incidence of dyskinesia for the lowest rotigotine dose (4 mg delivered or 9 mg total patch content) in patients who were not treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of dizziness with the two rotigotine doses (i.e., 8, and 12 mg rotigotine delivered or 18, and 27 mg rotigotine patch content) and any rotigotine dose in patients who were treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of dyskinesia with two rotigotine doses (i.e., 4 and 8 mg rotigotine delivered and 9 and 18 mg rotigotine patch content) and any rotigotine dose in patients who were treated with a concomitant vasodilator/hypotensive medication. However, there was an increased risk for the incidence of dyskinesia for the lowest rotigotine dose (4 mg delivered or 9 mg total patch content) in patients who were not treated with a concomitant vasodilator/hypotensive medication.

RLS

Summary of treatment effect with a ≥5% difference between any rotigotine dose and placebo in either subgroup for TEAEs by vasodilator/hypotensive medication during treatment by randomized dose (Pool RS1)

SOC HLT Preferred term	Subgroup	ROT 0.5mg/24h – Placebo (%)	ROT 1mg/24h – Placebo (%)	ROT 2mg/24h - Placebo (%)	ROT 3mg/24h - Placebo (%)	Any ROT - Placebo (%)
Nausea	Yes	0.8	10.0	21.5	5.1	11.1
	No	11.4	3.4	9.5	12.6	9.0
Headache	Yes	15.6	5.0	7.2	8.9	8.1
	No	8.0	4.0	6.2	2.9	4.8
Sexual desire disorders	Yes	11.1	6.8	7.9	3.8	7.0
	No	0.1	-0.8	-2.0	0.7	-0.5
Hypertension	Yes	7.4	1.7	4.8	15.4	7.0
	No	1.4	0.0	0.0	0.6	0.4

Reviewer Comments

- There was an increased risk for the incidence of nausea with two rotigotine doses (i.e., 1, and 2 mg rotigotine delivered or 2.25, and 4.5 mg rotigotine patch content) in patients who were treated with a concomitant vasodilator/hypotensive medication. However, there was an increased risk for the incidence of nausea for two other rotigotine doses (i.e., 0.5 and 3 mg delivered or 1.125 and 6.75 mg total patch content) in patients who were not treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of headache with two rotigotine doses (i.e., 0.5, and 3 mg rotigotine delivered or 1.25, and 6.75 mg rotigotine patch content) in patients who were treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of sexual desire disorders with three rotigotine doses (i.e., 0.5, 1, and 2 mg rotigotine delivered or 1.25, 2.25 and 6.75 mg rotigotine patch content) and any rotigotine dose in patients who were treated with a concomitant vasodilator/hypotensive medication.

- There was an increased risk for the incidence of hypertension with two rotigotine doses (i.e., 0.5, and 3 mg rotigotine delivered or 1.25, and 6.75 mg rotigotine patch content) and any rotigotine dose in patients who were treated with a concomitant vasodilator/hypotensive medication.

Concomitant Medication Differences

Reviewer Comments

- Although the sponsor also presented similar analyses of treatment differences of $\geq$ 5.0 % for many other groups of concomitant medications, I did not find any other differences that were notable here.

4 SAFETY UPDATE (SU)

Final Safety Update Rotigotine Advanced Parkinson's Disease and RLS (This is second SU, first SU was 120 Day SU submitted during initial review cycle)

Overview of the Safety Update

This final safety update includes new safety data obtained between the clinical cutoff date of the Supplemental New Drug Application (sNDA) (31 Jan 2007) and 31 Oct 2008, the clinical cutoff for this final safety update. The sources for these new safety data are the open-label (OL) clinical trials in subjects with advanced-stage Parkinson's disease (APD) (SP516, SP650OL, SP833,

SP882, SP908, and SP915) and Restless Legs Syndrome (RLS) (SP710, SP791, and SP793). Adverse event (AE) and exposure data from early-stage Parkinson's disease trials (N=1220 subjects), including data from OL studies (SP512OL, SP513OL, SP788, SP833, SP882, SP908, and SP915) are also included. In addition, updated postmarketing safety information is included .

During the course of the rotigotine clinical development program, criteria for writing narratives have evolved based on feedback from Food and Drug Administration (FDA). Narratives provided in the sNDA for the advanced-stage Parkinson's and RLS indications were based upon the advanced-stage Parkinson's disease pre-NDA Meeting (9 Nov 2006). For this final safety update, narratives are provided for deaths, serious adverse events (SAEs), and AEs leading to discontinuation.

Data within each section are presented first for advanced-stage Parkinson's disease and then for RLS followed by a summary for each indication. Within each indication, data from the OL safety pool (Pools AS2 and RS2 for advanced-stage Parkinson's disease and RLS, respectively) are discussed first, followed by data from the pool of all subjects who were exposed to rotigotine (Pool AS3 and RS3). Where applicable, data from subjects with early-stage Parkinson's disease follow the RLS sections. Pools are described in detail in Section 1.2.3 for advanced-stage Parkinson's disease, Section 1.3.3 for RLS, and Section 1.4.1 for early-stage Parkinson's disease. A total of 1401 rotigotine-treated subjects with advanced-stage Parkinson's and a total of 1309 rotigotine-treated subjects with RLS are included in this final safety update. In subjects with early-stage Parkinson's disease, a total of 1249 subjects were exposed to rotigotine. Overall, 3959 subjects with Parkinson's disease or RLS have been exposed to rotigotine for this final safety update.

The clinical development program for rotigotine in advanced-stage Parkinson's disease consists of 13 clinical trials in Phase 2 and 3, of which 3 were placebo-controlled. Subjects in the 2 Phase 2a trials and the placebo-controlled Phase 2b dose-response trial (SP511) had a maximum exposure to trial medication of 3 months. The exposure to drug in the double-blind portion of the 2 Phase 3 trials was up to 7 months in SP650DB and up to 6 months in SP515. **Open-label extensions of both Phase 3 trials (SP650OL and SP516) are sources of new information for advanced-stage Parkinson's disease in this final safety update. Subjects in the 2 Phase 3b trials (SP824 and SP826) had the opportunity to continue in the OL extension trial SP833. Trial SP833 is also a source of new information for advanced-stage Parkinson's disease in this final safety update. Subjects in 2 additional Phase 3b OL trials (SP908 and SP915) had a maximum exposure to trial medication of up to 28 days and 1 year, respectively. One Phase 4 OL pilot trial (SP882) was conducted in which subjects had a maximum exposure to trial medication of up to 14 days.**

The clinical development program for rotigotine in subjects with RLS consists of 1 Phase 1 trial (SP628 which is not contained in the ISS database), 8 clinical trials in Phase 2 and 3, of which 5 were placebo-controlled. Subjects in the Phase 2a trial (SP666) had a maximum exposure to trial medication of 1 week, whereas in the Phase 2b trial (SP709) the double-blind trial medication exposure was 6 weeks. The exposure to drug in the double-blind portion of the Phase 3 trials, SP790, SP792, and SP794, was up to 7 months. **Open-label extensions of the**

Phase 2b and Phase 3 trials (SP710, SP791, and SP793) are the sources of new information for RLS in this final safety update. The open-label extension of the Phase 2b trial SP710 was ongoing at the time of the clinical cutoff; all other trials were completed.

All individual trials included in the final safety update expressed the rotigotine dose as the total drug load per patch (mg/day) while the proposed marketed doses will be expressed as the dose delivered per 24 hours (nominal dose; mg/24h). Text and in-text tables in the final safety update express the dose as mg/24h, but the supporting statistical tables use the previous format of mg/day. The table below provides the equivalence between these 2 dosing conventions. The dosing conventions will be used jointly as needed for clarity. Doses were converted using the following formula: dose in mg/24h=dose in mg/day divided by 2.25.

Rotigotine dose description

Nominal dose delivered/24 hours (mg/24h)	Total drug content (mg/day)	Patch surface area (cm^2)
0.5	1.125	2.5
1	2.25	5
2	4.5	10
3	6.75	15
4	9	20
6	13.5	30
8	18	40
10	22.5	50
12	27	60
14	31.5	70
16	36	80
18	40.5	90
20	45	100
22	49.5	110
24	54	120

Note: Doses over 8mg/24h (40cm^2 patch) require multiple patches

Overall Summary of Adverse Events

Advanced-stage Parkinson's disease

In this final cumulative analysis, most (85%) subjects in Pool AS2 experienced at least 1 TEAE. Treatment-emergent adverse events with the highest incidence were somnolence (33%), application and instillation site reactions (25%), fall (20%), perception disturbances (15%), and nausea (16%). Results of the final cumulative analysis were very similar to those reported in the sNDA for Pool AS2.

In this final safety update, 333/1006 (33%) rotigotine-treated subjects in Pool AS2 had at least 1 TEAE of severe intensity. Incidences of specific severe TEAEs were low, with the most common being Parkinson's disease (4%), fall (3%), perception disturbances (2%), and dyskinesia (2%). Twelve subjects (1%) in Pool AS2 had a severe application and instillation site reaction.

Almost all TEAEs had a rate of <1 event per 100 person-months in Pool AS2. The only TEAEs with a rate of at least 1 event per 100 person-months were application and instillation site reactions (1.454), fall (1.517), and somnolence (1.823). Given that the incidence of TEAEs remained relatively stable between the sNDA and the final cumulative analysis and that the rates of exposure-adjusted incidence of TEAEs tended to decrease over time suggests that long-term exposure to rotigotine does not appear to be associated with cumulative toxicity in this patient population.

The AE profile observed with Pool AS3 was generally comparable to the one observed with Pool AS2 and consistent with that reported in the sNDA.

Restless Legs Syndrome

In this final cumulative analysis, most (83%) subjects in Pool RS2 experienced at least 1 TEAE. Treatment-emergent adverse events with the highest incidence were application and instillation site reactions (38%) and nausea (11%). The incidence of application and instillation site reactions was comparable among the 4 lower rotigotine doses (range: 30% [0.5mg/24h] to 38% [3mg/24h]) and higher in subjects who received 4mg/24h rotigotine (60%). Results of the final cumulative analysis indicated a slight increase in the number of TEAEs compared to those reported in the sNDA for Pool RS2, which was not unexpected given the extended reporting period. However, exposure-adjusted analysis indicated that the rates of TEAEs did not differ appreciably between the sNDA and the final cumulative data.

In this final safety update, 21% (196/915) of rotigotine-treated subjects in Pool RS2 had at least 1 TEAE of severe intensity. Incidences of severe TEAEs were generally low; the most common severe events were application and instillation site reaction (60/915, 7%), myocardial infarction (1%), asthenic conditions (1%), and nausea (1%).

Almost all TEAEs had a rate of <1 event per 100 person-months in Pool RS2. In all rotigotine treated subjects, the only TEAE with a rate of at least 1 event per 100 person-months was application and instillation site reaction (3.606). Rate of onset of application and instillation site reaction ranged from 2.302 with 4mg/24h rotigotine to 5.278with 1mg/24h rotigotine.

The AE profile observed with Pool RS3 was similar to the one observed with Pool RS2 and consistent with that reported in the sNDA.

Early-stage Parkinson's disease

During this final safety update period, most (71%) of subjects in Pool S3 experienced at least 1 TEAE. TEAEs with the highest incidence were somnolence (12%) and fall (8%). No dose-related trends were observed for incidences of specific TEAEs. No new trends in the incidence of adverse events were observed during this safety update period.

Deaths

Information on deaths that occurred up to the 31 Jan 2007 data cutoff for the sNDA can be found in ISS Section 3.3.

Advanced-stage Parkinson's disease

FSU APD Table 82.3 presents the incidence of events leading to death for Pool AS3 by SOC, HLT, PT, treatment group, and dose of longest duration. Specific information on subjects who died during treatment or the 30-day Safety Follow-Up Period is provided in FSU APD Table 81.1 (by randomized dose) and FSU APD Table 81.2 (overall summary) for Pool AS3. Subjects who died since the data cutoff for the sNDA are listed in FSU APD Table 581.1, and summarized below.

Treatment-emergent deaths in rotigotine-treated subjects that occurred since the cutoff date of the sNDA (Pool AS3)

Trial/subject number	No. days of exposure[a] (relative day of AE onset[b])	Last dose of trial medication	MedDRA Preferred term	Causality (per investigator)
SP516/105707	942 (+4)	rotigotine 8mg/24h	Loss of consciousness	Not related
SP650OL/010309	1743 (1743)	rotigotine 14mg/24h	Pneumonia aspiration	Not related
SP650OL/010502	1704 (1704)	rotigotine 16mg/24h	Cardiac failure congestive	Unlikely
SP650OL/10811	1716 (+9)	rotigotine 6mg/24h	Parkinsons's disease	Unlikely
SP650OL/013206	1311 (1310)	rotigotine 12mg/24h	Cerebrovascular accident	Unlikely
SP516/107601	1029 (1029)	rotigotine 6mg/24h	Cardiovascular disorder	Not related
	1029 (1029)	rotigotine 6mg/24h	Respiratory failure	Not related
SP516/108008	939 (939)	rotigotine 16mg/24h	Myocardial infarction	Possible
SP516/108021	666 (665)	rotigotine 16mg/24h	Cerebral haemorrhage	Not related
SP516/108610	1348 (1312)	rotigotine 16mg/24h	Bronchial carcinoma	Not related
SP516/100604	1328 (1052)	rotigotine 16mg/24h	Parkinson's disease	Not related
SP516/106109	1113 (1113)	rotigotine 16mg/24h	Narcotic intoxication	Not related
SP516/010507	1953 (+12)	rotigotine 16mg/24h	Parkinson's disease	Not related
SP650OL/011001	2283 (2253)	rotigotine 16mg/24h	Non-Hodgkin's lymphoma	Not related
SP650OL/011810	1682 (+22)	rotigotine 10mg/24h	Cardio-respiratory arrest	Not related
	1682 (+22)	rotigotine 10mg/24h	Pneumonia aspiration	Not related
SP650OL/013028	1385 (1385)	rotigotine 14mg/24h	Circulatory collapse	Unlikely
SP650OL/013031	1687 (1687)	rotigotine 4mg/24h	Acute respiratory failure	Unlikely
SP650OL/013111	1564 (1551)	rotigotine 16mg/24h	Acute respiratory distress syndrome	Not related
SP65OL0/014810	1455 (1455)	rotigotine 14mg/24h	Parkinson's disease	Not related
SP650OL/015812	1371 (1369)	rotigotine 16mg/24h	Sepsis	Not related
SP915/012702	323 (323)	rotigotine 8mg/24h	Death	Unlikely

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OL=open-label

a. For subjects originally randomized to placebo, days of exposure only counts exposure to rotigotine during the open-label period.

b. "+" prefixed numbers denote days since last dose; unsigned numbers denote days from randomization.

Data source: FSU APD Table 581.1

Of the 50 deaths reported in the advanced-stage Parkinson's disease program, 2 deaths were considered by the investigator to be attributed to trial medication, 1 death due to circulatory collapse and 1 death due to myocardial infarction.

Of the 19 deaths that occurred since the cutoff date for the sNDA, 1 death was attributed by the investigator to trial medication. Subject SP516/108008 in SP516, an elderly man with a history of heart disease, died of myocardial infarction on (b) (6). The investigator considered the event to be highly probably related to the subject's cardiac disease, but he also assessed the event as possibly related to trial medication.

Restless Legs Syndrome

FSU RLS Table 84 lists subjects in Pool RS3 who died during treatment or the 30-day Safety Follow-Up Period. Subjects who died since the cutoff date for the sNDA are listed in FSU RLS Table 584. Two deaths occurred since the sNDA, as shown below.

Treatment-emergent deaths in rotigotine-treated subjects that occurred since the cutoff date of the sNDA (Pool RS3)

Trial/subject number	No. days of exposure[a] (relative day of AE onset[b])	Dose of trial medication at onset of AE	MedDRA Preferred term	Causality (per investigator)
SP709OL/010703	1562 (1563)	rotigotine 2mg/24h	Myocardial infarction	Not related
SP790OL/018205	572 (575)	rotigotine 2mg/24h	Myocardial infarction	Not related

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OL=open-label

a. For subjects originally randomized to placebo, days of exposure only counts exposure to rotigotine during the open-label period.

b. "+" prefixed numbers denote days since last dose

Data source: FSU RLS Table 584

Narrative Summary for Subject 10703

Subject 10703 was a 59-year-old white post-menopausal female. Her medical history included stomach pain (2003), ischialgia (2003) and hypothyroidism (1968). The subject entered SP709 with idiopathic Restless Legs syndrome and completed the double-blind (DB) phase of the trial. She entered the open-label (OL) phase of the trial (SP710) on 12 Nov 2003 and began dosing with rotigotine 1.125mg/day on the same day and subsequently was treated with 4.5 mg rotigotine for most of the OL extension study..

On 03 Jan 2008, during the Maintenance Period of the OL trial (SP710), the subject experienced myocardial infarction (posterior myocardial infarction) of severe intensity. According to the safety report, an ECG on 31 Dec 2007 had not revealed any pathological findings (results not available). During the course of (b) (6), after initial improvement under antibiotic therapy, the subject experienced a heart attack. Reanimation was not successful, and the subject died. The

investigator reported that the subject did not drop out of the trial before death. The final outcome of the event was reported as fatal on (b) (6) *At the time of the serious AE of myocardial infarction, the subject was taking rotigotine 4.5mg/day and had been at this dose level for 1458 days (total exposure to trial medication 1563 days).*

The patient had multiple ECGs during treatment. Only one ECG (11/17/04) while taking 4.5 mg rotigotine during the OL study had QTc prolongation (QTcB = 477 msecs; QTcF = 445 msecs).

Narrative Summary for Subject 18205

Subject 18205 was a 72-year-old white male. His medical history included angina pectoris (1986) and hypertension (1986). He entered the trial on 15 Nov 2005 with idiopathic Restless Legs Syndrome. The subject was randomized to rotigotine 4.5mg/day on 21 Nov 2005.

On 31 May 2006, during the Taper Period of study SP790, an isolated occurrence of prolonged QTcB (493ms) was recorded. At Baseline (21 Nov 2005), the subject's mean QTc interval was normal, as were all other recorded electrocardiogram (ECG) values. At the time of the prolonged QTc, the subject was taking rotigotine 4.5mg/day and had been at this dose level for 185 days (total exposure to trial medication was 192 days).
There were no other changes in ECG findings, there were no adverse events at the time of the prolonged QTcB, and only 1 laboratory abnormality (glucose 150mg/dL; normal range: 70-120mg/dL) was reported at the time of the prolonged QTcB.

After completing the preceding double-blind (DB) SP790 trial, he entered the open-label (OL) SP791 trial on 09 Jun 2006 and began dosing with rotigotine 2.25mg/day on that same day.

Concomitant medications at the time of the myocardial infarction included candesartan/hydrochlorothiazide 16/12.5mg/day, isosorbide mononitrate 50mg/day, and acetylsalicylic acid 160mg/day. Additional concomitant medications at the time of the myocardial infarction included glibenclamide 1.75mg/day.

The QTcB prolongation was not recorded as an adverse event and was not considered clinically relevant by the investigator. The investigator considered the QTcB abnormality to be related to trial medication.

At the time of the serious adverse event of myocardial infarction, the subject was taking rotigotine 4.5mg/day and had been at this dose level for 359 days (total exposure to trial medication was 566 days).The myocardial infarction was reported as a serious adverse event (categories: results in death, requires inpatient hospitalization or prolongation of existing hospitalization). The myocardial infarction was considered not related to the trial medication by the investigator. The subject took his last dose of study medication on (b) (6) *and was withdrawn from the trial on the same day because of the fatal myocardial infarction.*

Summary of Deaths

Advanced Parkinson's Disease

As of the clinical cutoff (31 Oct 2008) for this final safety update, 50 deaths have been reported in the advanced-stage Parkinson's disease program among the 1407 subjects treated with rotigotine. Of these 50 deaths, 20 occurred since filing the sNDA.

In the cumulative analysis, the most common events that led to death were cerebrovascular accident (5 subjects), myocardial infarction (4 subjects), Parkinson's disease (6 subjects), death/cardiac death (3 subjects), pneumonia aspiration (3 subjects), and sepsis/septic shock (3 subjects). Of the 50 deaths that occurred in Pool AS3, 19 deaths occurred 2 to 75 days after last dose of trial medication (FSU APD Table 81.1). The mortality rate per 100 patient exposure years was 2.08 (FSU APD Table 81.2). In the sNDA, the mortality rate was 1.67 (ISS APD Table 81.2).

RLS

As of the clinical cutoff (31 Oct 2008) for this final safety update, 3 deaths have been reported in the RLS program among the 1309 subjects treated with rotigotine. Of these deaths, 2 occurred since filing the sNDA. Subject 516/108008 died of myocardial infarction on (b) (6) . The investigator assessed both of these deaths as possibly related to trial medication. The remaining death was assessed by the investigator as unlikely or not related to trial medication.

Reviewer Comments

- I note that it is interesting that of the three deaths of RLS patients, the last 2 deaths were due to myocardial infarction. The only other death reported in the original ISS was for a 66 year old white female who died (not related to study medication) as a result of aortic valve replacement after being treated with for 184 days (4.5 mg/day last dose). It is difficult to cite any particular reason to suspect that these 2 myocardial infarctions in RLS patients were related to rotigotine, especially considering that the doses taken by these patients was much lower than those of Parkinson's Disease patients who died.

  In this cumulative safety updates of patients with Parkinson's Disease, there was one death due to myocardial infarction, and 4 other deaths with some cardiac relationship (i.e., cardiac failure congestive, cardiovascular disorder, cardiorespiratory arrest, circulatory collapse). In the cumulative analysis of all Parkinson's Disease deaths, there were 4 deaths with myocardial infarction, and 3 cardiac deaths.

  The sponsor noted that the overall mortality rate per 100 patient exposure years (Parkinson's Disease) was 2.08 as of this most recent Safety Update, and that the mortality rate in the sNDA was 1.67. The sponsor did not report the mortality rate associated with myocardial infarction or cardiac deaths for Parkinson's Disease nor any mortality rate for RLS patients.

- I believe that the mortality rate in both indications should be followed/monitored in future Safety Updates and particularly for deaths related to myocardial infarction and for any cardiac-related cause.

Summary of Other Serious Adverse Events (SAEs)

Advanced-stage Parkinson's disease
In Pool AS2, 38% of all rotigotine-treated subjects with advanced-stage Parkinson's disease had at least 1 SAE. Incidences of specific SAEs were low, with the most common being Parkinson's disease (5%), perception disturbances (2%), and fall (2%). There were 5 (<1%) serious cases of application and instillation site reactions. The SAE profile observed with Pool AS3 was comparable to the one observed with Pool AS2.

Results of the final cumulative analysis were similar to those reported in the sNDA for Pool AS2.

Restless Legs Syndrome
In Pool RS2, 14% of all rotigotine-treated subjects with RLS had at least 1 SAE. Incidences of specific SAEs were low; the only SAEs with an incidence of at least 1% were osteoarthritis (n=14, 2%) and myocardial infarction (n=6, 1%). The SAE profile observed with Pool RS3 was comparable to the one observed with Pool RS2. In Pool RS3, a total of 22/1309 (2%) rotigotine-treated subjects had at least 1 SAE assessed by the investigator as drug-related. Incidences of drug-related SAEs were very low, with the most common being application and instillation site reaction (n=6), nausea (n=2), syncope (n=2), and sleep attacks (n=2). Results of the final cumulative analysis were similar to those reported in the sNDA.

Early-stage Parkinson's disease
During this final safety reporting period, 17% of subjects with early-stage Parkinson's disease experienced at least 1 SAE. Serious adverse events occurring in >2 subjects were Parkinson's disease (6/472, 1%), vascular disorder (6/472, 1%), pneumonia (5/472, 1%), pulmonary embolism (4/472, 1%), contusion (3/472, 1%), femoral neck fracture (3/472, 1%), and osteoarthritis (3/472, 1%).

Summary of Other Significant Adverse Events Leading to Study Discontinuation

Advanced-stage Parkinson's disease
In Pool AS2, 20% of all rotigotine-treated subjects with advanced-stage Parkinson's disease had a TEAE leading to discontinuation of trial medication. Specific TEAEs leading to discontinuation of trial medication in at least 1% of all rotigotine-treated subjects were application and instillation site reactions (3%), perception disturbances (2%), and Parkinson's disease (1%). The profile of TEAE leading to discontinuation of trial medication was similar between Pools AS2 and AS3.

Results of the final cumulative analysis were very similar to those reported in the sNDA.

Restless Legs Syndrome
In Pool RS2, 21% of all rotigotine-treated subjects with RLS had a TEAE leading to discontinuation of trial medication. Specific TEAEs leading to discontinuation of trial medication in ≥1% of all rotigotine-treated subjects were application and instillation site reactions (13%) and nausea (1%). The profile of TEAE leading to discontinuation of trial

medication was similar between Pools RS2 and RS3.

Results of the final cumulative analysis were very similar to those reported in the sNDA.

Early-stage Parkinson's disease
During this final safety update reporting period, overall, 5% of subjects (25/472) in Pool S3 had a TEAE leading to discontinuation of trial medication.

Summary of Adverse Events of Special Interest

Advanced-stage Parkinson's disease
In this final safety update, the following TEAEs of special interest occurred at an incidence of ≥1% in Pool AS2: events suggestive of falls (30%), cardiac arrhythmias (10%), syncope (5%), compulsive behavior (5%), sleep attack/sudden onset of sleep (2%), and valvulopathy (1%). Results from Pool AS3 were similar to those observed in Pool AS2.
Results of the final cumulative analysis were similar to those reported in the sNDA, with the exception of a slight increase in incidence of compulsive behavior in the final cumulative analysis compared to the sNDA.

Restless Legs Syndrome
In Pool RS2, the following TEAEs of special interest occurred at an incidence of ≥1%: events suggestive of falls (8%), cardiac arrhythmias (5%), syncope (2%), compulsive behavior (2%), and sleep attack/sudden onset of sleep (1%). Results from Pool RS3 were similar to those observed in Pool RS2.

Results of the final cumulative analysis were generally comparable to those reported in the sNDA, with the exception of a slight increase in incidence of compulsive behavior in the final cumulative analysis compared to the sNDA.

Summary of Other Adverse Events of Clinical Interest

Advanced-stage Parkinson's disease
Based on final cumulative data, 252 (25%) subjects had a treatment-emergent application and instillation site reaction in Pool AS2. Most cases of application and instillation site reaction were mild or moderate in intensity. Twelve (1%) subjects had a severe event. Five (<1%) subjects had an application and instillation site reaction reported as an SAE. Three percent of subjects discontinued trial medication due to an application and instillation site reaction. The majority of cases of application and instillation site reaction resolved. The cumulative rate of application and instillation site reactions through the cutoff date was 36%. For the subgroup of subjects who had an application and instillation site reaction, median time to first onset was 108 days.

A total of 168 (17%) subjects in Pool AS2 experienced treatment-emergent nausea and vomiting symptoms. Most cases of nausea and vomiting symptoms were mild or moderate in intensity. Twelve (1%) subjects had severe nausea and vomiting symptoms. Two (<1%) subjects had nausea and vomiting symptoms that met the criteria for seriousness. Seven (<1%) subjects discontinued trial medication as a result of nausea and vomiting symptoms.

Other events of clinical interest that occurred in at least 10% of subjects in Pool AS2 included somnolence (33%), edema (15%), perception disturbances (15%), disturbances in initiating and maintaining sleep (13%), dizziness (12%), and dyskinesia (11%). There was one case of treatment-emergent gynecomastia; the event was mild in intensity and did not result in discontinuation of trial medication. There were no cases of neuroleptic malignant syndrome. Most AEs of clinical interest were mild or moderate in intensity, and relatively few subjects discontinued due to these events. Very few other AEs of clinical interest met the criteria for seriousness.

Results from Pool AS3 were generally similar to those observed in Pool AS2. Further, results of the final cumulative analysis were similar to those reported in the sNDA.

Restless Legs Syndrome

Based on final cumulative data, 349 (38%) subjects had a treatment-emergent application and instillation site reaction in Pool RS2. In the analysis by dose of longest duration, the incidence of application and instillation site reactions tended to be higher with the 4mg/24h dose (60%) compared with the lower doses (range: 30% to 38%). A consistent dose-related trend was observed in the incidence of application and instillation site reactions by dose at onset: 5%, 10%, 16%, 22%, and 37% with the 0.5mg/24h, 1mg/24h, 2mg/24h, 3mg/24h, and 4mg/24h doses at onset, respectively. Most cases of application and instillation site reaction were mild or moderate in intensity. A total of 60 (7%) subjects had a severe event. No subjects in Pool RS2 had an application and instillation site reaction reported as an SAE. A total of 117 (13%) subjects discontinued trial medication due to an application and instillation site reaction. The majority of cases of application and instillation site reaction resolved. The cumulative rate of application and instillation site reactions through the cutoff date was 55%. For the subgroup of subjects who had an application and instillation site reaction, median time to first onset was 208 days.

A total of 116 (13%) subjects in Pool RS2 experienced treatment-emergent nausea and vomiting symptoms. Most cases of nausea and vomiting symptoms were mild or moderate in intensity. Eight (1%) subjects had severe nausea and vomiting symptoms. Two (<1%) subjects had nausea and vomiting symptoms that met the criteria for seriousness. Eleven (1%) subjects discontinued trial medication as a result of nausea and vomiting symptoms.

Other events of clinical interest that occurred in at least 5% of subjects in Pool RS2 were dizziness and somnolence (6% each). There was 1 case of gynecomastia and no cases of neuroleptic malignant syndrome. Most AEs of clinical interest were mild or moderate in intensity, and relatively few subjects discontinued due to these events. Very few other AEs of clinical interest met the criteria for seriousness.

Results from Pool RS3 were generally similar to those observed in Pool RS2. Further, results of the final cumulative analysis were similar to those reported in the sNDA.

POSTMARKETING DATA

Rotigotine has been approved in the US for the treatment of early-stage Parkinson's disease since May 2007. Rotigotine has been approved in Europe for the treatment of early-stage Parkinson's disease since Feb 2006, for advanced-stage Parkinson's disease since Jan 2007, and for

idiopathic RLS since Aug 2008. Information on AEs and SAEs from spontaneous reports and from ongoing postmarketing observational (noninterventional) surveillance up to the cutoff date of 15 Feb 2009 is summarized in this section. At the time of the cutoff date of 15 Feb 2009, the estimated total exposure to rotigotine was 73,606 patient-years. All AEs summarized in this section were coded using MedDRA Version 12.0.

Safety data from spontaneous reports

A summary of all spontaneous AEs and SAEs is presented in the Safety Listing of Spontaneous Reports of All Adverse Events–Postmarketing. Each listing provides information on individual cases and a summary of events by SOC and PT.

Overall, there were a total of 2214 cases. Of these, 261 cases were serious, and 1953 cases were non-serious. Of the 261 serious cases, there were a total of 506 SAEs and 155 nonserious AEs. Of the 1953 nonserious cases, there were a total of 4369 nonserious AEs.

Spontaneous AE reports (nonserious and serious) are summarized in the table below by SOC. By definition, all AEs were considered related to treatment with rotigotine.

Spontaneous reports of postmarketing adverse events by SOC

System Organ Class	Number of AEs
Total AEs (nonserious and serious)	5030
General disorders and administration site conditions	2011
Application and instillation site reactions[a]	1082
Nervous system disorders	717
Skin and subcutaneous tissue disorders	609
Psychiatric disorders	465
Gastrointestinal disorders	293
Musculoskeletal and connective tissue disorders	188
Injury, poisoning and procedural complications	166
Investigations	112
Surgical and medical procedures	99
Vascular disorders	69
Eye disorders	60
Respiratory, thoracic and mediastinal disorders	47
Cardiac disorders	39
Metabolism and nutrition disorders	27
Renal and urinary disorders	26
Infections and infestations	24
Immune system disorders	20
Social circumstances	17
Ear and labyrinth disorders	13
Reproductive system and breast disorders	11
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6
Hepatobiliary disorders	5
Blood and lymphatic system disorders	3
Endocrine disorders	2

AE=adverse event

a. MedDRA high-level term

b. MedDRA preferred term

Note: Adverse events were coded using MedDRA Version 12.0.

Data source: Safety Listing of Spontaneous Reports of All Adverse Events–Postmarketing

Spontaneous AEs were reported primarily (in descending order) in the general disorders and

administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, psychiatric disorders, and gastrointestinal disorders SOCs. **The most common PTs reported across all SOCs were application site erythema (282 reports), application site reaction (250 reports), application site pruritus (206 reports), nausea (135 reports), tremor (134 reports), dizziness (113 reports), and erythema (104 reports).**

All spontaneous SAE reports are summarized in the table below by SOC.

Spontaneous reports of postmarketing serious adverse events by SOC

System Organ Class	Number of SAEs
Total SAEs	506
Blood and lymphatic system disorders	2
Cardiac disorders	25
Ear and labyrinth disorders	2
Endocrine disorders	1
Eye disorders	7
Gastrointestinal disorders	32
General disorders and administration site conditions[a]	112[a]
Hepatobiliary disorders	4
Immune system disorders	2
Infections and infestations	7
Injury, poisoning and procedural complications	28
Investigations	22
Metabolism and nutrition disorders	4
Musculoskeletal and connective tissue disorders	18
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6
Nervous system disorders	86
Psychiatric disorders	80
Renal and urinary disorders	9
Respiratory, thoracic and mediastinal disorders	7
Skin and subcutaneous tissue disorders	31
Social circumstances	1
Surgical and medical procedures	9
Vascular disorders	21

SAE=serious adverse event

a. These SAEs include the following reports of preferred terms pertaining to the high level term of application and instillation site reactions: 14 reports of application site erythema; 8 reports of application site pruritus; 7 reports of application site reaction; 4 reports of application site vesicles; 3 reports each of application site exfoliation, application site hypersensitivity, application site pain, and application site rash; 2 reports each of application site discharge, application site eczema, and application site irritation; and 1 report each of application site bleeding, application site burn, application site dermatitis, application site swelling, and application site ulcer.

Note: Adverse events were coded using MedDRA Version 12.0.

Data source: Safety Listing of Spontaneous Reports of Serious Adverse Events–Postmarketing

Of the 506 SAEs reported, the following SAEs were reported more than twice (PTs): visual hallucination (16 reports), application site erythema (14 reports), fall (13 reports), hallucination (13 reports), allergic dermatitis (11 reports), nausea (10 reports), dizziness (9 reports), Parkinson's Disease (9 reports), applicaton site pruritus (8 reports), syncope (8 reports), application site reaction (7 reports), atrial fibrillation (7 reports), tremor (6 reports), confusional state (5 reports), diarrhea (5 reports), fatigue (5 reports), hypertension (5 reports), movement disorder (5 reports), sleep attacks (5 reports), vomiting (5 reports), application site vesicles (4 reports), edema peripheral (4 reports), hypotension (4 reports), renal failure (4 reports), somnolence (4 reports), suicidal ideation (4 reports), akinesia (3 reports), anxiety (3 reports), application site exfoliation (3 reports), application site hypersensitivity (3 reports), application site rash (3 reports), application site pain (3 reports), back pain (3 reports), blood pressure increased (3 reports), circulatory collapse (3 reports), constipation (3 reports), convulsion (3 reports), dyskinesia (3 reports), dyspnea (3 reports), erythema (3 reports), loss of consciousness (3 reports), mobility decreased (3 reports), muscle spasm (3 reports), myocardial infarction (3 reports), pain in extremity (3 reports), pneumonia (3 reports), psychotic disorder (3 reports), pyrexia (3 reports), rash (3 reports), and restlessness (3 reports).

Nine deaths were reported from spontaneous sources by the data cutoff of 15 Feb 2009. With the exception of pneumonia, which was reported with an outcome of fatal in 2 patients, no other PT had an outcome of fatal in more than 1 patient.

Safety Data from Postmarketing Observational Studies

A summary of all AEs and SAEs reported during ongoing postmarketing observational surveillance is presented in the Safety Listing of All Adverse Events from Ongoing Postmarketing Studies. Each listing provides information on individual cases and a summary of events by SOC and PT. These 5 ongoing studies have not been integrated in the 120-day safety database.

Across all postmarketing observations studiers and the named patient programs, there were a total of 320 cases. Of these, 92 cases were serious, and 228 cases were non-serious. Of the 92 serious cases, there were a total of 115 SAEs and 36 non-serious AEs. Of the 228 non-serious cases, there were a total of 422 non-serious AEs.

All AEs (non-serious and serious) reported during postmarketing surveillance are summarized in the table below by SOC. By definition, all AEs were considered related to treatment with rotigotine.

Summary of Postmarketing Data

The overall AE profile based on spontaneous reports and the postmarketing observational (noninterventional) studies is consistent with the profile observed in the pooled analysis of data collected during interventional trials. The most commonly reported events from either source were associated with local skin reactions to application of the patch (application site erythema, application site pruritus, erythema, and pruritus), gastrointestinal effects (primarily nausea), nervous system effects (dizziness, tremor), and psychiatric disorders.

Of note, a total of 26 sleep attacks were reported (17 spontaneous AE reports [5 of which were SAEs] and 9 nonserious reports in the postmarketing surveillance).

Reviewer Comments

- **My review of the sponsor's Safety Update does not suggest any substantial or notable change in the safety profile for the label for rotigotine treatment of early Parkinson's Disease nor for the safety profile characterized for advanced Parkinson's Disease and RLS based upon our safety review of the sponsor's original NDA submission for these indications.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS

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

/s/

LEONARD P KAPCALA
04/20/2010

GERALD D PODSKALNY
04/21/2010

CLINICAL REVIEW OF EFFICACY

Application Type	NDA
Submission Number	21829
Submission Code	SE1 001
Letter Date	10/05/07
Stamp Date	10/11/07
PDUFA Goal Date	11/11/08
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	11/26/08
Established Name	rotigotine
(Proposed) Trade Name	Neupro
Therapeutic Class	Dopaminergic agonist
Applicant	UCB Pharma/Schwarz Pharma
Priority Designation	S
Formulation	Patch
Dosing Regimen	Once daily
Indication	Adjunctive Treatment of Advanced Parkinson's Disease
Intended Population	Advanced Parkinson's Disease

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend a complete response action for rotigotine for advanced Parkinson's Disease based upon :

- the unacceptable fact that there is crystal formation with the present patch;
- that additional safety analyses need to be completed and submitted :

    - Conduct analyses of TEAEs that might possibly reflect events (regardless of level of severity) suggestive of the occurrence of hypotension/orthostatic hypotension/postural dizziness for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792).

    - Conduct subgroup analyses of TEAEs occurring in certain subgroups (i.e., age, gender, concomitant medication such as vasodilator/hypotensive agents) for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792). In each of these requested subgroup analyses, the sponsor should compare the incidence of TEAEs in each pool's subgroup among each randomized rotigotine group and any rotigotine group with that of the respective placebo group in each pool's subgroup. The sponsor's subgroup analyses of TEAEs **only** considered the frequency of TEAEs for rotigotine treatment relative to each subgroup comparison and did not consider the frequency for placebo treatment in each subgroup analysis. Although the incidence of a certain TEAE such as vomiting could appear to be increased for females (vs males) if the frequency was 20 % for rotigotine treatment in females and 10 % for rotigotine treatment in males. However, if the incidence of vomiting with placebo treatment was 20 % and 10 % respectively, for females and males, there would not be any suggestion of an increased risk for vomiting in females.

    - Review CRFs to see if more specific characterizations can be made for certain vague, nebulous preferred terms (PTs) such as "visual disorder," "visual disturbance," and "sleep disorder." If a more specific characterization has been made after this review, please submit the new incidence analyses for the PTs that have been altered. Please submit this for the TEAE analyses for the whole study period, the titration period, the maintenance period, TEAE persisting from titration into maintenance period according to treatment/randomized rotigotine dose for studies 650, and 790, and 792 separately, and for pools AS1 and RS1

An integrated safety review was jointly conducted by Dr. Dave Podskalny and me regarding advanced Parkinson's Disease and RLS treatment indications. Certain safety sections were reviewed by each of us. Our joint safety review is presented in a separate Integrated Clinical Review of Safety (see this document).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

I agree with the sponsor's risk management plan that is primarily based upon providing known toxicity and safety information in the label/package insert and conducting routine pharmacovigilance and monitoring results from ongoing and future clinical trials with rotigotine.

1.2.2 Required Phase 4 Commitments

A dose-response study should be conducted to characterize the rotigotine dose-response for efficacy and safety for advanced Parkinson's Disease.

1.2.3 Other Phase 4 Requests

- Not applicable to clinical review for advanced Parkinson's Disease other than as noted above in section 1.2.2.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

A total of 1476 subjects with advanced-stage Parkinson's disease (1217 subjects treated with rotigotine) are included in this submission. The clinical development program for rotigotine in advanced-stage Parkinson's disease consists of 10 clinical trials in Phase 2 and 3, of which 3 were placebo-controlled and considered to be "pivotal" trials. Subjects in the 2 Phase 2a trials and the placebo-controlled Phase 2b dose-response trial (study 511) had a maximum exposure to trial medication (treatment with up to 27 mg/day rotigotine) and) of 3 months. The exposure to drug in the double-blind (DB) portion of the 2 Phase 3 trials was up to 7 months in SP650DB (treatment with up to 27 mg rotigotine) and up to 6 months in SP515 (treatment with up to 36 mg/day rotigotine) and. Open-label (OL) extensions of both Phase 3 trials (SP650OL and SP516) are ongoing and all subjects have been enrolled. Subjects in the 2 Phase 3b trials (SP824 and SP826) had the opportunity to continue in the ongoing open-label extension trial SP833.

One double-blind, placebo and moxifloxacin-controlled Phase 1 trial was also conducted in advanced-stage Parkinson's disease subjects to investigate the effect of rotigotine on the QT/QTc-interval (SP864). Subjects in this trial had a maximum exposure to rotigotine (treatment with up to 54 mg/day) and of 6 weeks followed by a 10-day De-escalation period.

1.3.2 Efficacy

Rotigotine is effective treatment of advanced Parkinson's Disease at doses ≥ 18 mg/day patch content (i.e., 8 mg delivered dose) based upon results of studies 650 and 515. The only recommended dose of rotigotine at this time is 18 mg /day because the dose-response study (650) showed that there was no additional clinical benefit of a higher dose (i.e., 27 mg/day). More specifically, reduced efficacy for the primary efficacy endpoint with the 27 mg/day dose (vs the 18 mg/day dose) was observed and there was increased toxicity at the 27 mg/day dose.

1.3.3 Safety

The overall safety profile for rotigotine for advanced Parkinson's Disease is generally similar as that observed in the clinical development program for early Parkinson's Disease. I did not find any unique toxicities or safety issues in the clinical development program for advanced Parkinson's Disease compared to those that were characterized and described in the label for rotigotine treatment of early-stage Parkinson's Disease.

1.3.4 Dosing Regimen and Administration

Rotigotine is applied once a day to the skin. The application site should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days and should not be placed on skin that is oily, irritated, or damaged, or where it will be rubbed by tight clothing. The system should be pressed firmly in place for 20 to 30 seconds, making sure there is good contact, especially around the edges. The prescribed dose may be achieved using single or multiple patches.

(b) (4)

1.3.5 Drug-Drug Interactions

The influence of rotigotine on oral contraceptives (i.e., ethinyl estradiol-Nordette, levonorgestrel-Nordette), and on omeprazole were investigated. The conclusions of our Clinical Pharmacology review is that no dose adjustment of rotigotine is necessary.

The Clinical Pharmacology review noted that the Clinical Pharmacology review for the original NDA submission for rotigotine for treatment of early Parkinson's Disease noted :

(b) (4)

The sponsor has apparently not made attempts to address this in the Advanced Parkinson's supplemental NDA for rotigotine patches. However, it is also not clear that a DNP recommendation to address these drug-drug interactions has ever been communicated to the sponsor.

1.3.6 Special Populations

There was no clear effect of subgroup/special populations with respect to efficacy of rotigotine.

The safety analyses need to be redone (see section 1.1 above) to explore possible effects of subgroup/special populations on the safety of rotigotine.

2 INTRODUCTION AND BACKGROUND

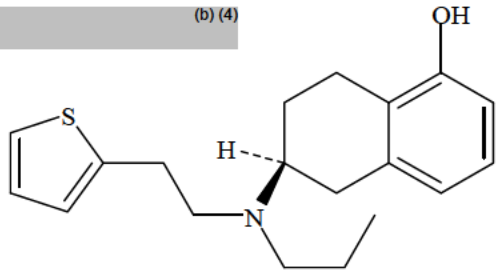
2.1 Product Information

a) Proprietary Name: Neupro
b) Non-Proprietary Name (USAN): rotigotine
c) Code Name/#: SPM 962

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

(b) (4)

$C_{19}H_{25}NOS$ Formula Weight (b) (4)



Neupro (rotigotine transdermal system) is an adhesive patch available in four strengths consisting of three layers. The first layer, the backing film, is a flexible, beige to light brown colored backing film, imprinted with identification. The second layer is the drug matrix. The drug matrix consists of (b) (4) of povidone and rotigotine with (b) (4), ascorbyl palmitate and *dl*-α-tocopherol (b) (4) dispersed in a blend of two grades of silicone adhesive. The third layer is a protective (b) (4) that consists of a (b) (4) that is coated on one side with a fluoro-polymer. The fluoro-polymer contacts the drug/adhesive matrix. The patch is applied to the skin of the patient (thighs, abdomen or upper arms) once daily at approximately the same time. (The liner is removed and the new patch is placed in a location different from the previous patch that is removed.) The patches are packaged in (b) (4) pouches. (b) (4) (b) (4) (b) (4) (b) (4)

The drug substance content of the patch exceeds the delivered dose. The dose is proportional to the area of the patch. The composition of the drug/adhesive matrix is identical for all strengths. The relationship amongst variables such as drug delivered, drug content of patch, and patch size is shown below in the following table.

Rotigotine dose equivalence

Dose delivered/24 hours (mg/24h)	Drug load (mg/day)	Patch surface area (cm^2)
0.5	1.125	2.5
1	2.25	5
2	4.5	10
3	6.75	15
4	9	20
6	13.5	30
8	18	40
10	22.5	50
12	27	60
14	31.5	70
16	36	80
18	40.5	90
20	45	100
22	49.5	110
24	54	120

Note: Doses over 8mg/24h (40cm^2 patch) require multiple patches

Square rotigotine patches in three strengths containing 4.5, 9.0 or 13.5 mg rotigotine and providing nominal delivery to the skin of 2, 4 or 6 mg of rotigotine per day have been authorized in the US for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease (Neupro®). A fourth strength containing 18 mg rotigotine corresponding to a nominal delivery of 8 mg per day has been used for clinical trials and stability studies. The quantitative composition per cm^2 is identical for all strengths. The different strengths correspond to patch 40 cm^2, respectively.

The proposed two new strengths of rotigotine patches contain 2.25 and 6.75 mg rotigotine for treatment of RLS and provide nominal delivery to the skin of 1 and 3 mg of rotigotine per day, respectively. The quantitative composition per area is identical for all strengths and is the same as for the authorized rotigotine patches. The two new strengths correspond to patch sizes of 5 and 15 cm^2.

2.2 Currently Available Treatment for Indications

Levodopa (LD) and Compounds Prolonging the Effects of LD

In the mid-1960's, it was discovered that Parkinson's disease was caused by a deficit of dopamine in the brain. Subsequently, the discovery that levodopa (LD), an amino acid precursor to dopamine, was able to replenish the depleted neural dopamine and greatly ameliorate the symptoms of Parkinson's disease has been considered a major advancement in medical treatment. These findings revolutionized the management of Parkinson's disease. Subsequently, many other therapeutic advances have been made that further enhanced the management of Parkinson's disease. These advances included the introduction of : 1) peripheral dopa decarboxylase inhibitors (DDI) such as carbidopa (approved in U.S.) and benzerazide (used outside the U.S.); 2) catecholamine-O-methyl transferase (COMT) inhibitors (e.g. entacapone and tolcapone); and 3) monoamine oxidase-B inhibitors (MAO-B inhibitors), selegiline is the only MAO-B inhibitor approved for Parkinson's Disease in the U.S. All of these drugs are considered to prolong the half-life of endogenous and exogenous LD and/or dopamine and, thus, prolong the action of dopamine at the receptor.

LD has been the most important drug treatment of Parkinson's disease for more than 3 decades. However, chronic LD therapy is associated with the development of adverse effects in the majority of patients. These include motor fluctuations, dyskinesias, and neuropsychiatric problems. The extent to which these symptoms represent progression of the disease and how much they may relate to LD therapy is not known. Recent evidence, however, suggests treatment with agonists may delay the onset of dyskinesia. Other clinical features (e.g. "freezing" and dementia) develop with the progression of the disease and do not respond to LD. Gradually, after several years of LD therapy, the duration of therapeutic benefit (i.e. "on" period) from LD progressively shortens, and the lack of therapeutic benefit (i.e. "off" period) is prolonged. During the early (first few) years, motor fluctuations are predictably associated with the dosing time of LD. However, as the motor fluctuations become more troublesome, some occurrences of motor fluctuations become less predictable in their timing in relationship to LD intake, especially "freezing-in-place." Dyskinesias also are commonly associated with LD therapy. Initially the dyskinesias are mild and not disabling but usually progress to become severely disabling. The incidence and severity of the dyskinesias are believed to increase not only with the duration of LD therapy but also with the daily dose. Although the pathophysiological mechanism responsible for the development of these motor complications in patients chronically treated with LD is not considered to be known, the pulsatile stimulation of dopamine receptors resulting from administration of several daily doses of LD and the increase of oxidative stress has been implicated by several researchers as possibly responsible.

Amantadine

The antiparkinsonian effects of amantadine were discovered almost 35 years ago, when a patient with Parkinson's disease took this drug as influenza A prophylaxis. The mechanism of action of amantadine in Parkinson's disease is not clear, but much evidence suggests that its effects are mediated through the dopamine system and additionally, through the inhibition of N-methyl-D-aspartate (NMDA) receptors. Amantadine has been used both in early-stage Parkinson's disease as monotherapy and as adjunctive therapy to LD in advanced-stage disease. Gastrointestinal

discomfort, nausea, sleep disturbance, hallucinations, and nervousness are frequent side effects of amantadine.

Anticholinergics

Anticholinergics were introduced in treatment of post-encephalitic parkinsonism and idiopathic Parkinson's disease in the mid- to late-1920s. Their beneficial effects are mediated by blockade of the central nervous system (CNS) muscarinic acetylcholine receptors. Anticholinergics are used as monotherapy in untreated, early-stage Parkinson's disease and as adjunct therapy in patients already on other therapies. These medications appear to provide the most benefit with rigidity and tremor. Peripheral side effects include dry mouth, blurred vision, and constipation, whereas central side effects include dizziness, confusion, memory loss, hallucinations, and dyskinesia. These adverse events are more frequent in the elderly patients

Monoamine Oxidase Inhibitors

Monoamine oxidases (MAO; isozymes A and B) are intracellular enzymes that play a role in the catabolism of neuroactive amines such as dopamine; inhibitors of the enzyme provide benefit in Parkinson's disease. The most widely used compound in this group for treatment of Parkinson's disease is selegiline, a selective, irreversible inhibitor of MAO B. Selegiline monotherapy provides modest symptomatic benefit in early-stage Parkinson's disease and allows symptomatic control with lower LD doses in advanced stages of Parkinson's disease. The most frequent side effects are increase in dyskinesia, nausea, dizziness, dryness of mouth, sleep disturbances, confusion, anxiety, hallucinations, and orthostatic hypotension.

Dopaminergic Agonists

In comparison with LD, dopaminergic agonists selectively interact with specific dopaminergic and non-dopaminergic receptor subtypes. During the past several years, considerable evidence suggests that motor fluctuations and dyskinesias may be more related to the duration of LD therapy than to disease progression. Therefore, newly introduced oral dopaminergic agonists have received widespread clinical acceptance because they can not only delay the initiation of LD therapy, but also because their use might delay progression of the disease and the onset of motor complications. A survey of the available scientific literature and the current market suggests that these dopamine agonists are gaining acceptance as the drug of choice not only for advanced-stage, idiopathic Parkinson's disease but also for the initial treatment of drug treatment-naïve Parkinson patients. Taking these findings into account, guidelines published in the American Academy of Neurology journal, Neurology, suggest the use of dopaminergic agonists as a possible first-line treatment over LD in Parkinson's disease. This is a change from earlier therapeutic concepts, which were primarily based on the use of LD.

In general, the non-ergolinic compounds pramipexole and ropinirole are relatively selective in stimulating D_2 and D_3 dopaminergic receptor subtypes and have a better side effect profile than the ergolinic dopamine agonists such as bromocriptine (approved for Parkinson's Disease in U.S), pergolide (approved for Parkinson's Disease in U.S), lisuride, and cabergoline. Both

ergot and non-ergot dopamine agonists share a variety of peripheral and central adverse affects. The most common "peripheral" dopaminergic adverse events are nausea, vomiting and orthostatic hypotension. Central dopaminergic adverse events are dominated by psychiatric symptoms, similar to LD. They include mood disturbances (such as depression, irritability, euphoria, and hypomania), inappropriate sexual behavior, hallucinations, delusions, agitation, confusion, and paranoid psychosis. Other reactions, which are common to all dopamine agonists are peripheral edema and reduction of anterior pituitary hormone secretion, particularly prolactin. Ergot derivatives are associated with pleuropulmonary, cardiac (pericardial and particularly valvular), and retroperitoneal inflammatory-fibrotic pathology. The non-ergolinics, pramipexole and ropinirole, are generally well tolerated.

Sponsor's Rationale for Treatment with Rotigotine

The currently marketed non-ergolinic dopamine agonists pramipexole and ropinirole are relatively short-acting, and, consequently, patients take multiple oral doses throughout the day. Oral dopamineric agonists approved for Parkinson's disease in various markets have generally not yielded ideal, stable 24-hour blood levels. The daily "peak and trough" blood levels produced by multiple daily doses of an oral agonist result in a fluctuating stimulation of the dopaminergic neurons. This fluctuation may contribute to the pathogenesis of the motor complications in Parkinson's disease. Preclinical studies and clinical trials using continuous intravenous or subcutaneous drug administration support this hypothesis, but these routes of administration are not practical for daily routine clinical use. To date, only limited methods of chronic, 24-hour drug delivery of a dopaminergic agonist are available and none is approved in the U.S. One is the invasive treatment with subcutaneous apomorphine pumps, which is inconvenient for patients. The other option is the use of the ergolinic compound cabergoline; however, both compounds are only available in a limited number of countries and have the disadvantage of possible ergolinic side effects. Subcutaneous prn injection of apomorphine, a dopaminergic agonist, is also used throughout the world (including the U.S.) as treatment for acute "rescue" for "off" periods

Rotigotine is a non-ergolinic $D_3/D_2/D_1$ dopamine agonist. Although the sponsor proposes that the therapeutic benefit of rotigotine occurs via the simultaneous activation of the D_3, D_2, and D_1 receptors of the caudate-putamen in the brain, the precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown. The sponsor notes that this simultaneous activation of receptors is considered to have advantages over the activation of individual dopamine receptors with the modulatory role of the D_3 receptor being demonstrated in a recent review. Rotigotine has a high in vitro affinity at all dopamine receptor subtypes which is particularly high at the D_3 receptor (K_i 0.71nM), about 10-fold less at the D_2, (i.e. less potent), and about 100-fold less at the D_1 receptor. Rotigotine also has high intrinsic (agonistic) activity on all dopamine receptor subtypes which, again, is particularly high for the D_3 subtype. The very high in vitro activity is reflected in a very high in vivo efficacy with an estimated minimum effective dose of 10µg/kg in MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-hemilesioned monkeys. There is also evidence that rotigotine has antagonistic activity at α_2 adrenergic receptors. Considering that activation of α_2 adrenergic receptors (e.g. as occurs with clonidine treatment) lowers blood pressure, presumably by inhibiting adrenergic activation

via activation of presynaptic α_2 adrenergic receptors that inhibit adrenergic output, it is conceivable that this pharmacological activity could result in increased blood pressure.

Rotigotine effectively improved motor deficits and disability in animal models of Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered transdermally**.** Rotigotine is intended to be administered continuously using a transdermal delivery system. Once daily application of Neupro produces relatively continuous rotigotine plasma levels. In animal models of Parkinson's disease the presence of continuous plasma levels of dopamine agonists, including rotigotine, resulted in a lower incidence of dyskinesias compared to pulsatile plasma levels produced by intermittent administration.

The sponsor considers that rotigotine is an ideal candidate for delivery via a transdermal patch. A transdermal delivery system provides a vehicle to non-invasively administer a dopamine agonist like rotigotine in a more continuous fashion. Schwarz Biosciences, Inc. and Schwarz Biosciences GmbH, affiliates of Schwarz Pharma, have undertaken the development of rotigotine (a new chemical entity) in the United States (U.S.) and Europe to provide sustained drug delivery that may provide more continuous plasma concentrations of a dopaminergic agonist (compared to orally administered drugs) with once daily dosing for the treatment of patients with early- and advanced-stage Parkinson's disease and Restless Legs syndrome.

2.3 Availability of Proposed Active Ingredient in the United States

Rotigotine has been approved (2/06) by EMEA for treatment of early Parkinson's Disease. Responder analyses were the primary statistical analyses for the primary efficacy endpoint for EMEA instead of the change from baseline that was the primary statistical analysis for the Agency.

Rotigotine was approved by the Agency for treatment of patients with early-stage Parkinson's Disease on 5/9/07 for doses ranging from 4.5 to 13.5 mg total drug patch content.

However, rotigotine has been voluntarily withdrawn from the U.S. market because of CMC problems with crystal formation of the rotigotine patch during storage and the sponsor's inability to convince the Agency that appropriate, clinically effective treatment is being provided by these patches with crystals.

2.4 Important Issues With Pharmacologically Related Products

Issues of significant concern, particularly for safety, for dopaminergic agonists (and essentially all drug increasing dopaminergic tone) include hypotension/orthostatic hypotension, falls, dizziness/light-headedness, nausea/vomiting, somnolence/sleep attacks, melanoma, retinal toxicity (particularly based upon animal toxicology results), pathological gambling, and hypersexuality.

2.5 Presubmission Regulatory Activity

The sponsor had a Pre-NDA meeting with the DNP on 11/9/06 to plan this NDA submission for advanced Parkinson's Disease and RLS. All relevant issues were considered for all review disciplines. Many clinical recommendations were made with regard to the content and format for efficacy and safety analyses for both indications. It is worthy of note that this reviewed attended this Pre-NDA meeting and provide recommendations for many of the analyses.

2.6 Other Relevant Background Information

The only other relevant background information worthy of discussion here is that rotigotine has been approved in Europe for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy and as adjunctive therapy with levodopa for advanced-stage Parkinson's disease.

The following press release (6/4/08) was noted on the EMEA website :

"The European Medicines Agency (EMEA) has recommended the immediate implementation of changes to the product information for Neupro (rotigotine), from Schwarz Pharma Ltd, stating that it must be stored in a refrigerator (at a temperature of between 2ºC and 8ºC). The new storage conditions are intended to reduce the possible occurrence of crystallisation of the active substance which has been reported in patches of Neupro."

The status of marketing of rotigotine for treatment of Parkinson's Disease globally is as shown below here according to a communication from the sponsor on 11/13/08.

(b) (4)

(b) (4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The following comments and recommendations have been made by the Chemistry (i.e., CMC reviewer), Julia C. Pinto, Ph.D., Chemist.

Advanced Parkinson's Disease

. **Comments:** This Prior Approval supplement provides for a new indication, for use of Neupro® in the treatment of Advanced Stage Parkinson's Disease and for approval of the 8mg/40cm^2 dosage. This dosage system was approved in the original submission of the NDA and reviewed by D. Claffey,Ph.D., (see CMC Reviews 1, 2 and 3, February 2006). However, it was not marketed at the time of approval. All batch data, stability data, specifications and analytical methods are referenced to the original submission. There is no additional data or changes to the CMC data. The specifications (shown below) for the 8mg /40cm^2 transdermal patch are as approved in the original submission.

Evaluation and Recommendations: Inadequate. *While the CMC data supports the addition of the 8mg/40cm^2 Neupro® patch, recent concerns of crystallization of the drug substance on the patch has caused the drug product to be withdrawn from the market. Therefore, from the CMC standpoint, it is recommended to not approve this supplement, pending resolution of the crystallization problem.*

Restless Leg Syndrome (RLS)

. **Comments:** This Prior Approval supplement provides for a new indication, for use of Neupro® in the treatment of Restless Leg Syndrome and for addition of two new dosage strengths, 2.25mg/5cm^2 and 6.75mg/15cm^2 patches. The rotigotine patches strengths proposed to treat RLS, are 5/10/15 cm^2 with a declared drug content of 2.25/4.5/6.75mg of rotigotine base respectively. Batch formulation, release data, specifications and stability data are provided in support to the two new strengths.

Evaluation and Recommendations: Inadequate. *Batch release data and stability data support the new proposed strengths 2.25mg/5cm^2 and 6.75mg/15cm^2. All data on* (b) (4) *batches is within approved specifications. No changes are proposed to the manufacturing method, specifications and container/closure system, from those approved in the original submission and reviewed by D.Claffey, Ph.D. (CMC reviews 1 to 3, February 2006). While the CMC data supports the addition of the* 2.25mg/5cm^2 and 6.75mg/15cm^2 *Neupro® patches, recent concerns of crystallization of the drug substance on the patch has caused the drug product to be withdrawn*

from the market. Therefore, from the CMC standpoint, it is recommended to not approve this supplement, pending resolution of the crystallization problem.

3.2 Animal Pharmacology/Toxicology

Pharmacology

The sponsor submitted several pharmacology studies seeking insight into the pathophysiology of dyskinesia and the potential role of rotigotine.

Toxicology

The sponsor submitted the following toxicology studies and key study findings from a draft review by Dr. Terry Peters (Pharmacologist/Toxicologist) is provided.

Study title: **Rotigotine: A subcutaneous study of embryo-fetal development in the mouse**

Sponsor's conclusion : Although maternal toxicity was evident at all dose levels, there was no adverse foetal toxicity, as lower foetal weights were due to lower maternal bodyweight gains. Therefore, the no-observed-adverse-effect-level for embryo-foetal development was considered to be 90 mg/kg/day.

Reviewer's (Dr. Peters) Key study findings: In this subcutaneous study in mice with rotigotine at 10, 30 or 90 mg/kg/d, maternal toxicity was found at all dose levels (decreased body weight) with 3 premature decedents from the 90 mg/kg/d group. As a result of the decreased maternal weights, pup weights from the 30 and 90 mg/kg/d groups were significantly decreased with concomitant decreased ossification. Neither terata nor other adverse findings were noted. The NOAEL for embryo-fetal development in the mouse is considered to be 90 mg/kg/d by the sponsor. However the decreased body weights and decreased ossification noted in the pups, while attributable to the decreased body weights and feed intake of the dams, are considered adverse effects and the NOAEL is determined to be 10 mg/kg/d for this mouse study.

Study title: **Rotigotine: A subcutaneous study of embryo-fetal development in the rabbit**

Sponsor's conclusion : Although maternal toxicity was evident at all dose levels, there was no adverse foetal toxicity. Therefore, the no-observed-adverse-effect-level (NOAEL) for embryo-foetal development was considered to be 30 mg/kg/day.

Reviewer's (Dr. Peters) Key study findings: Maternal toxicity was found at all doses (5, 10 and 30 mg/kg/d) in this subcutaneous study in pregnant rabbit does with test article administered during the period of organogenesis. There were no significant adverse effects on the pups except for an increase in extra ribs on the 1st lumbar vertebra at 5 and 10 mg/kg/d. These are considered to be a response to maternal toxicity and not a direct drug effect. The NOAEL for this embryo-fetal study is determined to be 30 mg/kg/d (highest dose tested).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents of this NDA submission is listed below:

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4.2 Tables of Clinical Studies

Advanced Parkinson's Disease

Protocol No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/ Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
5.3.5 Reports of Efficacy and Safety Trials							
5.3.5.1 Trial Reports of Controlled Clinical Trials Pertinent to the Claimed Indication							
SP511/ Europe, South Africa	Assess dose groups of rotigotine which shows efficacy with optimal benefit/risk ratio in subjects with advanced Parkinson's disease	Double-blind, randomized, placebo-controlled, parallel, fixed-dose, dose-ranging	Rotigotine/ 9mg, 18mg, 27mg/ silicone patch	12 weeks	84 placebo, 240 rotigotine 61% M/39% F	64 years/ (35-85)	Complete/ Full
SP515/ Europe, Israel, South Africa, Australia, and New Zealand	Evaluate efficacy and safety as an adjuvant therapy in subjects with advanced PD	Double-blind, double-dummy, placebo-controlled, parallel, optimal-dose	Rotigotine/ up to 36mg/ silicone patch Pramipexole/ up to 4.5mg/ oral	Up to 24 weeks	99 placebo, 205 rotigotine, 202 pramipexole 63% M/37% F	64 years/ (36-84)	Complete/ Full
SP650 Part I/ Canada, US	Evaluate efficacy and safety in subjects with advanced-stage PD	Double-blind, randomized, placebo-controlled, parallel, fixed-dose, dose-ranging	Rotigotine/ 18mg and 27mg/ silicone patch	30 weeks	120 placebo, 229 rotigotine/ 64% M/36% F	66 years/ (33-87)	Complete/ Full
5.3.5.2 Trial Reports of Uncontrolled Trials							
SP512 Part II (SP702)[b]/ Canada, US	Evaluate long-term safety	Open-label, extension of SP512 Part I	Rotigotine/ Year 1: up to 13.5mg; Years 2-4: up to 36mg/ silicone patch	Until commercially available	213 rotigotine/ 68% M/32% F	63 years/ (33-86)	Ongoing/ Abbreviated
SP513 Part II (SP716)[b]/ Europe, Israel, New Zealand, South Africa, Switzerland, Australia	Evaluate long-term safety	Open-label, extension of SP513 Part I	Rotigotine/ Year 1: up to 18mg; Years 2-4: up to 36mg/ silicone patch	Until commercially available	372 rotigotine/ 61% M/39% F	61 years/ (30-82)	Ongoing/ Abbreviated

SP516[b]/ Europe, Australia, Israel, New Zealand, South Africa	Assess the safety and tolerability of long-term treatment in subjects with advanced stage PD	Open-label, extension of SP515	Rotigotine/ up to 36mg/ silicone patch	Until commercially available	395 rotigotine 63.5% M/ 36.5% F	64 years/ (39-84)	Ongoing/ Abbreviated
SP833[b]/ Europe, Israel, South Africa, US	Assess the safety and tolerability of long-term treatment in subjects with idiopathic PD	Open-label, extension of SP824, SP825, and SP826	Rotigotine/ up to 36mg/ silicone patch	Until commercially available	Advanced PD: 111 rotigotine 68.5%M/ 31.5% F Early PD: 75 rotigotine 66.7% M/ 33.3%F	Advanced PD: 65 years/ (37-82) Early PD: 58 years/ (30-84)	Ongoing/ Abbreviated
SP650 Part II (SP715)[b]/ Canada, US	Evaluate long-term safety in subjects with advanced PD	Open-label, extension of SP650 Part I	Rotigotine/ up to 36mg/ silicone patch	Until commercially available	258 rotigotine/ 67% M/33% F	66 years/ (33-87)	Ongoing/ Abbreviated
SP788[b]/ United States, South Africa	Assess long-term safety and tolerability of rotigotine in subjects with early-stage, idiopathic PD	Open-label, multi-site, optimal-dose, extension of SP630	Rotigotine/ up to 36mg/ silicone patch	Until commercially available	62 rotigotine/ 53% M/47% F	64 years/ (38-81)	Ongoing/ Abbreviated
5.3.5.4 Other Trial Reports							
No additional trials conducted.							

BA=bioavailability; F=female; M=male; No.=number; PD=Parkinson's disease; US=United States of America

a Daily dose, unless otherwise specified.

b Report includes data available as of 31 Jan 2007.

Restless Leg Syndrome (RLS)

Protocol No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen*/ Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
5.3.5 Reports of Efficacy and Safety Trials							
5.3.5.1 Trial Reports of Controlled Clinical Trials Pertinent to the Claimed Indication							
SP666/ Germany	Evaluate the dose-response relationship, safety, and tolerability in subjects with idiopathic Restless Legs Syndrome (RLS)	Multicenter, double-blind, randomized, parallel-group, fixed-dose, placebo-controlled	Rotigotine/ 1.125mg, 2.25mg, and 4.5mg/silicone patch	7 days	14 placebo, 49 rotigotine/ 37% M/ 63% F	58 years/ (37-74)	Complete/ Full
SP709/ Europe	Investigate the efficacy of 5 different dosages of rotigotine in subjects with idiopathic RLS	Multicenter, double-blind, randomized, placebo-controlled, 6-arm, parallel-goup, dose-finding	Rotigotine/ 1.125mg, 2.25mg, 4.5mg, 6.75mg, and 9mg/silicone patch	7 weeks	55 placebo, 285 rotigotine/ 33% M/ 67% F	58 years/ (22-75)	Complete/ Full
SP790/ Europe	Demonstrate efficacy and investigate safety and tolerability of rotigotine in subjects with idiopathic RLS	Multicenter, multinational, randomized, double-blind, placebo-controlled, 4-arm, parallel-group, fixed-dose	Rotigotine/ 2.25mg, 4.5mg, and 6.75mg/ silicone patch	28 weeks	117 placebo, 341 rotigotine/ 27% M/ 73% F	58 years/ (23-78)	Complete/ Full
SP792/ United States	Demonstrate efficacy and investigate safety and tolerability of rotigotine in subjects with idiopathic RLS	Multicenter, randomized, double-blind, placebo-controlled, 5-arm, parallel-group, fixed-dose	Rotigotine/ 1.125mg, 2.25mg, 4.5mg, and 6.75mg/ silicone patch	29 weeks	100 placebo, 405 rotigotine/ 39% M/ 61% F	52 years/ (19-77)	Complete/ Full
SP794/ Europe	Demonstrate efficacy and investigate safety of rotigotine in subjects with idiopathic RLS under sleep lab conditions	Multicenter, double-blind, randomized, placebo-controlled, 2-arm, parallel-group, optimal-dose	Rotigotine/ 2.25mg, 4.5mg, and 6.75mg/ silicone patch	Up to 8 weeks	21 placebo, 46 rotigotine/ 27% M/ 73% F	59 years/ (35-75)	Complete/ Full
5.3.5.2 Trial Reports of Uncontrolled Trials							
SP710*/ Europe	Assess safety and tolerability and obtain data on changes in severity in RLS symptoms and quality of life under long-term transdermal application of rotigotine in subjects with idiopathic RLS	Open-label, optimal-dose, extension of SP709	Rotigotine/ 1.125mg, 2.25mg, 4.5mg, 6.75mg, and 9mg/ silicone patch	Up to 5 years	295 rotigotine/ 34% M/ 66% F	58 years/ (22-75)	Ongoing/ Abbreviated

SP791[d]/ Europe	Investigate the safety and tolerability of long-term treatment with transdermal rotigotine in subjects with idiopathic RLS and obtain data on changes in severity in RLS symptoms and quality of life under rotigotine long-term exposure	Open-label, multicenter, optimal-dose, extension of SP790 and SP794	Rotigotine/ 2.25mg, 4.5mg, and 6.75mg/ silicone patch	Up to 13 months	341 rotigotine/ 28% M/ 72% F	58 years/ (23-78)	Ongoing/ Abbreviated
SP793[d]/ United States	Investigate the safety and tolerability of long-term treatment with transdermal rotigotine in subjects with idiopathic RLS and obtain data on changes in severity of RLS symptoms and quality of life under long-term rotigotine exposure	Open-label, multicenter, optimal-dose, extension of SP792	Rotigotine/ 1.125mg, 2.25mg, 4.5mg, and 6.75mg/ silicone patch	Up to 13 months	278 rotigotine/ 46% M/ 54% F	54 years/ (19-77)	Ongoing/ Abbreviated

4.3 Review Strategy

Dr. Len Kapcala conducted the review of efficacy of rotigotine for advanced Parkinson's Disease and the safety review of various sections/topics/items for the advanced Parkinson's Disease development program and the restless leg syndrome (RLS) development program. Other sections of the safety review for both clinical development programs were conducted by Dr. Dave Podskalny. Dr. Podskalny conducted the efficacy review of rotigotine for RLS.

Dr. Kapcala focused the efficacy review for Parkinson's Disease primarily on Study 650, the randomized, double-blind, placebo-controlled, multiple fixed dose arm study but also reviewed data from 2 other pivotal studies (511 and 515). Study 511 was a phase 2 randomized, double-blind, placebo-controlled multiple fixed dose arm study that was a "failure" and did not show efficacy of rotigotine. Study 515 was a randomized, double-blind, placebo-controlled, flexible dose titration study that studied rotigotine doses up to 36 mg (total patch content; or 16 mg delivered dose) that was "positive" and showed efficacy of rotigotine vs placebo.

Dr. Kapcala's safety review for advanced Parkinson's Disease focused particularly on the fixed dose studies (511 and 650, pool AS1 or study 650). Dr. Kapcala's safety review for RLS focused particularly on the 2 randomized, double-blind, placebo-controlled, multiple, fixed dose arm studies (790 and 792), pool RS1).

4.4 Data Quality and Integrity

Data quality was considered to reasonably good with the exception that reproductive endocrine data collected for the RLS program were not collected with respect to the stage of the menstrual cycle in pre-menopausal females. Consequently, these data are of limited to no real value and consideration should be given to collecting appropriate data as part of a phase 4 commitment.

There were no questions related to the integrity of the data. Furthermore, DSI inspections of 3 sites (for study 650) for the advanced Parkinson's Disease clinical development program did not reveal serious problems/concerns.

The following overall assessment of the inspections of sites of 3 Principal Investigators that was abstracted from the DSI inspection letter is shown here.

"OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS
The inspection of Drs. Nausieda, Fazzini and Truong revealed no significant problem that would adversely impact data acceptability. Observations noted for these investigators are based on e-mail summary statements from the FDA field investigators; the EIRs for these inspections are currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIRs. The data submitted from the inspected sites are acceptable in support of the pending application.

4.5 Compliance with Good Clinical Practices

The studies appeared to have been conducted according to Good Clinical Practices.

4.6 Financial Disclosures

There were no problems/concerns with financial disclosures.

5 CLINICAL PHARMACOLOGY

See Clinical Pharmacology reviews by Veneeta Tandon, Ph.D., Clinical Pharmacology reviewer, and Hao Zhu, Ph.D., Pharmacometrics reviewer.

The following represent the Executive Summary and Recommendations from the reviews of Drs. Tandon and Zhu.

Executive Summary

Rotigotine (Neupro®), a non-ergolinc dopamine agonist is currently approved in the US for the treatment of signs and symptoms of early-stage, idiopathic Parkinson's disease (PD). It is also approved in the European Union (EU) for the treatment of signs and symptoms of Parkinson's disease (Early and Advanced PD). Schwarz is seeking approval

for the indication of the treatment of the signs and symptoms of primary Restless Legs Syndrome (RLS) and for the treatment of the signs and symptoms of advanced stage Parkinson's disease in sNDAs 035 and 036.

The sponsor proposed dosing regimen for RLS is once daily dosing of patches 1, 2 or 3 mg/24 hours (containing 2.25, 4.5 and 6.75 mg rotigotine per transdermal system), with doses being increased at weekly increments of 1mg/24 hours. The proposed dosing regimen for advanced PD is once daily dosing of patches 4, 6 or 8 mg/24 hours (containing 9, 13.5 and 18 mg rotigotine per transdermal system), with doses being increased at weekly increments of 2mg/24 hours.

The currently approved strengths of the rotigotine patches are 2, 4 and 6 mg/24 hour patches. In the original NDA submission of January 2005, the 8 mg patches were evaluated in clinical studies, (b) (4) The new patch strengths included in these supplements are 1, 3 and 8 mg/24 hours patches. The quantitative composition per area is identical for all strengths, and the nominal delivery per each cm^2 is 0.2mg/24 hours.

The following table shows the strengths of rotigotine transdermal system that have been proposed by the sponsor and also that have been used in the clinical development of both the proposed and the approved indications.

Rotigotine nominal dose/24h (mg)	Rotigotine content per transdermal system (mg)	Patch surface area (cm^2)	Indication
(b) (4)			
1	2.25	5	RLS
2	4.5	10	RLS and Early PD
3	6.75	15	RLS
4	9	20	Early and Advanced PD
6	13.5	30	Early and Advanced PD
8	18	40	(b) (4) Advanced PD

[a] used in clinical development only

From a clinical pharmacology perspective, to support the RLS indication, the supplement contains one Phase I study (SP871) that assesses the relative bioavailability of rotigotine after administration of rotigotine transdermal system 6.75mg ($15cm^2$) compared to combined application of one 2.25mg ($5cm^2$) system plus one 4.5mg ($10cm^2$) system. In addition to this, the sponsor has conducted two drug-drug interaction studies with oral

contraceptives and omeprazole. Oral contraceptive study was conducted as the RLS indication has high prevalence in women as well. Omeprazole study was conducted to evaluate the inhibition of CYP2C19 as original NDA had evaluated the inhibition of CYP2C19 using a non specific inhibitor, cimetidine.

To support the Advanced Parkinson's NDA the sponsor conducted a thorough QT/QTc study in patients with Parkinson's disease. This study was evaluated by the IRT team. Synonymous Terms: Throughout this application the internal codes used for rotigotine are 'N- 0923', and 'SPM 962'. In addition, rotigotine may be referred in study reports as rotigotine continuous delivery system or rotigotine transdermal system.

RECOMMENDATION

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-1 has reviewed the Clinical Pharmacology information submitted to sNDAs 21-829 (035 and 036) and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert. The following comment regarding the Pharmacometrics review should be conveyed to the sponsor.

1. We recommend in the future, the sponsor perform logistic regression analysis to direct link the exposure and incidence of adverse events for each individual.

5.1 Pharmacokinetics

See Clinical Pharmacology reviews by Veneeta Tandon, Ph.D., Clinical Pharmacology reviewer, and Hao Zhu, Ph.D., Pharmacometrics reviewer for additional details.

5.2 Pharmacodynamics

See Clinical Pharmacology reviews by Veneeta Tandon, Ph.D., Clinical Pharmacology reviewer, and Hao Zhu, Ph.D., Pharmacometrics reviewer for additional details.

5.3 Exposure-Response Relationships

See Clinical Pharmacology reviews by Veneeta Tandon, Ph.D., Clinical Pharmacology reviewer, and Hao Zhu, Ph.D., Pharmacometrics reviewer for additional details.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

The Advanced Parkinson's clinical development program consisted of two pivotal trials (SP650 and SP515), and a phase 2 study SP511. All three trials were randomized, placebo-controlled, multi-center parallel group studies with rotigotine dose ranging from 9 mg to 36 mg per day in subjects with advanced PD who were not well controlled on L-dopa.

SP650 had three treatment arms: rotigotine 18mg, rotigotine 27mg and placebo. The trial, which was conducted in North America, consisted of a titration period of up to 5 weeks followed by a maintenance period of 24 weeks. SP515 was conducted in Europe and South Africa. It was a flexible dose trial with per-day dose of rotigotine ranging from 9 mg to 36 mg. The duration of SP515 consisted of up to 7 weeks titration and 16 weeks of maintenance period. Additionally, SP511 was a dose finding study with 4 treatment groups: 9 mg, 18 mg, and 27 mg of rotigotine, and placebo. The trial was conducted in Europe and South Africa.

The common primary efficacy endpoint for the three studies was the reduction from baseline in absolute time spent "off".

Based upon regulatory agency acceptance, two different primary analyses, one for the US and one for the European Union (EU), were implemented. The primary efficacy endpoint accepted by the US Food and Drug Administration (FDA) was the reduction in absolute time spent "off" from Baseline to the end of the Double-Blind Maintenance Period. The EU primary efficacy endpoint was the proportion of responders, with a "responder" defined as a subject with at least 30% decrease in absolute time spent "off" from Baseline to the end of Double-Blind Maintenance Period.

The primary variable for the US served as a secondary variable for the EU, and correspondingly, the primary variable for the EU served as a secondary variable for the US.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was change from baseline in total "off" time (e.g., hours) in all pivotal studies (511, 515, 650). This is a common primary endpoint in pivotal studies for advanced Parkinson's Disease.

6.1.3 Study Design

Study 650

This trial was a Phase 3, randomized, double-blind, placebo-controlled, 3-arm parallel group trial of rotigotine in subjects with advanced-stage, idiopathic Parkinson's disease who were not well controlled on L-DOPA. The study consisted of a titration period of up to 5 weeks and a

maintenance period of 24 weeks. The trial was conducted in 55 sites in the United States and Canada.

Eligible subjects were randomized to receive either rotigotine at 1 of 2 target dose levels, or placebo. The target doses were 18 mg/day and 27 mg/day (total drug patch content). **The dose level of rotigotine/placebo was titrated at 7-day intervals from 9 mg until either the subject reached their "optimal" dose or the titration period was complete.**

The dose was regarded as "optimal" if the time per day that the subject spent in the "off" state was zero. Once the subjects "optimal" dose was identified or the titration period was complete, subjects commenced maintenance medication and remained at their optimal or maximum rotigotine/placebo dose, as appropriate. Subjects in the placebo group were randomized, in a ratio of 1:1, to either the placebo for rotigotine 18.0mg/day target dose group or the placebo for rotigotine 27.0mg/day target dose group. The following dosing/treatment scheme (shown below) was planned. **This dosing/treatment scheme during the titration phase differs from that of study 511 in that the target dose for those patients randomized to the 18 mg dose is achieved earlier than the time at which patients randomized to the 27 mg dose is achieved. In this study design the potential treatment time at the target/randomized dose differs compared to study 511 in which the total treatment time at the target/randomized dose is theoretically the same.**

Daily dose of rotigotine CDS or placebo during the dose titration phase

Week of escalation	Treatment group					
	Rotigotine-CDS target dose 18 mg/40 cm^2		Rotigotine-CDS target dose 27 mg/60 cm^2		Placebo	
	Rotigotine patches	Placebo Patches	Rotigotine patches	Placebo Patches	Rotigotine patches	Placebo patches
Week 1	1 x 20 cm^2	2 x 10 cm^2 1 x 20 cm^2	1 x 20 cm^2	2 x 10 cm^2 1 x 20 cm^2	-	2 x 10 cm^2 2 x 20 cm^2
Week 2	1 x 10 cm^2 1 x 20 cm^2	1 x 10 cm^2 1 x 20 cm^2	1 x 10 cm^2 1 x 20 cm^2	1 x 10 cm^2 1 x 20 cm^2	-	2 x 10 cm^2 2 x 20 cm^2
Week 3	2 x 20 cm^2	2 x 10 cm^2	2 x 20 cm^2	2 x 10 cm^2	-	2 x 10 cm^2 2 x 20 cm^2
Week 4	2 x 20 cm^2	2 x 10cm^2	1 x 10 cm^2 2 x 20 cm^2	1 x 10 cm^2	-	2 x 10 cm^2 2 x 20 cm^2
Week 5	2 x 20 cm^2	2 x 10 cm^2	2 x 10 cm^2 2 x 20 cm^2	-	-	2 x 10 cm^2 2 x 20 cm^2

A subject's L-dopa dose was to remain stable (i.e. no change in daily dose or dosing regimen) during the titration phase. Subjects will undergo the dose escalation scheme detailed below until the "optimal" dose has been achieved or the titration phase is complete.

The maintenance phase is 24 weeks (± 1 week) in duration. **During the maintenance phase the**

investigator had the opportunity to adjust a subject's total daily dose of L-dopa, after consultation with Schwarz BioSciences or it designee in the following circumstances:

1. During the first 2 weeks of the maintenance phase (Visits 7 to 8), if required in case of dopaminergic adverse events, a subject's L-dopa dose may be reduced.
2. A subject's L-dopa dose that was reduced during the first 2 weeks of the maintenance phase only, may be uptitrated to the original L-dopa dose (Visit 7), if required.

Other than these two instances, the subject's total daily dose of L-dopa must remain stable throughout the trial. Subjects who require further adjustment of L-dopa will be withdrawn from the trial after consultation with Schwarz BioSciences or its designee.

Subjects are not permitted to further adjust their total daily dose of L-dopa at any time during the course of the trial. Subjects will not be permitted to change their dose of rotigotine CDS/placebo during the maintenance phase.

Subjects will be required to apply the patch(es), once daily, to either the upper or lower abdomen (above the umbilicus), thigh, hip, flank, shoulder or upper arm. Subjects will be randomly allocated, in a ratio of 1:1:1 to receive rotigotine CDS at a target dose of either 18 mg or 27 mg or to receive placebo in a double-blind fashion.

The trial planned to enroll 460 subjects, and a total of 462 subjects were actually enrolled. Subjects who completed 6 months of double-blind maintenance treatment were provided with the opportunity to continue long-term rotigotine treatment. The tabular schedule of events/trial procedures is shown below here.

3.4 Tabular schedule of trial procedures

Period	Pretreat-ment	Treatment										Safety follow-up	With-drawal
Phase		Dose Escalation		Maintenance									
				Stable L-dopa dosing									
Week# (Day #)	-4 to -1 (-28 to -1)	1 (1)	2, 3, 4, 5 (8, 15, 22, 29)	1 (1)	3 (15)	5 (29)	9 (57)	13 (85)	17 (113)	21 (141)	25 (169)	29 (197)	
Visit#	1	2	3, 4, 5, 6	7*	8	9	10	11	12	13	14	15	
Informed Consent	X												
IVRS	X	X	X	X		X	X	X	X	X	X	X	X
Randomization		X											
Demographics	X												
Medical History	X												
Eligibility Criteria	X	X											
MMSE	X												
Hoehn & Yahr	X♦										X		X
CGI	X	X	X	X				X			X	X	X
UPDRS – Parts II - IV (on-state) **	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary (Issue)	X	X	X	X	X	X	X	X	X	X	X†††		
Diary (validation)		X††	X	X	X	X	X	X	X	X	X	X	X
Neurological Exam	X											X	X
Physical Examination	X											X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Application Site Assessment		X	X	X	X	X	X	X	X	X	X		X
Hematology, Chemistry, Urinalysis	X**	X		X				X			X	X**	X**
Pharmacokinetics °		X	X	X		X		X			X	X	X
12 Lead ECG	X	X***	X▲	X				X			X	X	X
Euroqol EQ-5D		X									X		X
Epworth scale		X		X				X			X		X
Rotigotine back-titration permitted			X										
L-dopa dose reduction permitted				X									
L-dopa dose uptitration permitted‡					X	X	X	X	X	X			
Record of L-dopa intake	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Patch Application/Removal Training	X												
Medication (issue)		X	X	X	X	X	X	X	X	X	X▼†		X▼†
Medication (return)			X	X	X	X	X	X	X	X	X	X	X
Safety Assessment (AE)	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit windows: for visits 3-7 are ± 3 days relative to visit 2, for visits 8 - 14 are ± 7 days relative to visit 7 and for visit 15 is ± 7 days relative to visit 13/withdrawal visit.

° at specified sites only
* at the end of dose escalation or when subject's optimal dose is achieved
▼ patches for treatment withdrawal to be dispensed.
*** 3 separate ECGs, at least 15 minutes apart.
▲ 12-lead ECG at Visits 3 and 5 only
‡ L-dopa dose return to baseline level permitted once during the maintenance phase
†† to include diary validation by investigator (4 of 6 diaries are valid)
† dose de-escalation by 10cm²/every 2 days. Maximum de-escalation of 8 days.
** analysis to include pregnancy test (if appropriate)
** UPDRS Part IV to be completed only at Visits 2, 7, 14 and at withdrawal
♦ Hoehn & Yahr at pre-treatment (Visit 1) must be completed in both "on" & "off" state
††† 3 diaries to be completed on 3 consecutive days immediately after de-escalation is complete

Protocol Amendments / Changes in the conduct of the trial

The original protocol, dated 12 Oct 2001, was amended 3 times following the start of the trial up to the completion of the double-blind portion (i.e., Part I) of the protocol. The protocol includes an open-label portion (i.e., Part II) to allow qualified subjects the opportunity to receive rotigotine treatment. The open-label portion of the protocol is ongoing; any amendments to the protocol after the double-blind database lock are not described in this report.

The purpose of the amendments up to the completion of the double-blind part of this trial was to allow for changes in the conduct of the trial, changes in the procedures followed, and administrative changes. The amendments are summarized here.

Amendment 1 (24 Apr 2002): Amendment 1 provided subjects who completed 6 months of double-blind maintenance treatment the opportunity to continue long-term rotigotine treatment. The open-label extension part provided long-term safety and tolerability data of uninterrupted rotigotine treatment in subjects with advanced-stage idiopathic Parkinson's disease. In addition, the amendment included corrections of administrative errors as well as updated and/or changed information.

Amendment 2 (02 Jun 2003): Amendment 2 changed the primary analyses in the protocol. At a

Food and Drug Administration (FDA) End-of-Phase 2 meeting held on 14 June 2001, SCHWARZ BIOSCIENCES, Inc. (SB) proposed using 2 different endpoints, with a continuous endpoint for a US marketing application and a dichotomized response endpoint for an EU marketing application. Based on regulatory agency acceptance, 2 different primary analyses, 1 for the US and 1 for the EU, were added to the protocol. In addition, this amendment included administrative corrections and updates.

Amendment 3 (03 Mar 2004): Amendment 3 altered the process for reporting adverse events, including serious adverse events, events leading to withdrawal, and events of special interest. The new process reflected a change in the reporting procedures conducted by SB. In addition, this amendment included administrative corrections and updates.

In addition to these amendments, the time point for obtaining blood samples for pharmacokinetic analysis after patch application was changed from "60 minutes" to "at least 1 hour but no greater than 4 hours after application of the new patch." This information was documented in the Laboratory Manual and made available to all sites.

Summary of Diagnosis Main Inclusion and Exclusion Criteria

Inclusion Criteria

Subjects were included if they were ≥30 years of age with idiopathic Parkinson's disease of >3 years duration as defined by the cardinal Parkinsonian sign of bradykinesia, plus the presence of at least one of the following cardinal features: resting tremor, rigidity, impairment of postural reflexes, and without any other known or suspected cause of Parkinsonism. Subjects were required to be Hoehn & Yahr stage II through IV in both the "on" and "off" states and have a Mini-Mental State Examination (MMSE) score of ≥25. Subject were on a stable dose of L-DOPA of at least 200mg/day (administered in at least 2 daily intakes), either short-acting or sustained release (in combination with benserazide or carbidopa) for at least 28 days prior to Baseline (Visit 2) and were not adequately controlled on a L-DOPA dose that was judged by the treating physician to be optimal. Subjects receiving an anticholinergic agent, a monoamine oxidase B (MAO-B) inhibitor, or an N-methyl-D-aspartate (NMDA) antagonist, were on a stable dose for at least 28 days prior to Baseline and were maintained on that dose for the duration of the trial. Subjects were on stable doses of all anti-Parkinsonian medications for at least 20 days prior to completing the 6 Baseline diaries.

Exclusion Criteria

Subjects were excluded from the trial if they had atypical Parkinson's syndrome(s) due to drugs (e.g., metoclopramide, flunarizine), metabolic neurogenetic disorders (e.g., Wilson's disease), encephalitis, cerebrovascular disease or degenerative disease (e.g., progressive supranuclear palsy); or if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant; were receiving therapy with a dopamine agonist currently or had done so within

28 days prior to Baseline; had received within 28 days prior to the Baseline visit therapy with methylphenidate, amphetamine, or catechol-O-methyl transferase (COMT) inhibitors.

Study 515

This trial was a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, flexible-dose parallel-group trial of rotigotine in subjects with advanced-stage, idiopathic Parkinson's disease who experienced wearing-off type motor-fluctuations on L-dopa. Eligible patients were randomized in a ratio of 2:2:1 to receive rotigotine, pramipexole, or placebo. The per-day dose of rotigotine ranged from 9 mg to 36 mg. Subjects went through up to 7 weeks of titration period and a 16-week maintenance period, followed by a dose de-escalation phase of up to 6 days and a 4-week follow-up phase. The trial was conducted in 17 countries in Europe and South Africa.

The Tabular Schedule of Trial Events is shown below here.

TABLE 1: TABULAR SCHEDULE OF TRIALS EVENTS

Period	Pre-treatment	Treatment		Maintenance						Safety Follow-up	With-drawal
Phase		Dose Escalation				Stable L-dopa dosing					
Week# (Day #)	-4 to –1 (-28 to –1)	1 (1)	2, 3, 4, 5, 6, 7 (8, 15, 22, 29, 36, 42)	0 (1)	2 (15)	4 (29)	8 (57)	12 (85)	16 (113)	20 (141)	
Visit#	1	2	3, 4, 5, 6, 7, 8	9*	10	11	12	13	14	15	
Informed Consent	X										
IVRS	X	X	X	X		X	X	X	X	X	X
Randomization		X									
Demographics	X										
Medical History	X										
Eligibility Criteria	X	X									
MMSE	X										
Hoehn & Yahr	X♦								X		X
CGI	X	X	X	X			X		X	X	X
UPDRS – Parts II - IV (on-state) **	X	X	X	X	X	X	X	X	X	X	X
Diary (issue)	X	X	X	X	X	X	X	X	X†††		
Diary (validation)		X††	X	X	X	X	X	X	X	X	X
Neurological Exam	X								X	X	X
Physical Examination	X								X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X
Application Site Assessment		X	X	X	X	X	X	X	X		X
Hematology, Chemistry, Urinalysis	X*	X		X					X	X*	X*
Pharmacokinetics ***		X	X	X		X		X	X	X	X
PDSS		X							X		X
12 Lead ECG	X	X**	X▲	X					X	X	X
PDQ-39		X							X		X
Epworth Sleepiness Scale		X		X					X		X
Medication back-titration permitted			X								

L-dopa dose reduction permitted				X	X						
L-dopa dose up-titration permitted ‡					X	X	X	X			
Record of L-dopa intake	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Patch Application/Removal Training	X										
Medication (issue)		X	X	X		X	X	X	X'†		X'†
Medication (return)			X	X	X	X	X	X	X	X	X
Safety Assessment (AE)	X	X	X	X	X	X	X	X	X	X	X

Visit windows: for visits 3-8 are + 3/-2 days relative to previous visit, for visits 10 - 14 are ± 7 days relative to visit 9 and for visit 15 is ± 7 days relative to visit 14/withdrawal visit.

▼UPDRS Part IV to be completed only at Visits 2, 9, 14 and at withdrawal

° at the end of dose escalation or when subject's optimal dose is achieved

▾ patches for treatment withdrawal to be dispensed.

‡ L-dopa dose return to baseline level permitted once during the maintenance phase

▲ 12-lead ECG at Visits 3, 5 and 7 only

** 3 separate ECGs, at least 15 minutes apart

* to include pregnancy test if appropriate

*** at specified sites only

†† to include diary validation by investigator (4 of 6 diaries are valid)

† dose de-escalation starts. Maximum de-escalation of 6 days

♦ Hoehn & Yahr at pre-treatment (Visit 1) must be completed in both 'on" & "off" state

††† 3 diaries to be completed on 3 consecutive days immediately after de-escalation is complete

Study 511

SP511 was a Phase 2b, 4-arm, dose-finding trial. The study consisted of a pretreatment Run-In Phase of up to 6 weeks, during which any dopamine agonist was withdrawn and L-dopa doses were adjusted and kept stable, followed by a 12-week Treatment Phase, which consisted of 5 weeks of titration and 7 weeks of maintenance. Subjects were randomized to treatment with patches delivering 1 of 3 active target doses of rotigotine (9.0mg, 18.0mg, or 27.0mg) or placebo. The following dosing/treatment scheme (shown below) in which patients were potentially on the target rotigotine dose for the same time was planned.

Dosing Scheme for SP511

Dose-escalation to the randomized target dose will be done as follows: Applying 4 patches, starting with either placebo or 9.0mg, increments of 4.5mg every 7th day. Please see scheme below.

Target Dose	Week					
	Titration					Maintenance
	1	2	3	4	5	6
Placebo	□□□□	□□□□	□□□□	□□□□	□□□□	□□□
9.0mg (20cm²)	□□□□	□□□□	□□□□	□□□□	■□□□	■□□
18.0mg (40cm²)	□□□□	□□□□	■□□□	■□■□	■■□□	■■□
27.0mg (60cm²)	■□□□	■□■□	■■□□	■■■□	■■■■	■■■

■ Active 20cm² □ Placebo 20cm²
■ Active 10cm² □ Placebo 10cm²

For patients who have been on a dopamine agonist therapy, the pre-treatment period may last up to a maximum of 42 days as the following will be done: the dopamine agonist will be withdrawn and L-Dopa dose will be adjusted according to the patients' requirements and the investigators decision. The L-Dopa dose may be increased during a period of maximally 28 days. The washout period will be dependent on the plasma-half life of the dopamine agonist. The recommended duration of the washout period is equal to 5 half-lives of the particular dopamine agonist. Afterwards the patients have to be on a stable dose of L-Dopa (without any concomitant dopamine agonist) 14 days prior to baseline visit. "Stable" is defined as ± 1 dose of L-Dopa per day. If reduction of L-Dopa-dose is required, it is allowed further to do so up to end of week 7. Criteria for L-Dopa reduction are L-Dopa related side effects as nausea, vomiting, orthostatic dysregulation, hallucinations and dyskinesias. For patients who had no prior dopamine agonist therapy, the pre-treatment phase will last 14 days as they have to be on a stable dose of L-Dopa for 14 days prior to baseline visit.

On each scheduled dose escalation day, each subject was assessed for clinically significant changes in vital sign measurements, clinically significant ECGs, and intolerable AEs to determine whether a subject should go into the next titration step. If there were no clinically significant findings in vital sign measurements, ECGs, or intolerable AEs, the subject went into the next titration step.

If an intolerable AE such as nausea and vomiting occurred, the subject's dose of L-dopa was reduced. If the AE did not resolve, the reduction of all other anti-Parkinson-medication was recommended. If the subject still did not tolerate his/her medication, the subject was back titrated to the next lower dose group using a blinded procedure.

Back titration could only be done once during the entire Titration Phase. Once a back titration was done, the subject stayed on that dose for the remainder of the trial. If another dose reduction was needed, the subject was withdrawn from the trial.

Subjects having reached their randomized target dose of either 9.0, 18.0, or 27.0mg of rotigotine or placebo during the Titration Phase then continued the 7-week Maintenance Phase.

The primary efficacy variable was the absolute change from Baseline to end of treatment in absolute time spent "off". A closed test procedure was used to identify the minimal effective dose using the pre-assigned order from the highest dose (rotigotine 27 mg) to the lowest (rotigotine 9 mg). The test procedure was used in conjunction with an ANCOVA with treatment group and country as factors, and baseline time "off" as a covariate. Data from countries for which less than 20 subjects were randomized were pooled (Latvia, United Kingdom, Germany, The Netherlands and Finland).

The Time and Event Schedule is shown below here.

TIME AND EVENT SCHEDULE														
PERIOD	PRETREATMENT		TREATMENT										SAFETY FOLLOW -UP	
PHASE	L-Dopa adjustment	Stable dose of L-Dopa	TITRATION					MAINTENANCE						
WEEK#	-6 to -2	-2 to -1	1	2	3	4	5	6	8	9	11	12	14	
DAY#	-42 to -15	-14 to -1	1	8	15	22	29	36	50	57	71	85	99	
VISIT#		1	2 Baseline	3	4	5	6	7	Call ☎	8	Call ☎	9	10	Prema-ture with-drawal
informed consent	X													
randomization			X											
demographics	X													
medical history	X[1]													
physical examination	X											X	X	X
recording of concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X
vital signs (BP,HR,T,RR)	X[2]		X	X	X	X	X	X		X		X	X	X
neurological examination	X		X									X	X	X
hematology, blood chemistry, urinalysis	X		X					X		X		X	X	X
measurement of pharmacokinetics [3]			X[4]	X[5]	X[5]	X[5]	X[5]	X[6]		X[5]		X[7]		X[7]
pregnancy test (in female patients)	X[8]											X[8]		X[8]
12-lead ECG	X[9]		X[10]	X[11]	X[11]	X[11]	X[11]	X[11]		X[11]		X[12]	X[9]	X[12]
application site assessment	X		X	X	X	X	X	X		X		X	X	X
record of current L-Dopa intake	X		X	X	X	X	X	X		X		X	X	X
Hoehn & Yahr staging	X												X	X
full UPDRS			X					X				X		X
patch application and removal session			X[13]											
individual definition of "Off"	X													
diary (issue)	X[14,15]		X[15]		X[15]		X[15]	X[15]		X[15]		X[15]		
diary (verification)			X	X	X	X	X	X		X		X[16]	X	X
medication (issue)			X	X	X	X	X	X		X				
medication (return)				X	X	X	X	X		X		X		X
safety assessment (AE)														

Footnotes:

1 including height & weight
2 including assessment of orthostatic hypotension
3 in a subset of trial population at predefined sites
4 immediately prior to patch application and at the following timepoints after new patch application:2h; 6h; 12h; 24h
5 at the following timepoints after the application of the last patch of the dose (prior to each dose-escalation):23h; 23,5h
6 at the following timepoints after the application of the last patch: 23h; 23,5h and at the following timepoints after new patch application:2h; 6h; 12h; 24h
7 immediately prior to patch removal (if still) on and at the following timepoints post patch removal:1h; 2h; 4h; 6h; 8h
8 blood for pregnancy test will be collected with hematology and biochemistry in female patients
9 2 ECG's recorded approximately 15 minutes apart
10 2 ECG's recorded approximately 15 minutes apart prior to new patch application and 2 ECG's recorded approximately 15 minutes apart after new patch application
11 2 ECG's recorded approximately 15 minutes apart prior to patch removal and 2 ECG's recorded approximately 15 minutes apart after new patch application
12 2 ECG's recorded approximately 15 minutes apart prior to patch removal (if still on)
13 Placebo patch should be applied by the patient the evening prior to the baseline visit
14 including 4h-classification of "on" and "off" of both subject and investigator
15 diary to be filled in on 3 consecutive days prior to the next clinic visit
16 last verification of the diary will be done 3 days after patch removal at the end of the treatment period

6.1.4 Efficacy Findings

Study 650

Populations Analyzed

The following table shows the various populations analyzed by randomized treatment group.

Analysis populations in SP650

Population	Randomized treatment group, n (%)			
	Placebo (N=120)	Rotigotine 18.0mg/day (N=120)	Rotigotine 27.0mg/day (N=111)	Overall (N=351)
Subjects randomized but not treated	0	2 (2)	0	2 (<1)
Safety Set (SS)	120 (100)	118 (98)	111 (100)	349 (>99)
Full Analysis Set (FAS)	119 (>99)	113 (94)	109 (98)	341 (97)
Per Protocol Set (PPS)	85 (71)	84 (70)	78 (70)	247 (70)

Data Source: Table 3.3

Subject Disposition

Subject is shown in the following table. A similar percentage of patients discontinued prematurely in each randomized group. The percentage reasons for discontinuation in each randomized group was generally similar. Not surprisingly, discontinuation for adverse event was the most common reason in rotigotine-treated patients and lack of efficacy was the most common reason for premature study termination in placebo patients.

Table 3.1
Subject Disposition After Randomization
(Rand)

Parameter	Placebo N=120 n	(%)	18mg/day Rotigotine N=120 n	(%)	27mg/day Rotigotine N=111 n	(%)	Overall N=351 n	(%)
Subjects completing the trial [1]	92	(77)	87	(73)	81	(73)	260	(74)
Subjects prematurely discontinuing trial	28	(23)	33	(28)	30	(27)	91	(26)
Reasons for premature trial discontinuation [2]:								
Major protocol violation	2	(2)	3	(3)	1	(<1)	6	(2)
Lack of efficacy	11	(9)	7	(6)	5	(5)	23	(7)
Adverse event	11	(9)	18	(15)	17	(15)	46	(13)
Unsatisfactory compliance of subject	2	(2)	1	(<1)	3	(3)	6	(2)
Subject withdrew consent	8	(7)	5	(4)	8	(7)	21	(6)
Lost to follow-up	0		0		0		0	
Other	0		3	(3)	2	(2)	5	(1)
Subjects rolling over into OL extension	92	(77)	86	(72)	80	(72)	258	(74)

[1] Completion of trial is defined as having the full 24 weeks of Maintenance Phase medication.
[2] A subject can have more than one reason for trial discontinuation.

Reference: Subject Data Listing 1
Program Name: P:\SCHWARZBIO\SP650\FINAL\TABLES\DISP_RAND.SAS 10:17 Page 1 of 1

Protocol Deviations

The following table shows the percentages of patients with major protocol deviations (e.g., those that could potentially affect efficacy analyses. There did not appear to be noteworthy difference in the proportion of patients with major protocol deviations according to randomized treatment.

Table 3.3
Summary of Subject Populations and Protocol Deviations
(Rand)

Parameter	Placebo N=120 n	(%)	18mg/day Rotigotine N=120 n	(%)	27mg/day Rotigotine N=111 n	(%)	Overall N=351 n	(%)
Subjects not treated	0		2	(2)	0		2	(<1)
Population: Safety Set	120	(100)	118	(98)	111	(100)	349	(>99)
Population: Full Analysis Set	119	(>99)	113	(94)	109	(98)	341	(97)
Population: Per-protocol Set	85	(71)	84	(70)	78	(70)	247	(70)
Subjects with less than 8 weeks maintenance exposure or at least one major protocol deviation	35	(29)	36	(30)	33	(30)	104	(30)
Subjects with at least 8 weeks maintenance exposure	96	(80)	97	(81)	91	(82)	284	(81)
Subjects with less than 8 weeks maintenance exposure	24	(20)	23	(19)	20	(18)	67	(19)
Subjects without any major protocol deviations	107	(89)	105	(88)	93	(84)	305	(87)
Subjects with at least one major protocol deviation	13	(11)	15	(13)	18	(16)	46	(13)

Reference: Subject Data Listings 1, 4
Program Name: P:\SCHWARZBIO\SP650\FINAL\TABLES\PRODEV_RAND.SAS 10:17 Page 1 of

Demographic and other Baseline characteristics

The demographic characteristics for age, gender, race, weight, and height were generally similar amongst the treatment groups.

Table 4.2
Demographic Characteristics
(FAS)

Parameter	Statistic	Placebo N=119	18mg/day Rotigotine N=113	27mg/day Rotigotine N=109	Overall N=341
Age (years)	n	119	113	109	341
	Mean	66.3	66.7	64.6	65.9
	Std.Dev.	9.66	9.57	10.47	9.91
	Median	68.0	68.0	65.0	66.0
	Minimum	42	33	39	33
	Maximum	87	83	83	87
Age Category (years)					
Less than 65	n (%)	43 (36)	44 (39)	54 (50)	141 (41)
65 and greater	n (%)	76 (64)	69 (61)	55 (50)	200 (59)
Less than 75	n (%)	95 (80)	86 (76)	89 (82)	270 (79)
75 and greater	n (%)	24 (20)	27 (24)	20 (18)	71 (21)
Gender					
Male	n (%)	73 (61)	76 (67)	71 (65)	220 (65)
Female	n (%)	46 (39)	37 (33)	38 (35)	121 (35)

Race					
White	n (%)	113 (95)	104 (92)	100 (92)	317 (93
Black	n (%)	0	0	3 (3)	3 (<1
Asian	n (%)	2 (2)	3 (3)	3 (3)	8 (2
Other	n (%)	4 (3)	6 (5)	3 (3)	13 (4
Height (cm)	n	119	113	109	341
	Mean	170.6	170.6	171.6	170.9
	Std.Dev.	11.12	9.36	10.49	10.34
	Median	171.0	170.0	173.0	171.0
	Minimum	145	150	147	145
	Maximum	196	188	201	201
Weight (kg)	n	118	113	109	340
	Mean	78.648	77.778	78.217	78.221
	Std.Dev.	19.8772	16.4219	17.8502	18.0859
	Median	78.020	77.570	75.300	77.110
	Minimum	43.09	48.20	46.27	43.09
	Maximum	161.93	137.44	157.85	161.93

Baseline Disease Characteristics

At screen for the SS datset, the mean time since subjects were first diagnosed with Parkinson's disease was 7.7 years; the mean MMSE score was 28.66; the majority of subjects (60% overall; range 55%-64%) had a CGI score of 4 indicating moderate illness. The majority (52%) of all subjects were classified as Hoehn & Yahr Stage 3 during the off state, 30% of subjects were classified as Hoehn & Yahr Stage 2, and 15% as Stage 4. No subjects were enrolled having a Hoehn &Yahr stage indicative of a more mild Parkinson's disease (i.e., Hoehn & Yahr = 0 or 1). Approximately half of all subjects had a UPDRS II score of 10-<20, and 21% had a UPDRS II score of 5-<10. Approximately half of all subjects had a UPDRS III score of 10-<30, and 23% had a UPDRS III score of 30-<40.

At Baseline for the SS, the majority of subjects (58%) had a CGI score of 4 indicating moderate illness. The mean and median absolute "off" times at baseline were greater in the rotigotine 18.0mg/day group (6.7hr and 6.3hr, respectively) than in the placebo group (6.4hr and 6.1 hr, respectively) or the 27.0mg/day group (6.3hr and 6.1 hr, respectively). Sixty-three percent of subjects overall had a UPDRS II score of ≤14, and 85% had a UPDRS II score of ≤19 (the maximum [worst] UPDRS II score in the trial was 36). Sixty-four percent of subjects overall had a UPDRS III score of ≤29, and 86% had a UPDRS III score of ≤39 (the maximum [worst] UPDRS III score in the trial was 83). Fifty-three percent of subjects overall had a UPDRS IV score of 5-<10, and 39% had a UPDRS IV score of 0-<5 (the maximum [worst] UPDRS IV score in the trial was 15).

The following table shows the "off" time characteristics by randomized treatment group.

Table 8.2.1
Parkinson's Disease Severity at Baseline
(SS)

Parameter	Statistic	Placebo N=120	18mg/day Rotigotine N=118	27mg/day Rotigotine N=111	Overall N=349
Daily Diary Card Data	n	120	117	111	348
Absolute Off-time (hrs)	Mean	6.400	6.734	6.292	6.478
	Std.Dev.	2.6047	2.5145	2.6302	2.5823
	Median	6.083	6.333	6.083	6.141
	Minimum	2.59	1.25	2.38	1.25
	Maximum	14.67	15.00	15.08	15.08
Relative Off-time (%)	n	120	117	111	348
	Mean	39.956	41.899	38.726	40.217
	Std.Dev.	15.7299	15.0152	16.6017	15.7887
	Median	38.388	39.736	36.994	38.690
	Minimum	15.63	8.43	13.68	8.43
	Maximum	82.63	100.00	92.59	100.00

Note: Relative OFF time = percentage of awake time spent in OFF state.

Reference: Subject Data Listings 8.1.2, 8.2, 9

Other than the relatively small differences in absolute “off” time between treatment groups at Baseline, there did not appear to noteworthy or important differences in Baseline characteristics across treatment groups in the SS or the PPS at Baseline.

Concomitant Diseases/Disorders and Prior Medications/Therapies

There did not appear to be any major/noteworthy differences in the concomitant disease/disorders and prior therapy (Parkinson's Disease or non-Parkinson's Disease medications) amongst the 3 treatment groups. In particular, the following table shows the distribution of anti-Parkinson's Disease medications prior to the study.

Summary of anti-Parkinson's disease medications taken within the 28 days prior to treatment in SP650 (SS)

Medication class	Treatment group, n (%)		
	Placebo (N=120)	Rotigotine 18.0mg/day (N=118)	Rotigotine 27.0mg/day (N=111)
Any anti-Parkinson's medications	120 (100)	118 (100)	111 (100)
Dopa and dopa derivatives	120 (100)	118 (100)	111 (100)
Monoamine oxidase type B inhibitors	20 (17)	23 (19)	16 (14)
Adamantane derivatives	17 (14)	17 (14)	17 (15)
Other dopaminergic agents	2 (2)	5 (4)	3 (3)
Dopamine agonists	1 (<1)	2 (2)	3 (3)
Anticholinergic agents			
Tertiary amines	7 (6)	18 (15)	6 (5)
Ethers of tropine or tropine derivatives	1 (<1)	2 (2)	1 (<1)
Ethers chemically close to antihistamines	1 (<1)	0	0

SS=Safety Set

Data Source: Table 7.2

Efficacy Results Reported by the Sponsor

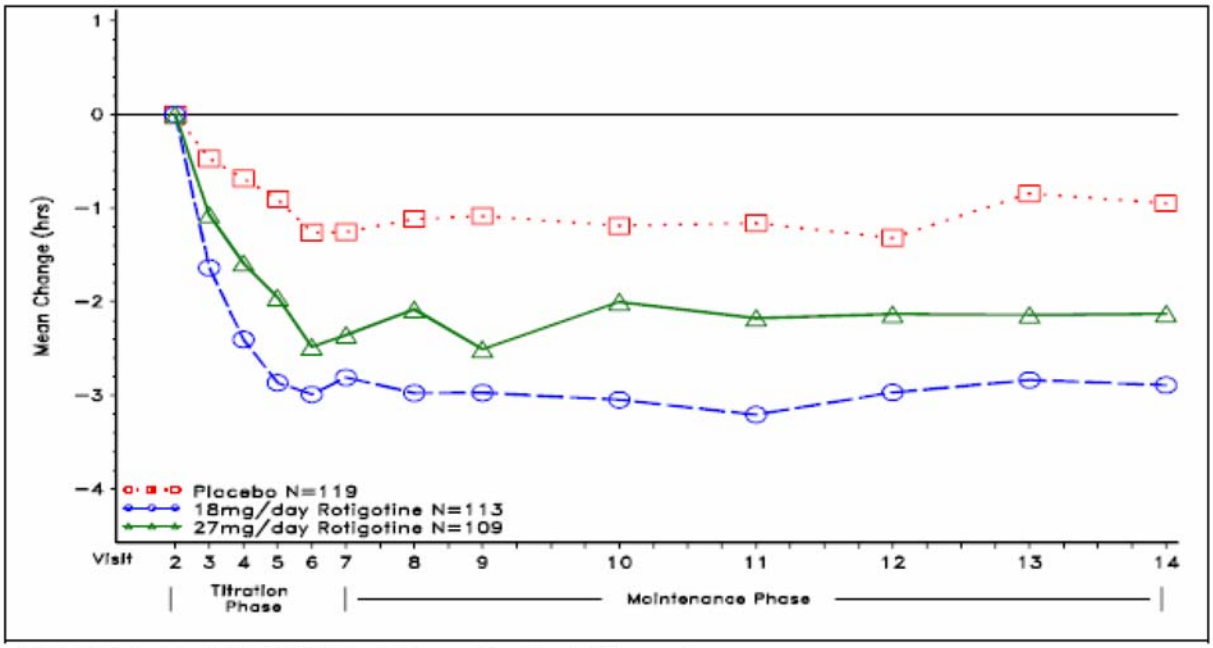
Primary Analysis for US – Change from Baseline in Absolute Time "Off"

The sponsor reported that at the end of treatment period, rotigotine 18.0mg/day and 27.0mg/day decreased the absolute "off" time by 2.7 hours and 2.1 hours, respectively, compared with a decrease of 0.9 hour in placebo-treated subjects. The mean baseline values were 6.4, 6.8, and 6.3 hrs respectively for placebo, 18 mg/day, and 27 mg/day. The decreases in "off" time for both rotigotine treatment groups are statistically significantly different from the decrease in the placebo group ($p<0.001$ for the 18.0mg/day group; $p=0.003$ for the 27.0mg/day group). The primary efficacy analysis for the primary efficacy endpoint is shown here. The percentage decrease in "Off" time was approximately 16 %, 43 % and 32 %, respectively for the placebo, 18mg/day, and 27 mg/day groups.

Efficacy Analysis - ANCOVA Results for Absolute Time Spent 'Off' (hrs)
(FAS With LOCF)

Response Variable	Treatment Group	n	LS Means (SE)	Treatment Comparison	Result (SE)	P-value[1]	95% C.I.
Change from Baseline to end Of Maintenence	Placebo	119	-0.9 (0.30)	27mg/day Rotig.-Placebo	-1.2 (0.41)	0.003	(-2.0,-0.4)
	18mg/day Rotig.	113	-2.7 (0.32)	18mg/day Rotig.-Placebo	-1.8 (0.41)	<0.001	(-2.6,-1.0)
	27mg/day Rotig.	109	-2.1 (0.32)				

The following figure presents the mean change from baseline in "off" times, by visit, for the FAS based upon LOCF. Data show that the maximal change for each treatment group occurred between the end of the titration period and early part of the maintenance period.



FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Visit 2 = Baseline; Visits 3, 4, 5, and 6 correspond to the beginning of dose Titration Phase Weeks 2, 3, 4, and 5, respectively; Visits 7, 8, 9, 10, 11, 12, 13, and 14 correspond to the beginning of Maintenance Phase Weeks 1, 3, 5,

Figure 1 Mean change in absolute "off" time (hours) by visit in SP650 (Source: Figure 4 of study report)

The following table shows the ANCOVA results for the treatment differences for the primary efficacy endpoint for different datasets The treatment differences were generally similar for the LOCF analysis, the per protocol analysis, and the completer analysis. The 2-sided p-values for all these treatment difference vs placebo were < 0.001 with the exception of $p < 0.003$ for the treatment difference for placebo and 27 mg/d for the FAS (e.g., LOCF).

ANCOVA results for change from Baseline to end of maintenance phase for mean change in absolute "off" time in SP650

Analysis	Treatment comparison	Treatment difference	p-Value (95% CI)
FAS, with LOCF	Rotigotine 27.0mg/day – placebo	-1.2	0.003 (-2.0, -0.4)
	Rotigotine 18.0mg/day – placebo	-1.8	<0.001 (-2.6, -1.0)
PPS, with LOCF	Rotigotine 27.0mg/day – placebo	-1.9	<0.001 (-2.8, -1.0)
	Rotigotine 18.0mg/day – placebo	-2.5	<0.001 (-3.4, -1.6)
End of Maintenance Visit Completers	Rotigotine 27.0mg/day – placebo	-1.7	<0.001 (-2.6, -0.8)
	Rotigotine 18.0mg/day – placebo	-2.2	<0.001 (-3.1, -1.4)

ANCOVA=Analysis of Covariance; CI=Confidence interval; FAS=Full Analysis Set; LOCF=Last Observation Carried Forward; PPS=Per Protocol Analysis Set

Data Source: Table 10.1, Table 10.2, Table 10.3

Primary analysis for the EU – Response Analysis
The sponsor reported that rotigotine 18.0mg/day and 27.0mg/day both resulted in a higher proportion of subjects who had a > 30% reduction in the absolute amount of "off" time at the end of treatment (57% and 55%, respectively) compared with placebo (34%). The proportions of responders in both rotigotine treatment groups are statistically significantly different from the proportion of responders in the placebo group ($p<0.001$ for both the 18.0mg/day and 27.0mg/day rotigotine groups).

Selected Secondary Efficacy Endpoints

Typically, the sponsor did not present nominal p-values for the treatment differences observed for secondary efficacy endpoints.

Change in L-DOPA Treatment
Mean daily doses from Baseline to Visit 14 were similar among treatment groups and ranged from 737mg-761mg in the placebo group, 680mg-770mg in the 18.0mg/day rotigotine group, and 723mg-769mg in the 27.0mg/day rotigotine group. The mean L-DOPA dose at baseline was approximately 753, 760, and 741 mg/day for placebo, 18 mg/day, and 27 mg/day, respectively. The mean change and percent change from Baseline in L-DOPA usage at each visit is summarized in the following table.

Summary of mean change and percent change from Baseline in L-DOPA consumption (SS)

Visit	Treatment group								
	Placebo (N=120)			Rotigotine 18.0mg/day (N=118)			Rotigotine 27.0mg/day (N=111)		
	n	Mean change (mg)	% Change	n	Mean change (mg)	% Change	n	Mean change (mg)	% Change
Titration period									
2	120	-	-	118	-	-	111	-	-
3	115	-1.3	-0.2	111	-3.6	-0.2	104	-2.9	-0.3
4	107	-11.7	-1.1	99	-8.1	-0.4	94	-6.4	-0.8
5	103	-5.3	-0.8	88	0.0	0.0	85	-7.6	-1.0
6	92	-6.0	-0.9	82	-2.4	-0.6	79	-9.0	-1.1
Maintenance period									
7	104	-10.1	-1.0	107	-27.1	-3.1	102	-12.8	-1.6
8	101	-18.3	-1.8	105	-31.4	-3.4	97	-32.0	-3.6
9	100	-22.0	-2.0	101	-22.8	-2.3	93	-44.2	-4.6
10	95	-11.6	-0.9	96	-22.9	-2.3	91	-45.7	-4.8
11	93	-17.7	-2.0	94	-23.4	-2.3	89	-46.7	-5.0
12	93	-11.3	-1.1	91	-25.3	-2.5	84	-34.6	-4.1
13	92	-12.5	-1.3	88	-23.9	-2.0	81	-39.0	-4.4
14	92	-13.6	-1.8	86	-26.7	-2.6	80	-39.5	-4.5

SS=Safety Set

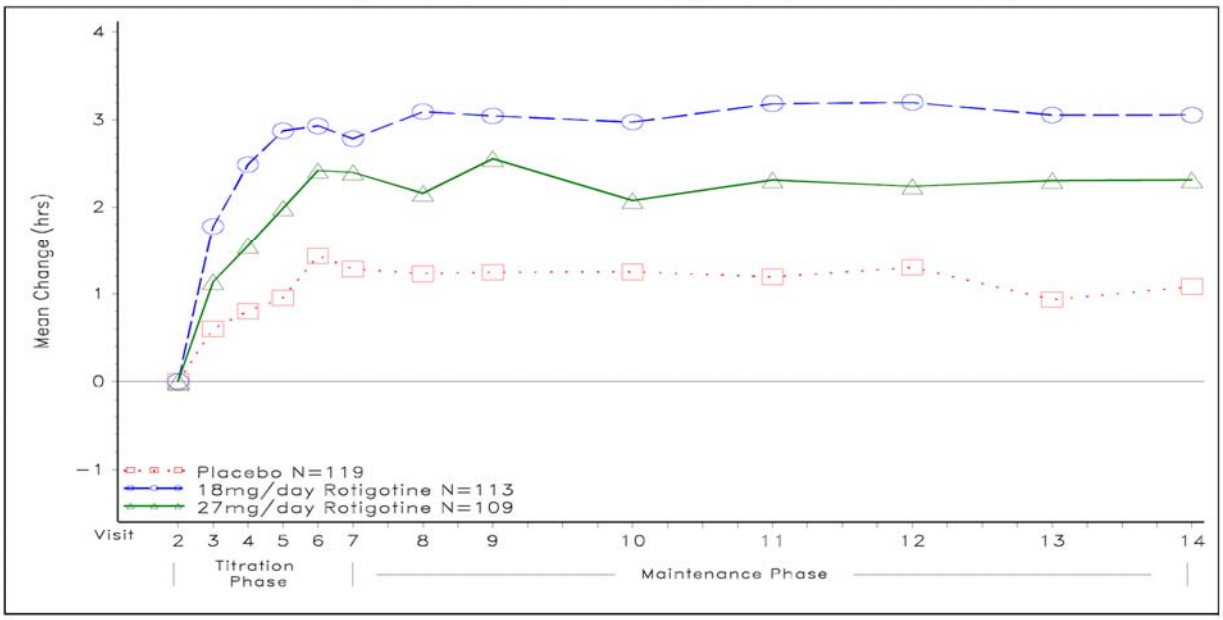
Data Source: Table 35.5.1, Table 35.5.2

At the end of the Maintenance Phase, all treatment groups showed a reduction in mean L-DOPA dose compared with Baseline (-13.6 to -39.5mg). The largest mean percentage changes in LDOPA dose were -2.0% (Visit 9, Visit 11) in the placebo group, -3.4% (Visit 8) in the 18.0mg/day rotigotine group, and -5.0% (Visit 11) in the 27.0mg/day rotigotine group. Data analyses showed that these changes in L-dopa doses during treatment occurred in few subjects in each treatment group (9/120 in the placebo group, 11/118 in the 18.0mg/day group, and 15/111 in the 27.0mg/day group). Thus, these results show that L-DOPA dosing was relatively stable across the treatment groups throughout the trial and changes occurred in few subjects across all treatment groups, although reductions were greater in the 2 rotigotine groups. L-DOPA dose adjustments were permitted during the first 2 weeks of maintenance, but were to remain stable throughout the remainder of the trial.

The most noteworthy result in the table below is the increase from baseline for the 18 mg/day treatment (+ 3.1 hrs) and for the 27 mg/day treatment (+2.3 hrs) vs placebo (+ 1.1 hrs). Similarly as with the beneficial reduction of "off" time from baseline, the lower dose showed a numerically greater benefit for an increase in "on" time as a change from baseline.

The mean change (e.g., increase) from baseline in "on" time according to treatment is shown over time at various visits based upon LOCF. As can be seen, the maximal change occurs essentially by the end of the titration phase and the effect is numerically greater for 18 mg/day than for 27 mg/day and both rotigotine treatments are numerically superior to the change for placebo. Of importance, the reduction in "off" time caused by rotigotine treatment appeared to be primarily related to a beneficial increase in "on" time.

Mean change in absolute "on" time, by visit (FAS with LOCF)



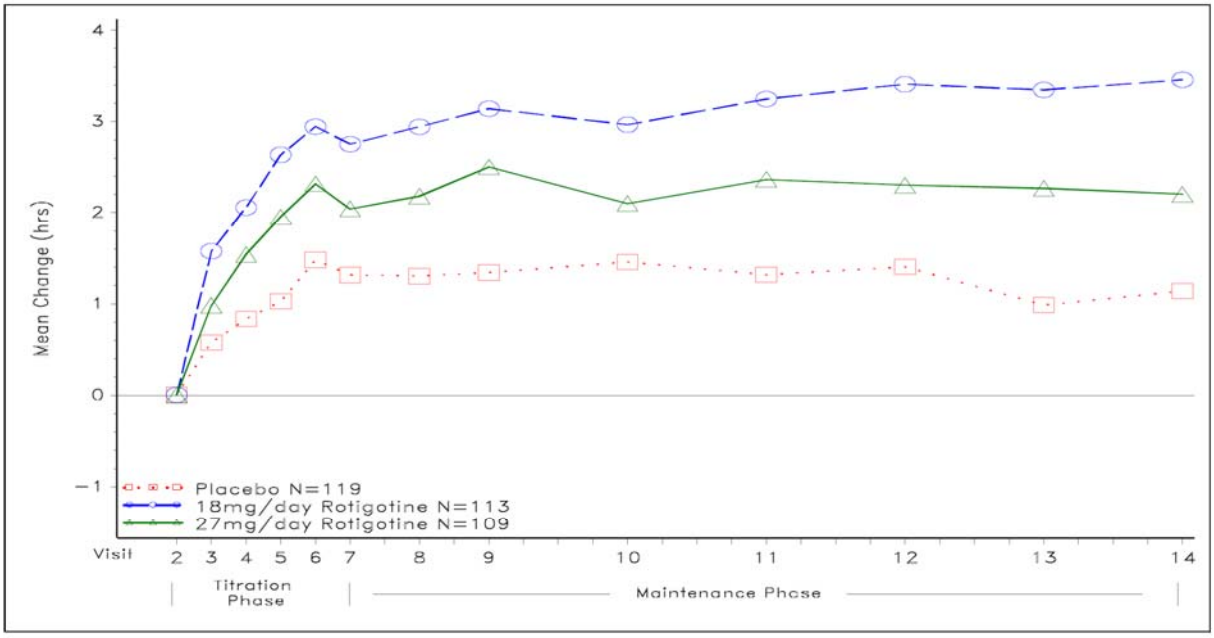
FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Visit 2 = Baseline; Visits 3, 4, 5, and 6 correspond to the beginning of dose Titration Phase Weeks 2, 3, 4, and 5, respectively; Visits 7, 8, 9, 10, 11, 12, 13, and 14 correspond to the beginning of Maintenance Phase Weeks 1, 3, 5, 9, 13, 17, 21 and 25, respectively.

Data Source: Figure 5.1

The table below shows the mean change (e.g., increase) from baseline in "on" time without troublesome dyskinesia over time throughout the study. Of significant relevance, the increase in "on" time resulting from rotigotine treatment was primarily related to an increase in "on" time without troublesome dyskinesia.

Mean change in absolute "on without troublesome dyskinesia" time, by visit (FAS with LOCF)



FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Visit 2 = Baseline; Visits 3, 4, 5, and 6 correspond to the beginning of dose Titration Phase Weeks 2, 3, 4, and 5, respectively; Visits 7, 8, 9, 10, 11, 12, 13, and 14 correspond to the beginning of Maintenance Phase Weeks 1, 3, 5, 9, 13, 17, 21 and 25, respectively.

Data Source: Figure 5.2

The table below shows that the % reduction in "off" time was primarily related to a similar % increase in "on" time without troublesome dyskinesia.

Summary of the percent change from Baseline at the end of the Maintenance Phase in the "on"/"off" status of subjects after waking (FAS with LOCF)

"On"/"off" status of subjects after waking	Placebo (N=119)	Rotigotine 18.0mg/day (N=113)	Rotigotine 27.0mg/day (N=109)
"Off" (%)	-9.1	-28.8	-22.6
"On" without troublesome dyskinesia (%)	8.5	27.0	20.9
"On" with troublesome dyskinesia (%)	0.6	1.8	1.7

FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Data Source: Table 24

The table below that each rotigotine treatment showed a similar, notable reduction in UPDRS subscale II (i.e., activities of daily living) that was greater than that for placebo and also a notable reduction in UPDRS motor subscale (vs placebo) but the reduction was greater for the higher rotigotine dose. There was no notable effect of rotigotine (vs placebo) for effects on various components of the UPDRS subscale IV for dyskinesia.

Summary of the change from Baseline at the end of the Maintenance Phase in the UPDRS Part II and III total scores, and UPDRS Part IV component scores (continuous data only) (FAS)

UPDRS Score	Placebo (n=89-92[a])	Rotigotine 18.0mg/day (n=84-87[a])	Rotigotine 27.0mg/day (n=79-81[a])
UPDRS II	-0.5	-3.1	-3.2
UPDRS III	-3.4	-6.8	-8.7
UPDRS IV - "What proportion of the waking day are dyskinesias Present?"	-0.1	-0.2	0.0
UPDRS IV - "How disabling are the dyskinesias?"	-0.1	-0.2	0.0
UPDRS IV - "How painful are the dyskinesias?"	-0.1	-0.1	0.0
UPDRS IV - "What proportion of the waking day is spent in the 'off', on average?"	-0.4	-0.6	-0.7

a The numbers of subjects with available data were not the same for each scale.

FAS=Full Analysis Set; UPDRS=Unified Parkinson's Disease Rating Scale

Data Source: Table 25, Table 26, Table 27.1.2, Table 27.2.2, Table 27.3.2, Table 27.8.2

Of significant interest and relevance, it is important to note that the reduction in "off" time from rotigotine treatment was not because of an increase in sleep as demonstrated in the table shown below here. There was not notable change (from baseline) in sleep time by any treatment.

Summary of the change from Baseline at the end of the Maintenance Phase in the number of hours subjects slept (FAS with LOCF)

	Placebo (N=119)	Rotigotine 18.0mg/day (N=113)	Rotigotine 27.0mg/day (N=109)
Change in number of hours subjects slept	-0.1	-0.2	-0.2

FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Data Source: Table 28

Study 515

Overview

Generally, similar advanced Parkinson's Disease patients were studied as in study 650. However, detailed data will not be presented as were presented for study 650, the main pivotal study supporting this NDA for advanced Parkinson's Disease. The Statistical Review by Dr.

Sharon Yan also contains more detailed info for study 515 results (see this review if more details are desired).

Primary Analysis for US – Change from Baseline in Absolute Time "Off"
At the end of the Maintenance Phase rotigotine decreased the absolute "off" time by 2.5 hours compared with a decrease of 2.8 hours in pramipexole-treated and 0.9 hour in placebo-treated subjects. The mean baseline "off" time was 6.6, 6.2, and 6.0 hrs for placebo, rotigotine, and pramipexole treatment groups, respectively. Decrease in "off" time for the rotigotine group is statistically significantly different from the decrease in the placebo group ($p<0.001$).

Figure 2 presents the absolute "off" times, by visit, for the FAS with LOCF.

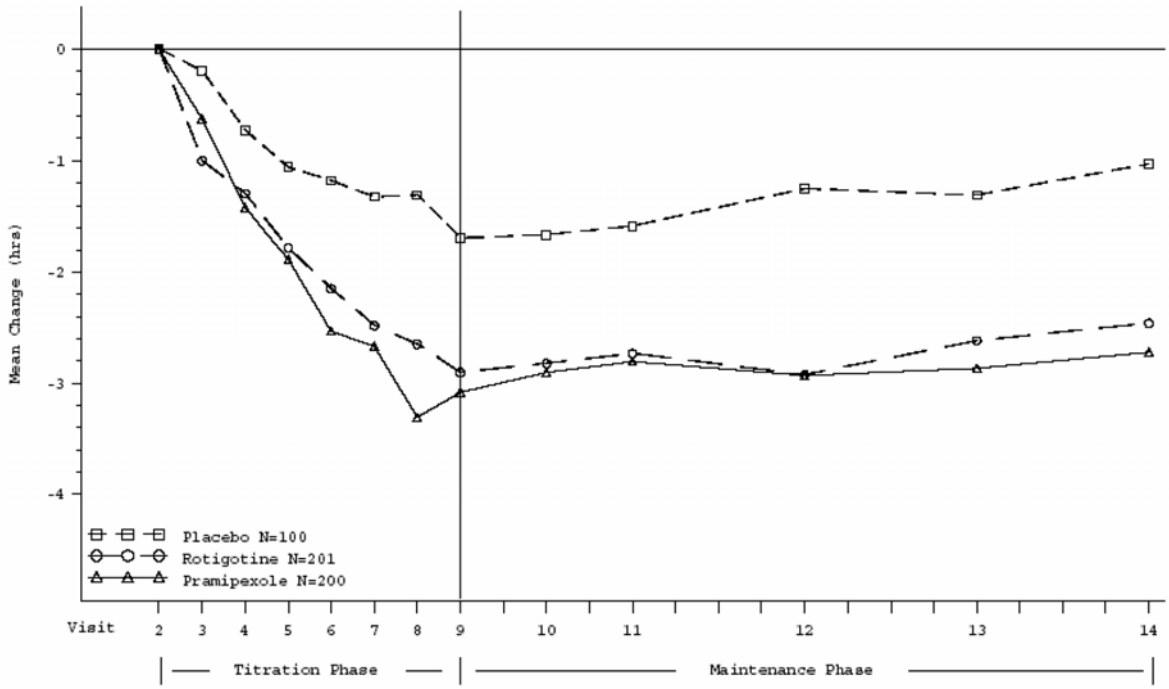


Figure 2 Mean change in absolute "off" time (hours) by visit in SP515 (Source: Figure 6.1 of study report)

ANCOVA results for change from Baseline to end of Maintenance Period for mean change in absolute "off" time in SP515

Analysis	Treatment comparison	Treatment difference	p-Value (95% CI)
FAS, with LOCF	Rotigotine–placebo	-1.58	<0.001 (-2.27, -0.90)
	Rotigotine–pramipexole	0.35	0.003[a] (-0.21, 0.92)
PPS, with LOCF	Rotigotine–placebo	-1.31	0.001 (-2.07, -0.55)
	Rotigotine–pramipexole	0.44	0.012[a] (-0.15, 1.03)
CS	Rotigotine–placebo	-1.50	<0.001 (-2.24, -0.77)
	Rotigotine–pramipexole	0.34	0.003[a] (-0.23, 0.91)

ANCOVA=Analysis of Covariance; CI=Confidence interval; CS=Completer Set; FAS=Full Analysis Set; LOCF=last observation carried forward; PPS=Per Protocol Analysis Set

a. p-value for noninferiority test with margin +1.2 hours

Data source: Table 10.1, Table 10.2, Table 10.3, Statistical Appendix

Study 511

Table 6 summarizes the absolute change from Baseline to end of treatment in absolute time spent "off" for the FAS, Randomized set. Improvement in time spent "off" was observed by Visit 3 in all treatment groups. At the end of treatment, all groups had a reduction from Baseline in the amount of time spent "off." The 27.0mg rotigotine group had the greatest improvement from Baseline, a 2.35-hour reduction in absolute time "off"; however, this improvement was not statistically significantly different from that in the placebo group (p=0.097).

Table 6 Summary of change from baseline in absolute "off" time in SP511 (Source: page 119 of study report)

Visit	Statistic	Placebo N=81	9.0mg Rotigotine N=77	18.0mg Rotigotine N=75	27.0mg Rotigotine N=77
Baseline (Visit 2)	Mean (SD), h	6.32 (2.48)	5.97 (2.54)	6.47 (2.63)	6.04 (2.85)
Visit 3	Mean (SD), h	6.05 (3.00)	5.71 (2.78)	5.92 (3.36)	4.85 (2.93)
Visit 4	Mean (SD), h	5.50 (3.01)	5.57 (3.55)	5.67 (2.99)	4.04 (2.98)
Visit 5	Mean (SD), h	5.48 (3.49)	4.84 (2.59)	4.76 (3.34)	3.93 (3.13)
Visit 6	Mean (SD), h	5.17 (3.25)	4.71 (2.90)	4.14 (3.33)	3.64 (3.06)
Visit 7	Mean (SD), h	4.67 (3.39)	3.90 (2.50)	4.03 (3.31)	3.79 (3.26)
Visit 8	Mean (SD), h	4.45 (3.38)	4.23 (3.19)	4.26 (3.24)	3.52 (3.10)
EOT (Visit 9)	Mean (SD), h	4.48 (3.44)	3.96 (3.17)	4.68 (3.43)	3.68 (3.54)
	Mean (SD) change from Baseline, h	-1.83 (3.13)	-2.00 (3.34)	-1.79 (2.94)	-2.35 (3.41)
	95% CI	-	-1.266 – 0.632	-0.867 – 1.049	-1.580 – 0.320
	p-value [a]	-	-	-	0.0965
	Adjusted mean (SED)	-1.81 (0.34)	-2.13 (0.35)	-1.72 (0.36)	-2.44 (0.35)
	Net effect [b] (SED)	-	-0.32 (0.48)	0.09 (0.49)	-0.63 (0.48)

Source Data: Table 20.1.2.1.1; Table 20.1.1.1.1
SD = standard deviation; h = hour; SED = standard error of the difference; EOT = end of treatment
a p-value based on ANCOVA; model included treatment group as a factor, country as a stratification factor, and Baseline value as a covariate.
b treatment adjusted mean minus placebo adjusted mean

Statistical Reviewer's Efficacy Analyses in Special/Subgroup Populations

Gender, Race and Age

Analyses of efficacy by gender and age group were performed for the primary endpoint of time spent "off". Study SP650 suggests that older patients may benefit more with rotigotine treatment. However, such finding is not confirmed by study SP515. 7 and 8 present the results from SP650 and SP515.

Table 7 Change from baseline in absolute "off" time by gender and age groups in SP650 (Source: Reviewer's analysis)

Study SP650	Placebo	Rotigotine	
		18 mg	27 mg
Time spent "off", mean (SD)			
Male			
n	73	76	71
Baseline	6.43 (2.69)	6.70 (2.42)	5.98 (2.29)
Change from baseline	-1.08 (2.64)	-2.96 (3.37)	-2.35 (3.38)
Female			
n	46	37	38
Baseline	6.35 (2.52)	7.05 (2.65)	6.87 (3.17)
Change from baseline	-0.75 (3.13)	-2.75 (3.32)	-1.71 (3.37)
Age < 65			
n	43	44	54
Baseline	6.69 (2.35)	6.71 (2.13)	6.44 (2.42)
Change from baseline	-0.27 (2.07)	-2.26 (2.99)	-1.62 (3.38)
Age ≥ 65			
n	76	69	55
Baseline	6.24 (2.76)	6.88 (2.71)	6.14 (2.87)
Change from baseline	-1.33 (3.13)	-3.29 (3.51)	-2.63 (3.32)

Table 8 Change from baseline in absolute "off" time by gender and age groups in SP515 (Source: Reviewer's analysis)

Study SP515	Placebo	Rotigotine	Pramipexole
Time spent "off", mean (SD)			
Male			
n	71	132	112
Baseline	6.74 (3.05)	6.25 (2.58)	5.99 (2.54)
Change from baseline	-1.19 (.68)	-2.44 (3.20)	-2.86 (3.23)
Female			
n	29	69	88
Baseline	6.17 (2.15)	6.23 (2.36)	5.98 (2.42)
Change from baseline	-0.62 (2.55)	-2.50 (2.81)	-2.54 (2.59)
Age < 65			
n	44	93	98
Baseline	6.91 (3.20)	6.6 (2.77)	5.95 (2.43)
Change from baseline	-0.84 (4.10)	-2.43 (3.08)	-2.31 (2.93)
Age ≥ 65			
n	56	108	102
Baseline	6.31 (2.48)	5.88 (2.19)	6.02 (2.54)
Change from baseline	-1.17 (2.74)	-2.49 (3.06)	-3.11 (2.95)

Other Special/Subgroup Populations

SP650 was mostly conducted in the United States except for the 5 subjects enrolled in Canada.

Analysis of the primary endpoint by region was performed for SP515, which was conducted in sites in Europe and South Africa. Countries with small number of subjects were not presented.

Large variations in baseline value and placebo response were observed. Overall, the efficacy of rotigotine found in those countries was not very different from the efficacy found in US trial SP650 except for New Zealand, which had a relatively small number of subjects. Results are presented in Table 9.

Table 9 Change from baseline in absolute "off" time by country in SP515 (Source: Reviewer's analysis)

SP515	Placebo	Rotigotine	Pramipexole
Time spent "off", mean (SD)			
Australia			
n	5	13	14
Baseline	7.77 (5.92)	7.14 (2.28)	6.85 (2.40)
Change from baseline	1.17 (2.25)	-3.52 (3.32)	-3.92 (3.28)
Croatia			
n	6	11	12
Baseline	5.21 (0.85)	4.83 (1.14)	4.93 (1.24)
Change from baseline	-0.60 (1.13)	-1.26 (2.40)	-2.52 (2.26)
Czech Republic			
n	13	23	22
Baseline	6.55 (2.62)	5.46 (2.52)	5.91 (2.12)
Change from baseline	-3.39 (2.83)	-2.48 (2.74)	-2.92 (2.45)
Israel			
n	6	14	14
Baseline	4.97 (1.24)	6.83 (1.97)	6.05 (1.86)
Change from baseline	-1.89 (3.77)	-2.70 (3.83)	-2.29 (2.04)
Italy			
n	11	22	18
Baseline	7.97 (2.58)	7.00 (2.58)	7.12 (2.79)
Change from baseline	-1.18 (4.59)	-2.16 (2.20)	-2.03 (4.31)
New Zealand			
n	4	7	8
Baseline	7.80 (2.79)	7.81 (4.85)	5.31 (1.73)
Change from baseline	-1.26 (8.13)	-6.29 (3.02)	-2.80 (1.84)
Norway			
n	2	6	7
Baseline	8.96 (3.82)	4.32 (1.71)	4.54 (1.83)
Change from baseline	0.17 (1.32)	-2.38 (2.65)	-0.95 (1.72)
Poland			
n	16	30	29
Baseline	5.25 (2.16)	6.50 (2.27)	5.50 (2.53)
Change from baseline	-0.11 (2.93)	-2.33 (2.69)	-2.50 (2.82)
South Africa			
n	14	27	25
Baseline	6.22 (2.33)	6.09 (2.56)	5.75 (2.61)
Change from baseline	-1.17 (2.78)	-2.08 (4.19)	-2.53 (3.36)
Spain			
n	11	20	19
Baseline	6.85 (2.32)	6.23 (2.51)	6.60 (2.75)
Change from baseline	-0.13 (2.30)	-1.66 (2.98)	-2.92 (3.51)
United Kingdom			
n	3	6	10
Baseline	9.69 (5.63)	6.13 (3.07)	6.90 (2.76)
Change from baseline	-0.18 (1.43)	-1.78 (3.72)	-4.31 (3.59)

Table 9 Change from baseline in absolute "off" time by country in SP515 (Source: Reviewer's analysis)

SP515	Placebo	Rotigotine	Pramipexole
Time spent "off", mean (SD)			
Australia			
n	5	13	14
Baseline	7.77 (5.92)	7.14 (2.28)	6.85 (2.40)
Change from baseline	1.17 (2.25)	-3.52 (3.32)	-3.92 (3.28)
Croatia			
n	6	11	12
Baseline	5.21 (0.85)	4.83 (1.14)	4.93 (1.24)
Change from baseline	-0.60 (1.13)	-1.26 (2.40)	-2.52 (2.26)
Czech Republic			
n	13	23	22
Baseline	6.55 (2.62)	5.46 (2.52)	5.91 (2.12)
Change from baseline	-3.39 (2.83)	-2.48 (2.74)	-2.92 (2.45)
Israel			
n	6	14	14
Baseline	4.97 (1.24)	6.83 (1.97)	6.05 (1.86)
Change from baseline	-1.89 (3.77)	-2.70 (3.83)	-2.29 (2.04)
Italy			
n	11	22	18
Baseline	7.97 (2.58)	7.00 (2.58)	7.12 (2.79)
Change from baseline	-1.18 (4.59)	-2.16 (2.20)	-2.03 (4.31)
New Zealand			
n	4	7	8
Baseline	7.80 (2.79)	7.81 (4.85)	5.31 (1.73)
Change from baseline	-1.26 (8.13)	-6.29 (3.02)	-2.80 (1.84)
Norway			
n	2	6	7
Baseline	8.96 (3.82)	4.32 (1.71)	4.54 (1.83)
Change from baseline	0.17 (1.32)	-2.38 (2.65)	-0.95 (1.72)
Poland			
n	16	30	29
Baseline	5.25 (2.16)	6.50 (2.27)	5.50 (2.53)
Change from baseline	-0.11 (2.93)	-2.33 (2.69)	-2.50 (2.82)

6.1.5 Clinical Microbiology

- Not applicable

6.1.6 Efficacy Conclusions

Sponsor's Efficacy Conclusions

The efficacy of rotigotine as therapy for advanced-stage Parkinson's disease has been established

in 3 randomized, double-blind, placebo-controlled, multicenter trials in 1177 subjects (SP511, SP650DB, and SP515). All 3 trials were designed to comply with appropriate regulatory guidance. In each of the pivotal trials, subjects had advanced-stage Parkinson's disease, based upon the facts that they had been diagnosed with idiopathic Parkinson's disease for more than 3 years, as defined by the United Kingdom Brain Bank criteria (cardinal sign, bradykinesia, plus the presence of at least 1 of the following: resting tremor, rigidity, or impairment of postural reflexes) and without any other known or suspected cause of Parkinsonism. The mean time since diagnosis was 8 years in these 3 trials, and the baseline "off" time was 6.3 hours.

Based on the results of these 3 trials, rotigotine at doses of 8mg/24h, 12mg/24h, and 16mg/24h are effective treatment for advanced-stage Parkinson's disease, although additional clinical benefit was not observed in doses above 8mg/24h.

Pooled results for change from Baseline in "off" time at Endpoint show that subjects with advanced-stage Parkinson's disease responded in a more pronounced manner to rotigotine than to placebo.

Statistical Reviewer's Efficacy Conclusions

Statistical Issues and Collective Evidence
No major issues were found in the two pivotal trials. Both pivotal trials have demonstrated that rotigotine is effective as a treatment for subjects with advanced Parkinson's disease who are not well controlled by levodopa.

Conclusions and Recommendations
The two pivotal studies showed that rotigotine is effective in the treatment of advanced Parkinson's disease as compared to placebo. The reduction in time spent "off" in rotigotine treated subjects was confirmed by increase in subjects' time spent "on" without an increase in time spent "on with dyskinesia". The rotigotine doses studied ranged from 9 mg to 36 mg, with doses of 18 mg and 27 mg studied in both pivotal studies. Both rotigotine 18 mg and 27 mg are found to be effective in the two pivotal studies. However, rotigotine 18 mg appeared to be more effective than rotigotine 27 mg. The non-inferiority claim of rotigotine to pramipexole could not be concluded.

Clinical Reviewer's Efficacy Conclusions

- Study 650 clearly shows statistically significant efficacy of rotigotine (vs placebo) for the primary analysis of the primary efficacy endpoint for both doses 18 and 27 mg (total drug patch content) daily in patients with advanced Parkinson's Disease.

- There was no additional efficacy and benefit of the 27 mg dose compared to the 18 mg dose for the primary efficacy endpoint. In fact, the 27 mg dose was numerically inferior to that of the 18 mg dose. This dose-response curve, that technically is an inverted "U" shaped curve, may merely reflect that daily doses at $\geq$ 18 mg produce maximal

population based efficacy and that efficacy at 18 mg and 27 mg may be statistically similar because 27 mg may not be statistically inferior to that of 18 mg.

- Considering that there is clearly increased toxicity at 27 mg vs 18 mg in a variety of safety analyses, and that there is no additional benefit of 27 mg vs 18 mg, the maximal dose that could be recommended would be 18 mg daily.

- The data indicate the need (as phase 4 commitment) for the sponsor to conduct a dose-response study to characterize the shape of the dose-response for efficacy and safety.

- The study design of study 650, that allowed patients potentially not to achieve their randomized treatment because patients were "optimally" treated in the titration period (and supposedly had 0 "off" hours), did not compromise the ability of this study to show dose-response data for efficacy. Only 12 total patients (N= 2 in Placebo; N=4 in18 mg dose group; N=6 in 27 mg dose) did not achieve their randomized treatment because of "optimal" efficacy. All 12 of these patients completed the trial.

- The analyses of the other diary categories (e.g., "on" time, "on" time with or without troublesome dyskinesia, sleep time), as secondary efficacy endpoints showed that the decrease in "off" time was primarily related to a desirable increase in "on" time and this increase in "on" time was primarily without troublesome dyskinesias. Neither did rotigotine produce noteworthy increase in sleep time.

- The sponsor did not provide nominal p-values for the secondary efficacy endpoints but the numerical changes/effects are consistent with potentially clinically important benefits.

- Not surprisingly, some patients treated with rotigotine may need to reduce their levodopa treatment.

- The results of study 515 show that rotigotine (at various "optimal" doses up to 36 mg daily) was statistically superior to placebo in decreasing "off" time. However, I did not consider results of this study to be very useful/helpful because most patients in this study were treated with doses > 18 mg daily, and study 650 did not suggest that doses above 18 mg provide additional therapeutic benefit.

- It is not clear why results from study 511 did not show that rotigotine treatment was statistically superior over that of placebo. One possibility explaining these negative results may be that the placebo response change was "excessive." In study 511, the mean change from baseline in "off" time at the end of the study was - 1.8 hrs, a potentially greater response than what one might expect. Of relevance to this issue, the mean change from baseline in "off" time for placebo at the end of study 650 and 515 was near – 1.0 hrs. In study 511, the mean change from baseline in "off" at the end of the study was about -2.0 hrs for 9 mg and about – 1.8 hrs for the 18 mg, potentially statistically similar changes. Of interest, the mean change from baseline in "off" at the end of the study for

the 27 mg dose was numerically greatest at -2.4 hrs. Furthermore, considering that the p-value the difference between 27 mg and placebo was 0.0965, with an adjusted mean of -1.8hrs for placebo , -2.4 hrs for rotigotine, and -0.6 hrs for an adjusted mean treatment difference/effect, I suggest that if the mean placebo response was much lower and approaching -1 hr, that a statistically significant difference (e.g., $p < 0.05$) would likely have been observed.

In my experience, a reduction in "off" time from baseline is not as large was observed in study 511 and more similar to those changes observed in studies 650 and 515. Results from other NDAs that I have reviewed support my hypothesis that the placebo response in study 511 was excessive. More specifically, in NDA 21479, the mean decrease in "off" from baseline at the end of the study was about – 2.5 hrs for Zydis selegiline and about -0.7 hrs for placebo. In NDA 21641 the mean decrease in "off" from baseline at the end of the study was about – 2 hrs for rasagiline and about -0.9 hrs for placebo. I think that an "excessive" placebo response largely accounts for the fact that this study was negative for showing that rotigotine is effective in advanced Parkinson's Disease.

- There were no major concerns about the efficacy of rotigotine based upon the review of Dr. Sharon Yan, Statistical Reviewer.

- The subgroup analyses did not suggest any significant concerns regarding the efficacy of rotigotine.

7 OVERALL ASSESSMENT

7.1 Conclusions

- I conclude that rotigotine is effective for adjunctive treatment (with levodopa) of patients with advanced Parkinson's Disease at a maximal dose of 18 mg/day (the only dose shown to be effective).

- At this time, a complete and final assessment of the safety of using rotigotine for adjunctive treatment of advanced Parkinson's Disease is not possible because there are safety issues that yet need to be addressed by the sponsor.

7.2 Recommendation on Regulatory Action

I recommend a complete response action for rotigotine for advanced Parkinson's Disease based upon :

- the unacceptable fact that there is crystal formation with the present patch;
- that additional safety analyses need to be completed and submitted :

- Conduct analyses of TEAEs that might possibly reflect events (regardless of level of severity) suggestive of the occurrence of hypotension/orthostatic hypotension/postural dizziness for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792).

- Conduct subgroup analyses of TEAEs occurring in certain subgroups (i.e., age, gender, concomitant medication such as vasodilator/hypotensive agents) for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792). In each of these requested subgroup analyses, the sponsor should compare the incidence of TEAEs in each pool's subgroup among each randomized rotigotine group and any rotigotine group with that of the respective placebo group in each pool's subgroup. The sponsor's subgroup analyses of TEAEs **only** considered the frequency of TEAEs for rotigotine treatment relative to each subgroup comparison and did not consider the frequency for placebo treatment in each subgroup analysis. Although the incidence of a certain TEAE such as vomiting could appear to be increased for females (vs males) if the frequency was 20 % for rotigotine treatment in females and 10 % for rotigotine treatment in males. However, if the incidence of vomiting with placebo treatment was 20 % and 10 % respectively, for females and males, there would not be any suggestion of an increased risk for vomiting in females.

- Review CRFs to see if more specific characterizations can be made for certain vague, nebulous preferred terms (PTs) such as "visual disorder," "visual disturbance," and "sleep disorder." If a more specific characterization has been made after this review, please submit the new incidence analyses for the PTs that have been altered. Please submit this for the TEAE analyses for the whole study period, the titration period, the maintenance period, TEAE persisting from titration into maintenance period according to treatment/randomized rotigotine dose for studies 650, and 790, and 792 separately, and for pools AS1 and RS1

7.3 Recommendation on Postmarketing Actions

7.3.1 Risk Management Activity

- I agree with the sponsor's risk management plan that is primarily based upon providing known toxicity and safety information in the label/package insert and conducting routine pharmacovigilance and monitoring results from ongoing and future clinical trials with rotigotine.

7.3.2 Required Phase 4 Commitments

A dose-response study should characterize the rotigotine dose-response for efficacy and safety for advanced Parkinson's Disease.

7.3.3 Other Phase 4 Requests

- Not applicable to clinical review for advanced Parkinson's Disease other than as noted above in section 1.2.2.

7.4 Labeling Review

- A formal labeling review was not completed because the DNP decided not to conduct a formal review because rotigotine cannot be approved at this time particularly because of CMC deficiencies .

7.5 Comments to Applicant

- Comments will be provided to the sponsor related to :

    - Conduct analyses of TEAEs that might possibly reflect events (regardless of level of severity) suggestive of the occurrence of hypotension/orthostatic hypotension/postural dizziness for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792).

    - Conduct subgroup analyses of TEAEs occurring in certain subgroups (i.e., age, gender, concomitant medication such as vasodilator/hypotensive agents) for pool AS1 (double-blind phase of studies 511 and 650) for advanced Parkinson's Disease and for pool RS1 (double-blind phase of studies 790 and 792). In each of these requested subgroup analyses, the sponsor should compare the incidence of TEAEs in each pool's subgroup among each randomized rotigotine group and any rotigotine group with that of the respective placebo group in each pool's subgroup. The sponsor's subgroup analyses of TEAEs **only** considered the frequency of TEAEs for rotigotine treatment relative to each subgroup comparison and did not consider the frequency for placebo treatment in each subgroup analysis. Although the incidence of a certain TEAE such as vomiting could appear to be increased for females (vs males) if the frequency was 20 % for rotigotine treatment in females and 10 % for rotigotine treatment in males. However, if the incidence of vomiting with placebo treatment was 20 % and 10 % respectively, for females and males, there would not be any suggestion of an increased risk for vomiting in females.

    - Review CRFs to see if more specific characterizations can be made for certain vague, nebulous preferred terms (PTs) such as "visual disorder,"

"visual disturbance," and "sleep disorder." If a more specific characterization has been made after this review, please submit the new incidence analyses for the PTs that have been altered. Please submit this for the TEAE analyses for the whole study period, the titration period, the maintenance period, TEAE persisting from titration into maintenance period according to treatment/randomized rotigotine dose for studies 650, and 790, and 792 separately, and for pools AS1 and RS1

APPENDICES

- Not applicable

REFERENCES

- Not applicable

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/s/

Leonard Kapcala
11/26/2008 09:32:26 PM
MEDICAL OFFICER

Norm, Here is my efficacy review for rotigotine for advanced PD. Dave is putting our joint safety review into DFS. Please let me know if any questions. Thanx. Len

Norman Hershkowitz
12/15/2008 01:17:59 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

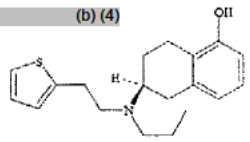
CHEMISTRY REVIEW(S)

Division of Post Approval Marketing Evaluation IV
Chemist Review of Supplement

1. Division of Post Approval Marketing IV
2. NDA Number: 21829
3. Supplement Numbers/Dates: SCM 035
   Letter Date: October 5, 2007
   Stamp Date: October 11, 2007
4. Date to Chemist: May 22, 2008

6. Applicant Name and Address: Schwarz Pharma
PO Box 110167
Research Triangle Park, NC 27709

7. Name of the Drug: Neupro® Transdermal Patch
8. Nonproprietary name: Rotigotine Transdermal System
9. Chemical Structure/ Chemical Name:



10: Dosage Form: transdermal patch
11. Potency: (b) (4) 2.25, (b) (4), (b) (4) 6.75 and 8 m
12. Pharmacological Category:
Restless Leg Syndrome
13. How Dispensed: XXX (RX) _____(OTC)
14. Records and Reports current XXX (yes) _____(No)
15. Related IND/NDA/DMF: _____(yes) _XXX__ (No)

17. **Evaluation: Inadequate**

This Prior Approval supplement provides for a new indication, for use of Neupro® Patches in the treatment of Restless Leg Syndrome and for the addition of two new dosage strengths, 2.25mg/5cm^2 and 6.75mg/15cm^2 patches. The manufacturing process and controls remains the same as the approved method for the preparation of Rotigotine. Batch release data, specifications and stability data are provided in support of the two new strengths. The formulation for each strength is the same, with the strength of the drug product, determined by the size of the patch. This supplement was submitted on October 11, 2007. Since the submission, the Agency was notified via correspondence dated December 6, 2007, of observed crystal formation on the patch, within (b) (4) of manufacture. Multiple discussions ensued about the impact of the crystallization on the marketed product, i.e. dose delivery. The Sponsor, via correspondence of March 21, 2008, informed the Agency of their intention to withdraw the product from the market by April 30, 2008 (see letters from Sponsor to Physicians/patients and pharmacists dated March 21, 2008.) Based on the above and due to the lack of product to market upon approval of this supplement, it is recommended to not approve this supplement at this time.

Recommendations: Non-Approval

19. Reviewer Name Julia C. Pinto, Ph.D., Chemist

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/s/

Julia Pinto
11/6/2008 04:55:06 PM
CHEMIST

Eric Duffy
11/6/2008 04:56:54 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	**21-829/036**
Drug Name:	Neupro® (Rotigotine Transderrmal System)
Indication(s):	Advanced Parkinson's Disease
Applicant:	Schwarz Pharma
Date(s):	**PDUFA Date: August 11, 2008**
Review Priority:	**Standard Review**
Biometrics Division:	**Division I**
Statistical Reviewer:	Sharon Yan
Concurring Reviewers:	**Kun Jin**
Medical Division:	**Division of Neurology Product**
Clinical Team:	**Leonard Kapcala, M.D., Clinical Reviewer**
	Norman Hershkowitz, M.D., Acting Clinical Team Leader
	Eric Bastings, M.D., Acting Deputy Director
Project Manager:	Susan Daugherty

Keywords:

Adverse event, analysis of covariance, closed-test procedure, confidence interval, double-blind, intent-to-treat, missing data, non-inferiority, one-sided/two-sided test, replication, subgroup analysis, superiority.

Table of Contents

1. EXECUTIVE SUMMARY

This submission is one of two supplemental NDAs being filed simultaneously for two indications: Restless Legs Syndrome (RLS) and Advanced Parkinson's Disease. This review is specific to the supplemental NDA for Neupro® for the treatment of the signs and symptoms of Advanced Parkinson's Disease.

1.1 Conclusions and Recommendations

The two pivotal studies showed that rotigotine is effective in the treatment of advanced Parkinson's disease as compared to placebo. The reduction in time spent "off" in rotigotine-treated subjects was confirmed by increase in subjects' time spent "on" without an increase in time spent "on with dyskinesia". The rotigotine doses studied ranged from 9 mg to 36 mg, with doses of 18 mg and 27 mg replicated in both pivotal studies. Both rotigotine 18 mg and 27 mg are found to be effective. However, rotigotine 18 mg appeared to be more effective than rotigotine 27 mg.

1.2 Brief Overview of Clinical Studies

The Advanced Parkinson's clinical development program consisted of two pivotal trials (SP650 and SP515) and a Phase II trial (SP511). Both pivotal studies are randomized, double-blind, placebo-controlled, parallel-group trial in subjects with Advanced-stage Parkinson's disease who are not well controlled on levodopa. Additionally, SP511 is a Phase IIb, randomized, double-blind, placebo-controlled, 4-arm dose finding trial. The daily dose of rotigotine studied in the trials ranged from 9 mg to 36 mg.

1.3 Statistical Issues and Findings

Both pivotal studies (SP650 and SP515) have showed that treatment of rotigotine resulted in a larger reduction in time spent "off" than treatment of placebo. Treatment difference between rotigotine and placebo reached statistical significance for both rotigotine doses 18 mg and 27 mg that were studied in SP650. Rotigotine 18 mg appeared to be more effective than rotigotine 27 mg in SP650 and this finding was confirmed in the flexible dose study SP515.

The non-inferiority claim with proposed margin of non-inferiority at 15% responder rate was for European registration purpose and was not pre-agreed by the Agency. The equvalence of the non-inferority margin for US endpoint and European endpoint was not established.

No major statistical issues were found.

2. INTRODUCTION

Rotigotine (Neupro®) is currently approved in the US for the treatment of signs and symptoms of early-stage, idiopathic Parkinson's disease (PD) at daily doses ranging from 1 to 3 mg. In the current submission, Schwarz Pharma proposes to expand the indication of rotigotine to include the treatment of signs and symptoms of advanced Parkinson's disease.

2.1 Overview

The Advanced Parkinson's clinical development program consisted of two pivotal trials (SP650 and SP515), and a phase II study SP511. All three trials are randomized, placebo-controlled, multi-center parallel group studies with rotigotine dose ranging from 9 mg to 36 mg per day in subjects with advanced PD who are not well controlled on L-dopa.

SP650 had three treatment arms: rotigotine 18mg, rotigotine 27mg and placebo. The trial, which was conducted in North America, consisted of a titration period of up to 5 weeks followed by a maintenance period of 24 weeks. SP515 was conducted in Europe and South Africa. It was a flexible dose trial with per-day dose of rotigotine ranging from 9 mg to 36 mg. The duration of SP515 consisted of up to 7 weeks titration and 16 weeks of maintenance period. Additionally, SP511 was a dose finding study with 4 treatment groups: 9 mg, 18 mg, and 27 mg of rotigotine, and placebo. The trial was conducted in Europe and South Africa.

The common primary efficacy endpoint for the three studies was the reduction from baseline in absolute time spent "off".

Based upon regulatory agency acceptance, two different primary analyses, one for the US and one for the European Union (EU), were implemented. The primary efficacy endpoint accepted by the US Food and Drug Administration (FDA) was the reduction in absolute time spent "off" from Baseline to the end of the Double-Blind Maintenance Period. The EU primary efficacy endpoint was the proportion of responders, with a "responder" defined as a subject with at least 30% decrease in absolute time spent "off" from Baseline to the end of Double-Blind Maintenance Period.

The primary variable for the US served as a secondary variable for the EU, and correspondingly, the primary variable for the EU served as a secondary variable for the US.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents of this NDA submission is listed below:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Pivotal Study SP650

3.1.1.1 Study Objectives

The primary objective of this trial was to show that rotigotine is efficacious as an adjuvant therapy in patients with advanced-stage idiopathic Parkinson's disease. A secondary objective was to demonstrate the tolerability and safety of rotigotine.

3.1.1.2 Study Design

This trial was a Phase 3, randomized, double-blind, placebo-controlled, 3-arm parallel group trial of rotigotine in subjects with advanced-stage, idiopathic Parkinson's disease who were not well controlled on L-DOPA. The study consisted of a titration period of up to 5 weeks and a maintenance period of 24 weeks. The trial was conducted in 55 sites in the United States and Canada.

Eligible subjects were randomized to receive either rotigotine at 1 of 2 target dose levels, or placebo. The target doses were 18 mg/day and 27 mg/day. Rotigotine was formulated in $10cm^2$, $20cm^2$, and $30cm^2$ silicone-based, transdermal patches containing 4.5mg, 9.0mg and 13.5mg rotigotine, respectively. The dose level of rotigotine/placebo was titrated at 7-day intervals from 9 mg until either the subject reached their 'optimal' dose or the titration period was complete. The dose was regarded as 'optimal' if the time per day that the subject spent in the 'off' state was zero. Once the subjects 'optimal' dose was identified or the titration period was complete, subjects commenced maintenance medication and remained at their optimal or maximum rotigotine/placebo dose, as appropriate. Subjects in the placebo group were randomized, in a ratio of 1:1, to either the placebo for rotigotine 18.0mg/day target dose group or the placebo for rotigotine 27.0mg/day target dose group.

The trial planned to enroll 460 subjects, and a total of 462 subjects were actually enrolled. Subjects who completed 6 months of double-blind maintenance treatment were provided with the opportunity to continue long-term rotigotine treatment.

3.1.1.3 Efficacy Evaluation

Based upon regulatory agency acceptance, 2 different primary analyses, 1 for the US and 1 for the European Union (EU), were implemented.

For US:

The primary efficacy endpoint accepted by the US Food and Drug Administration (FDA) was the reduction in absolute time spent "off" from Baseline to the end of the Double-Blind Maintenance Period.

For EU:

The EU primary efficacy endpoint was determined by the subject's response to therapy, with a "responder" defined as a subject with a $\geq$ 30% decrease in absolute time spent "off" from Baseline to the end of Double-Blind Maintenance Period.

A subject was considered "off" when he/she began to lose the optimum effects of the current anti-Parkinson medication. Absolute time "off" was defined as the number of hours marked "off" during a 24- hour period on the daily diary cards as filled out by the subjects. Specifically, the change that was examined was in the average daily time spent "off" among valid daily diaries provided just prior to Baseline and just prior to the end of Maintenance visit.

The primary variable for the US served as a secondary variable for the EU, and correspondingly, the primary variable for the EU served as a secondary variable for the US.

3.1.1.4 Statistical Analysis Methods

Estimates of the treatment effect were to be obtained by applying an analysis of covariance (ANCOVA) to the change from Baseline values in absolute time spent off, with treatment and the geographic region as factors and baseline absolute time "off" as a covariate. Comparative testing of the estimated treatment effect of each group was to be conducted using a closed test procedure starting with the comparison of 27.0mg/day rotigotine vs. placebo, using a t-test option from ANCOVA. If 27.0mg/day rotigotine proved to be significant against placebo, a second t-test was to be performed with 18.0mg/day rotigotine vs. placebo. In the event that the comparison of 27.0mg/day rotigotine vs. placebo failed to find statistical significance, the comparison of 18.0mg/day rotigotine vs. placebo was to be automatically declared to be statistically insignificant.

For EU, estimates of the effect of treatment were to be generated in the form of response rates and to be tested by large-sample normal approximation methods.

The primary analysis was to be based on the Full Analysis Set (FAS), which was defined as all randomized subjects receiving trial medication and having a valid baseline visit and having at least 1 valid post-baseline visit. Missing data due to missing or invalid diary cards were to be imputed based on a last-observation-carried-forward approach (LOCF).

3.1.1.5 Trial Population Results

3.1.1.5.1 Subject Disposition

A total of 462 subjects were enrolled in the trial. Of these, 351 subjects were randomized: 120 to receive placebo, 120 to receive 18.0mg/day rotigotine, and 111 to receive 27.0mg/day rotigotine. A slightly greater proportion of placebo-treated subjects completed the trial compared with rotigotine-treated subjects (77% for placebo-treated subjects, 73% for each of the 2 rotigotine-treated groups). This was mainly due to the slightly higher proportion of rotigotine-treated subjects who prematurely discontinued the trial for the occurrence of an AE (9% in the placebo group vs. 15% in each of the 2 rotigotine groups). Between treatment groups, similar proportions of subjects prematurely discontinued as a result of major protocol violations, unsatisfactory compliance, and withdrawal of consent. Fewer rotigotine-treated subjects (5%-6% across both groups) prematurely discontinued the trial due to lack of efficacy compared with placebo-treated subjects (9%).

3.1.1.5.2 Subject Demographics and Baseline Characteristics

Overall, the average age of randomized subjects was 66 years old with 42% of the subjects younger than 65 years old. The majority of subjects (64%) were male, and nearly all subjects (93%) were white. A greater proportion of subjects treated with 27.0mg/day rotigotine (50%) were < 65 years old compared to subjects treated with 18.0mg/day rotigotine (40%) or with placebo (37%).

At Baseline, the majority of subjects (58%) had a CGI score of 4, indicating moderate illness. The mean time since subjects were first diagnosed with Parkinson's disease was 7.7 years. The mean absolute "off" times at baseline were greater in the rotigotine 18.0mg/day group (6.7 hours) than in the placebo group (6.4 hours) or the 27.0mg/day group (6.3 hours). Overall, 63% of subjects had a UPDRS II score of $\leq$ 14, and the maximum (worst) UPDRS II score in the trial was 36. Sixty-four percent of subjects overall had a UPDRS III score of $\leq$ 29, and the maximum (worst) UPDRS III score in the trial was 83.

Other than the differences in absolute "off" time between treatment groups at Baseline, there were no important differences in Baseline characteristics across treatment groups.

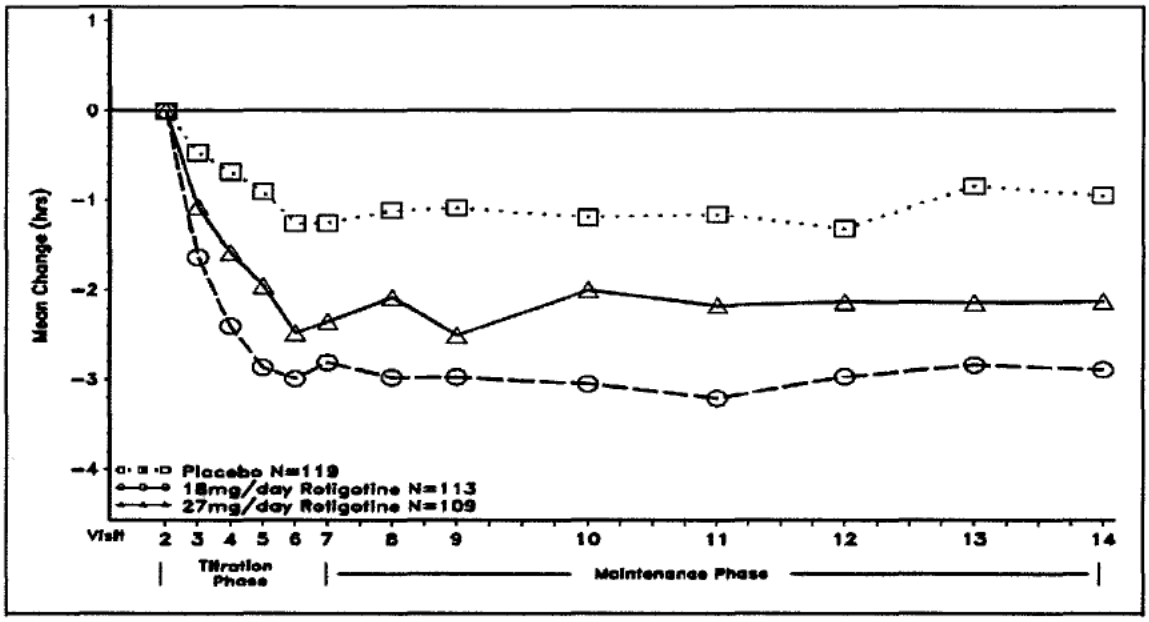
3.1.1.6 Efficacy Results Reported by the Sponsor

Primary Analysis for US – Change from Baseline in Absolute Time "Off"

The sponsor reported that at the end of treatment period, Rotigotine 18.0mg/day and 27.0mg/day decreased the absolute "off" time by 2.7 hours and 2.1 hours, respectively, compared with a decrease of 0.9 hour in placebo-treated subjects. The decreases in "off" time for both rotigotine

treatment groups are statistically significantly different from the decrease in the placebo group ($p<0.001$ for the 18.0mg/day group; $p=0.003$ for the 27.0mg/day group).

The following figure presents the absolute "off" times, by visit, for the FAS with LOCF.



FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Visit 2 = Baseline; Visits 3, 4, 5, and 6 correspond to the beginning of dose Titration Phase Weeks 2, 3, 4, and 5, respectively; Visits 7, 8, 9, 10, 11, 12, 13, and 14 correspond to the beginning of Maintenance Phase Weeks 1, 3, 5,

Figure 1 Mean change in absolute "off" time (hours) by visit in SP650 (Source: Figure 4 of study report)

Primary analysis for the EU – Response Analysis

The sponsor reported that rotigotine 18.0mg/day and 27.0mg/day both resulted in a higher proportion of subjects who had a $\geq$ 30% reduction in the absolute amount of "off" time at the end of treatment (57% and 55%, respectively) compared with placebo (34%). The proportions of responders in both rotigotine treatment groups are statistically significantly different from the proportion of responders in the placebo group ($p<0.001$ for both the 18.0mg/day and 27.0mg/day rotigotine groups).

3.1.1.7 Reviewer's Analysis Results

The results from the reviewer's analysis are slightly different from the ones reported by the sponsor.

Table 1 presents the results from analyses of primary endpoints for US and EU. Analyses of time spent "on" and "on with dyskinesia" were also presented to verify the primary endpoint.

Table 1 Efficacy results from reviewer's analysis – SP650

Study SP650	Placebo	Rotigotine	
	n=119	18 mg (n=113)	27 mg (n=109)
Time spent "off", mean (SD) (hour)			
Baseline	6.40 (2.62)	6.82 (2.49)	6.29 (2.65)
Change from baseline	-0.95 (2.83)	-2.89 (3.37)	-2.13 (3.37)
p-value		<.0001	0.003
Number (%) of responders	41 (34.45%)	64 (56.64%)	60 (55.05%)
p-value		0.0007	0.0018
Time spent "on" (hour)			
n	92	86	80
Baseline	9.85 (2.60)	9.37 (2.46)	10.11 (2.55)
Change from baseline	1.09 (2.78)	3.38 (3.33)	2.84 (3.03)
p-value		<.0001	<.0001
Time spent "on" with Dyskinsia (hr)			
n			
Baseline	92	86	80
Change from baseline	1.14 (2.04)	1.17 (2.22)	0.77 (1.78)
p-value	-0.23 (1.33)	-0.38 (1.73)	0.10 (1.96)
		0.4733	0.4073

Analysis using observed-case patient population yielded similar results, which are presented in the following table.

Table 2 Time spent "off" and response rate from observed case analysis

Study SP650	Placebo	Rotigotine	
	n=92	18 mg (n=86)	27 mg (n=80)
Time spent "off", mean (SD) (hour)			
Baseline	6.28 (2.60)	6.86 (2.57)	6.24 (2.34)
Change from baseline	-1.01 (2.83)	-3.36 (3.07)	-2.62 (3.19)
p-value		<.0001	.0005
Number (%) of responders	36 (39.13%)	55 (63.95%)	49 (61.25%)
p-value		.0009	.0038

3.1.2 Pivotal Study SP515

3.1.2.1 Study Objectives

The primary objective of this trial was to show that rotigotine is efficacious as an adjuvant therapy in subjects with advanced-stage Parkinson's disease. It was anticipated that rotigotine is more effective than placebo and is as efficacious as pramipexole.

3.1.2.2 Study Design

This trial was a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, flexible-dose parallel-group trial of rotigotine in subjects with advanced-stage, idiopathic Parkinson's disease who experienced wearing-off type motor-fluctuations on L-dopa. Eligible patients were randomized in a ratio of 2:2:1 to receive rotigotine, pramipexole, or placebo. The per-day dose of rotigotine ranged from 9 mg to 36 mg. Subjects went through up to 7 weeks of titration period and a 16-week maintenance period, followed by a dose de-escalation phase of up to 6 days and a 4-week follow-up phase. The trial was conducted in 17 countries in Europe and South Africa.

3.1.2.3 Efficacy measurements

The primary variable for the US was absolute change from Baseline in time spent "off", which served as a secondary variable for the EU. Correspondingly, the primary variable for EU, the proportion of responders, served as a main secondary efficacy variable for US. A responder was defined as a subject with a $\geq$ 30% decrease in absolute time spent "off."

3.1.2.4 Statistical Methods

The primary efficacy variable of change from baseline in time spent "off" was to be analyzed using an ANCOVA with treatment and country as factors and Baseline "off" time as a covariate. The treatment differences were to be tested in a pre-assigned order (closed testing procedure). The procedure started with a test between rotigotine and placebo. In case of rejection (i.e., rotigotine is superior to placebo), it was to be proceeded to a 1-sided full level α=2.5% non-inferiority test (the non-inferiority margin of -15% in the responder criterion was said to correspond to approximately 1.2 points in the absolute "off" time reduction) between rotigotine and pramipexole. If rotigotine proved to be non-inferior to pramipexole and if the corresponding confidence interval (CI) lied above 0, then a 2-sided p-value for superiority of rotigotine to pramipexole was to be calculated.

The proportion of responders was to be analyzed using normal approximation methods. The comparisons among the treatment groups were to follow the same procedure specified for the primary endpoint mentioned above.

The primary efficacy analysis for both variables was to be based on FAS.

3.1.2.5 Trial Population Results

3.1.2.5.1 Subject Disposition

Of the 604 subjects enrolled, 506 subjects were randomized: 101 subjects to receive placebo, 204 to receive rotigotine, and 201 to receive pramipexole. In general, a higher proportion of rotigotine- or pramipexole-treated subjects completed the trial compared with placebo-treated

subjects (74.3% of placebo-treated subjects, 88.7% of rotigotine, and 85.6% of pramipexole-treated subjects). Compared with the rotigotine and the pramipexole groups, a higher proportion of placebo-treated subjects prematurely discontinued the trial due to withdrawal of consent (7.9% of placebo-treated subjects, 3.9% of rotigotine, and 2.0% of pramipexole-treated subjects). For 6.9% of placebo-treated subjects, lack of efficacy was the reason to discontinue the trial prematurely (versus 1.5% in the rotigotine and the pramipexole groups). The rotigotine group had the lowest rate of discontinuations due to AEs (5.4% versus 7.0% in the pramipexole group and 5.9% in the placebo group).

3.1.2.5.2 Subject Demographics and Baseline characteristics

The average age of study subjects was 64.0 years. The subject's average age was similar across all treatment groups. The majority of subjects were male (70.7% in the placebo, 64.9% in the rotigotine, and 56.4% in the pramipexole group). Nearly all subjects (97.2%) were White. At Baseline, the majority of subjects (56.1%) had a CGI score of 4 indicating moderate illness. In the pramipexole group, the proportion of moderately ill subjects was lower than in the other 2 groups (48% vs. 61.0% and 62.6% in the rotigotine and placebo group, respectively). The mean time since subjects were first diagnosed with Parkinson's disease was 8.6 years.

The mean absolute "off" times at Baseline were 6.3 hours in the rotigotine group, 6.0 hours in the pramipexole group, and 6.5 hours in the placebo group. Overall, 71.9% of subjects had a UPDRS II score of ≤ 14, and the maximum (worst) UPDRS II score in the trial was 33. Overall, 65.2% of subjects had a UPDRS III score of ≤ 29, and the maximum (worst) UPDRS III score in the trial was 66.

3.1.2.6 Efficacy Results Reported by the Sponsor

Primary Analysis for US – Change from Baseline in Absolute Time "Off"

At the end of the Maintenance Phase rotigotine decreased the absolute "off" time by 2.46 hours compared with a decrease of 2.81 hours in pramipexole-treated and 0.88 hour in placebo-treated subjects. Decrease in "off" time for the rotigotine group is statistically significantly different from the decrease in the placebo group ($p<0.001$).

Figure 2 presents the absolute "off" times, by visit, for the FAS with LOCF.

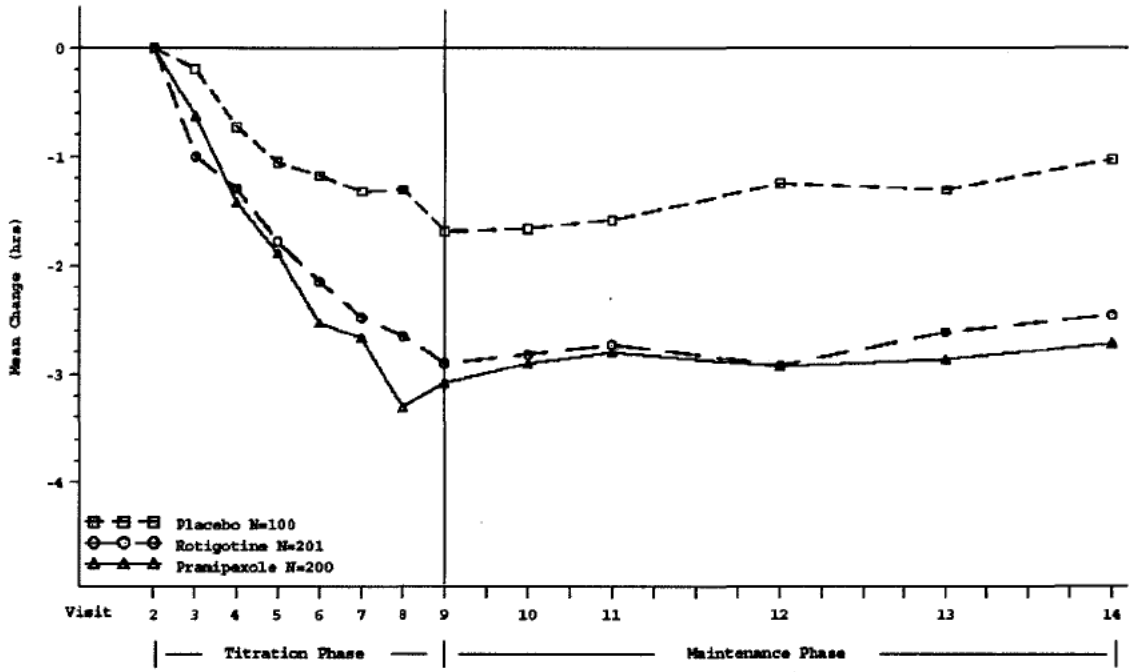


Figure 2 Mean change in absolute "off" time (hours) by visit in SP515 (Source: Figure 6.1 of study report)

Primary analysis for the EU – Response Analysis

Rotigotine and pramipexole treatment both resulted in a higher proportion of subjects who had a ≥ 30% decrease in the absolute amount of "off" time at the end of Maintenance (59.7% and 67.0%, respectively) compared with placebo (35.0%). The proportions of responders in the rotigotine group is statistically significantly different from the proportion of responders in the placebo group ($p<0.001$).

3.1.2.7 Reviewer's Analysis Results

The results obtained by the reviewer are slightly different from the ones reported by the sponsor. Table 3 presents the results from analyses of primary endpoints for US and EU. Results from analysis of related secondary endpoints are also presented.

Table 3 Efficacy results from reviewer's analysis – SP515

SP515	Placebo (n=100)	Rotigotine (n=201)	Pramipexole (n=200) (vs. rotigotine)
Time spent "off", mean (SD) (hr)			
n	100	201	200
Baseline	6.57 (2.82)	6.24 (2.50)	5.99 (2.48)
Change from baseline	-1.03 (3.39)	-2.46 93.07)	-2.72 (2.96)
p-value		<.0001	0.1883
Number (%) of responders	34 (34.34%)	122 (60.40%)	130 (65.66%)
		<.0001	.2759
Time spent "on"			
n	74	179	171
Baseline	9.80 (2.45)	9.83 (2.36)	9.92 (2.44)
Change from baseline	0.92 (3.31)	2.61 (2.99)	2.93 (2.75)
p-value		<.0001	.2194
Time spent "on" with Dyskinesia			
n	74	179	171
Baseline	1.01 (1.76)	1.44 (2.35)	1.49 (2.31)
Change from baseline	-0.43 (1.94)	-0.43 (2.14)	-0.03 (2.41)

Analysis using observed-case patient population yielded similar results, which are presented in the following table.

Table 4 Time spent "off" and response rate from observed case analysis

SP515	Placebo (n=74)	Rotigotine (n=179)	Pramipexole (n=171) (vs. rotigotine)
Time spent "off", mean (SD) (hr)			
Baseline	6.09 (2.40)	6.21 (2.49)	6.06 (2.41)
Change from baseline	-1.18 (3.26)	-2.69 (2.99)	-2.97 (2.78)
p-value		.0001	.2071
Number (%) of responders	30 (40.54%)	116 (64.80%)	120 (70.18%)
		.0004	.2838

The following table describes change from baseline in time spent "off" by dose exposure for rotigotine-treated patients.

Table 5 Change from baseline in absolute "off" time by dose exposure for rotigotine-treated subjects

Dose	9.0 mg	13.5 mg	18.0 mg	22.5 mg	27.0 mg	31.5 mg	36.0 mg
Number (%)of subjects	5 (2.5)	15 (7.6)	16 (8.1)	18 (9.1)	33 (16.7)	22 (11.1)	89 (44.9)
Change in time spent "off"							
n		36		50		111	
Mean (SD)		-2.77 (3.35)		-2.44 (3.31)		-2.43 (2.90)	
Median		-3.10		-2.54		-2.58	

Nearly half of the subjects were titrated to rotigotine 36 mg. It appears that rotigotine dose higher than 18 mg does not add benefit in efficacy, which confirms the findings from study SP650.

3.1.3 Study SP511

3.1.3.1 Description of the Study

SP511 was a Phase 2b, 4-arm, dose-finding trial. The study consisted of a pretreatment Run-In Phase of up to 6 weeks, during which any dopamine agonist was withdrawn and L-dopa doses were adjusted and kept stable, followed by a 12-week Treatment Phase, which consisted of 5 weeks of titration and 7 weeks of maintenance. Subjects were randomized to treatment with patches delivering 1 of 3 active target doses of rotigotine (9.0mg, 18.0mg, or 27.0mg) or placebo.

The primary efficacy variable was the absolute change from Baseline to end of treatment in absolute time spent "off". A closed test procedure was used to identify the minimal effective dose using the pre-assigned order from the highest dose (rotigotine 27 mg) to the lowest (rotigotine 9 mg). The test procedure was used in conjunction with an ANCOVA with treatment group and country as factors, and baseline time "off" as a covariate. Data from countries for which less than 20 subjects were randomized were pooled (Latvia, United Kingdom, Germany, The Netherlands and Finland).

3.1.3.2 Trial Population Results

All 45 participating centers in 12 countries in Europe and South Africa enrolled subjects. Of the 383 subjects enrolled, 324 subjects were randomized to treatment: 84 to the placebo group, 80 to the 9.0mg rotigotine group, 81 to the 18.0mg rotigotine group, and 79 to the 27.0mg rotigotine group.

Overall, most subjects completed the entire Treatment Phase (80% - 87%). The occurrence of an AE was the primary reason for trial discontinuation followed by consent withdrawal and "other." Over the entire Treatment Phase, the proportion of subjects with AE discontinuations ranged from 6% - 11% across treatment groups.

The 4 treatment groups were similar with respect to the demographic characteristics. The mean age of subjects was within the range of 62 to 65 years. Approximately 60% to 65% of the subjects were males, and nearly all subjects (98%) were white.

The mean number of years since diagnosis was similar across the treatment groups (range 7.3 - 7.9 years). The mean absolute "off" times at Baseline were 6.3 hours in the rotigotine group, 6.0 hours in the pramipexole group, and 6.5 hours in the placebo group. Across the treatment groups, the mean UPDRS II score was between 18.3 and 19.6, and the mean UPDRS III score was between 29.4 and 33.1.

3.1.3.3 Efficacy Results Reported by the Sponsor

Table 6Table 6 summarizes the absolute change from Baseline to end of treatment in absolute time spent "off" for the FAS, Randomized set. Improvement in time spent "off" was observed by Visit 3 in all treatment groups. At the end of treatment, all groups had a reduction from Baseline in the amount of time spent "off." The 27.0mg rotigotine group had the greatest improvement from Baseline, a 2.35-hour reduction in absolute time "off"; however, this improvement was not statistically significantly different from that in the placebo group (p=0.097).

Table 6 Summary of change from baseline in absolute "off" time in SP511 (Source: page 119 of study report)

Visit	Statistic	Placebo N=81	9.0mg Rotigotine N=77	18.0mg Rotigotine N=75	27.0mg Rotigotine N=77
Baseline (Visit 2)	Mean (SD), h	6.32 (2.48)	5.97 (2.54)	6.47 (2.63)	6.04 (2.85)
Visit 3	Mean (SD), h	6.05 (3.00)	5.71 (2.78)	5.92 (3.36)	4.85 (2.93)
Visit 4	Mean (SD), h	5.50 (3.01)	5.57 (3.55)	5.67 (2.99)	4.04 (2.98)
Visit 5	Mean (SD), h	5.48 (3.49)	4.84 (2.59)	4.76 (3.34)	3.93 (3.13)
Visit 6	Mean (SD), h	5.17 (3.25)	4.71 (2.90)	4.14 (3.33)	3.64 (3.06)
Visit 7	Mean (SD), h	4.67 (3.39)	3.90 (2.50)	4.03 (3.31)	3.79 (3.26)
Visit 8	Mean (SD), h	4.45 (3.38)	4.23 (3.19)	4.26 (3.24)	3.52 (3.10)
EOT (Visit 9)	Mean (SD), h	4.48 (3.44)	3.96 (3.17)	4.68 (3.43)	3.68 (3.54)
	Mean (SD) change from Baseline, h	-1.83 (3.13)	-2.00 (3.34)	-1.79 (2.94)	-2.35 (3.41)
	95% CI	-	-1.266 – 0.632	-0.867 – 1.049	-1.580 – 0.320
	p-value[a]	-	-	-	0.0965
	Adjusted mean (SED)	-1.81 (0.34)	-2.13 (0.35)	-1.72 (0.36)	-2.44 (0.35)
	Net effect[b] (SED)	-	-0.32 (0.48)	0.09 (0.49)	-0.63 (0.48)

Source Data: Table 20.1.2.1.1; Table 20.1.1.1.1

SD = standard deviation; h = hour; SED = standard error of the difference; EOT = end of treatment

a p-value based on ANCOVA; model included treatment group as a factor, country as a stratification factor, and Baseline value as a covariate.

b treatment adjusted mean minus placebo adjusted mean

Figure 3 illustrates efficacy by visit for the FAS, Randomized set.

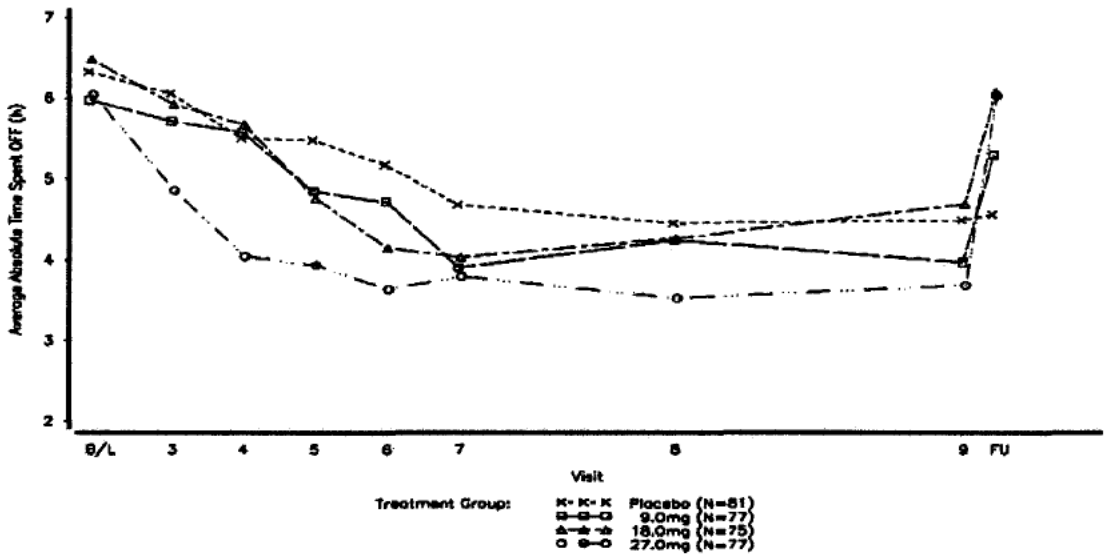


Figure 3 Average time spent "off" by visit in SP511 (Source: Figure 1.1.1.1 of study report)

It is notable that the placebo group had a higher than normal treatment effect and did not return to baseline after washout of trial medication.

3.2 Evaluation of Safety

Please refer to clinical review by Dr. Leonard Kapcala for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Analyses of efficacy by gender and age group were performed for the primary endpoint of time spent "off". Study SP650 suggests that older patients may benefit more with rotigotine treatment. However, such finding is not confirmed by study SP515. 7 and 8 present the results from SP650 and SP515.

Table 7 Change from baseline in absolute "off" time by gender and age groups in SP650 (Source: Reviewer's analysis)

Study SP650	Placebo	Rotigotine	
		18 mg	27 mg
Time spent "off", mean (SD)			
Male			
n	73	76	71
Baseline	6.43 (2.69)	6.70 (2.42)	5.98 (2.29)
Change from baseline	-1.08 (2.64)	-2.96 (3.37)	-2.35 (3.38)
Female			
n	46	37	38
Baseline	6.35 (2.52)	7.05 (2.65)	6.87 (3.17)
Change from baseline	-0.75 (3.13)	-2.75 (3.32)	-1.71 (3.37)
Age < 65			
n	43	44	54
Baseline	6.69 (2.35)	6.71 (2.13)	6.44 (2.42)
Change from baseline	-0.27 (2.07)	-2.26 (2.99)	-1.62 (3.38)
Age ≥ 65			
n	76	69	55
Baseline	6.24 (2.76)	6.88 (2.71)	6.14 (2.87)
Change from baseline	-1.33 (3.13)	-3.29 (3.51)	-2.63 (3.32)

Table 8 Change from baseline in absolute "off" time by gender and age groups in SP515 (Source: Reviewer's analysis)

Study SP515	Placebo	Rotigotine	Pramipexole
Time spent "off", mean (SD)			
Male			
n	71	132	112
Baseline	6.74 (3.05)	6.25 (2.58)	5.99 (2.54)
Change from baseline	-1.19 (.68)	-2.44 (3.20)	-2.86 (3.23)
Female			
n	29	69	88
Baseline	6.17 (2.15)	6.23 (2.36)	5.98 (2.42)
Change from baseline	-0.62 (2.55)	-2.50 (2.81)	-2.54 (2.59)
Age < 65			
n	44	93	98
Baseline	6.91 (3.20)	6.6 (2.77)	5.95 (2.43)
Change from baseline	-0.84 (4.10)	-2.43 (3.08)	-2.31 (2.93)
Age ≥ 65			
n	56	108	102
Baseline	6.31 (2.48)	5.88 (2.19)	6.02 (2.54)
Change from baseline	-1.17 (2.74)	-2.49 (3.06)	-3.11 (2.95)

4.2 Other Special/Subgroup Populations

SP650 was mostly conducted in the United States except for the 5 subjects enrolled in Canada. Analysis of the primary endpoint by region was performed for SP515, which was conducted in sites in Europe and South Africa. Countries with small number of subjects were not presented.

Large variations in baseline value and placebo response were observed. Overall, the efficacy of rotigotine found in those countries was not very different from the efficacy found in US trial SP650 except for New Zealand, which had a relatively small number of subjects. Results are presented in Table 9.

Table 9 Change from baseline in absolute "off" time by country in SP515 (Source: Reviewer's analysis)

SP515	Placebo	Rotigotine	Pramipexole
Time spent "off", mean (SD)			
Australia			
n	5	13	14
Baseline	7.77 (5.92)	7.14 (2.28)	6.85 (2.40)
Change from baseline	1.17 (2.25)	-3.52 (3.32)	-3.92 (3.28)
Croatia			
n	6	11	12
Baseline	5.21 (0.85)	4.83 (1.14)	4.93 (1.24)
Change from baseline	-0.60 (1.13)	-1.26 (2.40)	-2.52 (2.26)
Czech Republic			
n	13	23	22
Baseline	6.55 (2.62)	5.46 (2.52)	5.91 (2.12)
Change from baseline	-3.39 (2.83)	-2.48 (2.74)	-2.92 (2.45)
Israel			
n	6	14	14
Baseline	4.97 (1.24)	6.83 (1.97)	6.05 (1.86)
Change from baseline	-1.89 (3.77)	-2.70 (3.83)	-2.29 (2.04)
Italy			
n	11	22	18
Baseline	7.97 (2.58)	7.00 (2.58)	7.12 (2.79)
Change from baseline	-1.18 (4.59)	-2.16 (2.20)	-2.03 (4.31)
New Zealand			
n	4	7	8
Baseline	7.80 (2.79)	7.81 (4.85)	5.31 (1.73)
Change from baseline	-1.26 (8.13)	-6.29 (3.02)	-2.80 (1.84)
Norway			
n	2	6	7
Baseline	8.96 (3.82)	4.32 (1.71)	4.54 (1.83)
Change from baseline	0.17 (1.32)	-2.38 (2.65)	-0.95 (1.72)
Poland			
n	16	30	29
Baseline	5.25 (2.16)	6.50 (2.27)	5.50 (2.53)
Change from baseline	-0.11 (2.93)	-2.33 (2.69)	-2.50 (2.82)

South Africa			
n	14	27	25
Baseline	6.22 (2.33)	6.09 (2.56)	5.75 (2.61)
Change from baseline	-1.17 (2.78)	-2.08 (4.19)	-2.53 (3.36)
Spain			
n	11	20	19
Baseline	6.85 (2.32)	6.23 (2.51)	6.60 (2.75)
Change from baseline	-0.13 (2.30)	-1.66 (2.98)	-2.92 (3.51)
United Kingdom			
n	3	6	10
Baseline	9.69 (5.63)	6.13 (3.07)	6.90 (2.76)
Change from baseline	-0.18 (1.43)	-1.78 (3.72)	-4.31 (3.59)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major issues were found in the two pivotal trials. Both pivotal trials have demonstrated that rotigotine is effective as a treatment for subjects with advanced Parkinson's disease who are not well controlled by levodopa.

5.2 Conclusions and Recommendations

The two pivotal studies showed that rotigotine is effective in the treatment of advanced Parkinson's disease as compared to placebo. The reduction in time spent "off" in rotigotine-treated subjects was confirmed by increase in subjects' time spent "on" without an increase in time spent "on with dyskinesia". The rotigotine doses studied ranged from 9 mg to 36 mg, with doses of 18 mg and 27 mg studied in both pivotal studies. Both rotigotine 18 mg and 27 mg are found to be effective in the two pivotal studies. However, rotigotine 18 mg appeared to be more effective than rotigotine 27 mg. The non-inferiority claim of rotigotine to pramipexole could not be concluded.

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Sharon Yan
10/3/2008 02:28:06 PM
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James Hung
10/7/2008 09:52:35 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Rotigotine
PRODUCT (Brand Name):	NEUPRO
sNDA:	21-829 (091 and 092)
DOSAGE FORM:	Transdermal Patch
DOSAGE STRENGTHS:	1, 2, 3, 4, 6, 8 mg
INDICATION:	Treatment of Restless Legs Syndrome and Advanced stage Parkinson's Disease
NDA TYPE:	Efficacy Supplements Complete Response Resubmission
SUBMISSION DATES:	Dec 02, 2011 and March 19, 2012
SPONSOR:	UCB, Inc.
REVIEWER:	Hristina Dimova, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
PHARMACOMETRICS REVIEWER:	Satjit Brar, Ph.D.
PHARMACOMETRICS TEAM LEADER:	Atul Bhattaram, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

1.0 EXECUTIVE SUMMARY

Rotigotine (Neupro®), a non-ergolinc dopamine agonist was approved on May 9, 2007 in the US for the treatment of signs and symptoms of early-stage, idiopathic Parkinson's disease (PD). In August 2007, [redacted] (b) (4) was identified during the manufacturing of Neupro transdermal system (patches) resulting in the formation of crystals in the patches [redacted] (b) (4). As a result, all batches were recalled from the US market in April 2008.

On September 21, 2007 and October 05, 2007 the sponsor submitted supplements S-001 and S-002 to support the use of Neupro in patients with Restless Legs Syndrome (RLS) and advanced Parkinson's disease (APD), respectively (sNDAs 035 and 036). These supplements were reviewed and found acceptable from the clinical pharmacology perspective (Veneeta Tandon, Hao Zhu, 10/15/2008).

A Complete Response (CR) letter was sent to the sponsor on December 15, 2008 stating that, although substantial evidence of effectiveness for Neupro in patients with APD and in patients with RLS has been provided, the applications cannot be approved due to product quality concerns (formation of crystals in the patches).

On December 02, 2011 the sponsor submitted Efficacy Supplements Complete Response (sNDA 21-829 Submission Sequences No. 0091 and 0092). The following has been submitted:

- CMC information for patch [redacted] (b) (4) describing a reformulated product that is crystal-free throughout its shelf-life
- Bioequivalence and comparative in vivo adhesiveness data supporting the equivalence of the reformulated patch to the originally approved drug product
- Pediatric plan for RLS (the Pediatric plan was updated and re-submitted on March 19, 2012)
- Updated labeling and updated product safety information

The CMC information for patch [redacted] (b) (4), the bioequivalence and in vivo adhesiveness studies supporting the equivalence of the reformulated patch to the originally approved drug product are reviewed by the OPS/ONDQA team.

This review provides recommendations to the proposed updated labeling and the Pediatric plan for RLS. In addition, the reviewer provides comments to the pediatric plan for RLS.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-1 has reviewed the Clinical Pharmacology information submitted to sNDAs 21-829 (0091 and 0092) and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

PEDIATRIC DEVELOPMENT PLAN
CLINICAL PHARMACOLOGY REVIEW

1. Background

NDA 21829 Supplement S-001 submitted in support of Neupro for the treatment of the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS) included a waiver for development in patients under 8 years of age and a deferral for development in patients 8-17 years of age. Based on the Agency's request and the fact that the diagnosis of RLS and evaluation of symptoms relies on the subjective reporting of the patients, the waiver request is amended to include patients up to 12 years of age. The pediatric population to be studied with Neupro will be 13 to 17 years of age.

2. Pediatric Development Plan

Three clinical studies are planned for the pediatric clinical program in moderate to severe primary RLS: a pharmacokinetic (PK) study to assess rotigotine PK following multiple doses (SP1004), an open-label extension study to collect long-term tolerability and safety data (SP1005) and a double-blind, placebo-controlled study to assess efficacy and safety.

3. SP1004 Study Design

SP1004 will be a multicenter, open-label, 2-group dose-escalation, Phase 2 study with multiple administrations of the rotigotine transdermal system.

Objectives:

Primary: to determine the steady-state PK of rotigotine in adolescents with idiopathic RLS after multiple patch administration with weekly escalating doses.
Secondary: assessment of the safety, tolerability, and efficacy of rotigotine treatment in adolescents with idiopathic RLS.

Subjects: N=24 adolescent subjects, 13 to 17 years of age, with moderate to severe primary RLS.

Dosing will be dependent on subject body weight and will be divided into 2 groups (adolescents with body weight ≤50kg and adolescents with body weight >50kg).
The rotigotine dose will be increased weekly up to a maximum dose of 2mg/24h for the ≤50kg group and 3mg/24h for the >50kg group as detailed in the table below, unless safety and tolerability assessments do not allow for further dose titration.

Day	Body Weight ≤50kg	Body Weight >50kg
Day 1	0.2mg/24h (1cm^2)	0.5mg/24h (2.5cm^2)
Day 8	0.5mg/24h (2.5cm^2)	1mg/24h (5cm^2)
Day 15	1mg/24h (5cm^2)	2mg/24h (10cm^2)
Day 22	2mg/24h (10cm^2)	3mg/24h (15cm^2)

At Day 29, subjects will begin dose de-escalation by 1 dose step every 2 days until they reach the lowest dose for their dosing schedule for medication withdrawal.

Dosing Justification

The doses demonstrated to be effective for RLS in adults are 1, 2 and 3mg/24h.

Note: However the 1mg/24h dose was not superior to placebo in one of the trials.
These doses correspond to rotigotine AUC values of approximately 3 ng/mL*h, 6 ng/mL*h, and 9 ng/mL*h, respectively in adults. The target AUC for the first dose applied to adolescents will be 3 ng/mL*h, corresponding to the AUC for the lowest effective dose in adults. The doses needed to reach the respective exposure were calculated based on allometric scaling of the rotigotine clearance in adults and based on the following:

- Rotigotine is absorbed from the patch via the skin, following zero order kinetics. Approximately 45% of the rotigotine from the patch is released within 24 hours (0.2mg/cm2/24h). As the skin of children is considered to be comparable to adults at the age of 2 years and older, it can be assumed similar absorption rate in children to that in adults (Kearns et al 2003). However, as the study will be the first in the adolescent population, the sponsor assumed 100% absorption from the patch for starting dose estimation in adolescents.

Note: However, if the BA of rotigotine in children is similar to that in adults (as expected based on Kearns at al), the dose needs to be higher.

- Rotigotine is primarily eliminated by metabolism: conjugation (sulfation and glucuronidation) and oxidative desalkylation via cytochrome P450 enzymes with subsequent conjugation. All enzymes known to be involved in the metabolism show expression in the liver at 13 years of age close to the adult level (Johnson et al 2006, Vietri et al 2001). Hence, no change in intrinsic clearance of rotigotine is expected for children of ≥13 years of age compared to adults.
- Rotigotine is a lipophilic compound that is more likely to distribute into fatty tissue. The body composition of children is different at very low age, however, at the starting age for this study (13 years) body composition is similar to that of adults (Kearns et al 2003, Friis-Hansen 1983). As the body weight is lower in children compared with adults, dosing per kg body weight is being planned.

Note: No justification for the dose range division (by weight ≤50kg and >50kg) has been provided by the sponsor.

- As less than 1% of rotigotine is eliminated renally (Cawello et al 2009) and no difference is expected in renal elimination in the proposed age range of 13 to 17 years when compared to adults (Hines 2008), no adaptation for renal elimination was considered necessary.

Note: rotigotine metabolites are primarily renally eliminated.

- Rotigotine shows a relatively high protein binding of about 92%. However, a reduced amount of plasma protein is present only in neonates and infants; in children and adolescents, the amount of plasma protein is equivalent to adults (Ehrnebo et al 1971, Kurz et al 1977).

Pharmacokinetics
Plasma concentrations will be measured based on samples taken at pre-determined time points throughout the study after subjects have reached steady-state at each dose level. Unconjugated rotigotine concentrations will be analyzed using standard non compartmental analysis, leading to a reduced PK profile due to sparse sampling in this study. In addition, the data will be used to build a population PK model to evaluate potential differences in the PK of rotigotine over the investigated age range. All data will be analyzed in an exploratory manner.
Note: The sponsor needs to specify the time for blood samples collection.

Efficacy Analyses
Periodic limb movements will be measured at baseline and at end of each dose step via actimetry and will be summarized by dose step. A potential correlation of efficacy and PK variables will be investigated. A model-based approach may be used.

4. SP1005 Study Design
SP1005 will be a multicenter, open-label, single-arm, dose-escalation study of monotherapy of rotigotine transdermal system. This study will gather data on the long-term tolerability, safety, and efficacy of rotigotine transdermal system in adolescents with idiopathic RLS, allowing subjects from SP1004 and SP1006 to continue in SP1005. Subjects may remain in the study for 2 years after study entry.
Approximately 200 subjects may be eligible to enroll.
The primary objective of this study is to assess the long-term tolerability and safety of rotigotine. The secondary objective is to assess the long-term efficacy of rotigotine treatment in adolescents with idiopathic RLS.
Dosing
The study will begin with a Titration Period of up to 4 weeks (at maximum) with the aim of achieving the individually optimized dosage (with a maximum dose of 2mg/24h or 3mg/24h, depending on body weight). Titration will be followed by a Maintenance Period of up to 2 years, a 1-week Taper Period, and a 30-day Safety Follow-Up. Once a subject's dose has been optimized by the investigator, the subject should be maintained on that dose throughout the Maintenance Period.
Summary statistics will be provided for the efficacy variables by dose.

5. SP1006 Study design
SP1006 will be a randomized, multi-center, double-blind, parallel group, placebo-controlled, fixed dose efficacy and safety study of monotherapy administration of rotigotine transdermal patch in adolescent subjects, 13 to 17 years of age, with moderate to severe primary RLS. The primary objective of this study will be to assess the efficacy of rotigotine treatment in adolescents with moderate to severe primary RLS.
After completing a Screening Period, subjects will be randomized to either placebo or one of the active doses. Subjects will receive their first dose of rotigotine at Baseline.
Dose levels for the active arms will be defined based on the results of SP1004.
The number of subjects to be enrolled will be dependent on the final study design.
Dosing

The dose range will be determined based on results from the PK study SP1004. Subjects will be titrated to their randomized dose and undergo a 12-week Maintenance Period. After completing the Maintenance Period (or prematurely discontinuing the study), subjects will enter a De-escalation Period during which the dose will be decreased every other day as in the adult population.
The co-primary efficacy variables will be the change from Baseline to the end of the Maintenance Period in the sum score of the IRLS rating scale and in the sum score of CGI Item 1. Both co-primary endpoints must demonstrate significant results (at significance level 0.025) to demonstrate superiority of this dose level of rotigotine over placebo.
Population PK Analysis
Plasma concentrations of unconjugated rotigotine will be collected in SP1006. A population PK model will be developed to further describe the influence of age on the pharmacokinetics of rotigotine to support the results of SP1004. Efficacy variables may be added to the model to support a PK/PD relationship.

The clinical pharmacology comments to the Pediatric Plan were conveyed to the sponsor and the sponsor updated the pediatric development plan addressing these comments. Their responses to the individual comment are provided below and are considered acceptable.

- The PK study (SP1004) should be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for rotigotine in each age group to be studied.

We have modified the pediatric plan to include this requirement. The following paragraph has been added to the pediatric plan:

The study will be powered with 80% to target a 95% confidence interval within 60 and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution.

- You need to provide justification for the dose range division (by weight ≤50kg and >50kg) in study SP1004.

The dose range division was originally established based on attempts to cover anticipated weights associated with the age range of 13 to 17 and AUC projections. Following study initiation and further review, it has become apparent that this dose range division is no longer necessary. Accordingly, we have modified the pediatric plan and will amend the protocol to eliminate the dose range division.
The updated wording is provided below:

The rotigotine dose will be increased weekly up to a maximum dose of 3mg/24h as detailed in Table 2:1, unless safety and tolerability assessments do not allow for further dose titration.

Table 2:1. Dosing Schedule

Day	Dose
Day 1	0.5mg/24h (2.5cm^2)
Day 8	1mg/24h (5cm^2)
Day 15	2mg/24h (10cm^2)
Day 22	3mg/24h (15cm^2)

Population
Subjects will be aged 13 to 17 years and meet the diagnosis of RLS.

- You need to specify the time for blood samples collection.

The times for blood sample collection have been incorporated into the pediatric plan. The updated wording is provided below:

Pharmacokinetics
Plasma concentrations will be measured based on samples taken at pre-determined time points throughout the study after subjects have reached steady-state at each dose level. The pharmacokinetic data will be analyzed in an exploratory manner for predefined datasets. Unconjugated rotigotine concentrations will be analyzed using standard non-compartmental analysis, leading to a reduced PK profile due to sparse sampling in this study. In addition, the concentration data will be used to build a population PK model to evaluate potential differences in the PK of rotigotine over the investigated age range. All data will be analyzed in an exploratory manner. The pharmacokinetic sampling timepoints are listed in Table 2.2.

Table 2:2. Plasma and Urine Collection Schedule

Assessments	Visit 2 to 10 and WD					
	Day 1	Days 7, 14, 21 and 28				Days 8, 15, 22, 29 and WD
	Predose[a]	Predose[a]	1h postdose[b]	2h postdose[b]	7h-12h postdose	22h-24h postdose[c]
Plasma sampling	X	X	X	X	X	X
Urine collection		X[d]				

WD=withdrawal; h=hour

[a] Predose sample to be collected within 1 hour prior to patch application.

[b] Plasma samples to be collected within a ±15 minute window. A minimum of 45 minutes is required between the 1h and 2h postdose sample collections.

[c] Samples to be collected prior to removal of the previous day's patch.

[d] Urine sample to be collected at any time during the visit.

- The data from the relevant studies should be combined to develop exposure-response for safety and effectiveness endpoints. The goals of this analysis are: a) to provide supportive evidence of effectiveness and b) to support the dosing recommendations.

We have modified the pediatric plan to include the commitment to conduct the requested analyses. The following section has been added to the pediatric plan:

Exposure-response analyses
The data from SP1004, SP1005, and SP1006 will be combined to develop exposure-response for safety and efficacy endpoints. The goals of these analyses are a) to provide supportive evidence of effectiveness and b) to support the dosing recommendations.

- You need to correct the timetable for the studies, e.g. study SP1004: Protocol submission to FDA: October 2011

The dates for the SP1004 and SP1005 protocol submissions reflected their October filings to IND 63,902 on 14 October 2011 (Sequence No. 0533). Since these protocols will have to be amended to incorporate the requested changes, the dates have been revised to June 2012 in the pediatric plan. This allows for them to be submitted following the S-001/S-002 action date of 02 June 2012.

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/s/

HRISTINA DIMOVA
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SATJIT S BRAR
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VENKATESH A BHATTARAM
03/21/2012

YUXIN MEN
03/21/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**March 20, 2012**
To:	Russell Katz, MD, Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Patient Package Insert)
Drug Name (established name):	NEUPRO (rotigotine)
Dosage Form and Route:	transdermal system
Application Type/Number:	021829
Supplement Number:	S-001 S-002 (b) (4)
Applicant:	UCB, Inc

1 INTRODUCTION

NEUPRO (rotigotine) transdermal system was originally approved on May 09, 2007 for use in patients with early idiopathic Parkinson's disease.

On September 21, 2007 and October 5, 2007, UCB Inc, submitted supplements S-001 and S002 to support the use of NEUPRO in patients with Restless Legs Syndrome (RLS) and advanced Parkinson's disease (APD) respectively. NEUPRO was withdrawn from the US market in April 2008 due to (b) (4) (b) (4) (b) (4) the occurrence of crystals in the drug product.

On December 15, 2008 a complete response letter was issued by the agency. On July 17, 2009 and January 7, 2010, UCB submitted amendments to S-001 and S-002 providing complete responses to the CR letter. (b) (4)

On April 21, 2010 the agency issued a CR letter for S-001, S-002, (b) (4) stating that the effectiveness for NEUPRO in patients with APD and in patients with RLS was provided, but the applications could not be approved due to quality concerns. Additionally, the agency recommended reformulation of the drug product to prevent the formation of crystals. On December 11, 2011, UCB Inc, provided complete responses to the CR letter for S-001, S-002, (b) (4)

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for NEUPRO (rotigotine) transdermal system.

2 MATERIAL REVIEWED

- Draft NEUPRO (rotigotine) PPI received on December 2, 2011 and received by DMPP on March 13, 2012.
- Draft NEUPRO (rotigotine) Prescribing Information received December 2, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on March 16, 2011.
- Approved REQUIP (ropinirole) and REQUIP XL (ropinirole) comparator labeling dated April 10, 2009.
- Approved MIRAPEX (pramipexole dihydrochloride) comparator labeling dated May 13, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the **PPI** the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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SHARON W WILLIAMS
03/20/2012

MELISSA I HULETT
03/20/2012

LASHAWN M GRIFFITHS
03/20/2012

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Rotigotine
PRODUCT (Brand Name):	NEUPRO
DOSAGE FORM:	Transdermal Patch
DOSAGE STRENGTHS:	1, 2, 3, 4, 6, 8 mg
SNDA:	21-829 (035 and 036)
INDICATION:	Treatment of Restless Legs Syndrome and Advanced stage Parkinson's Disease
NDA TYPE:	Two Efficacy Supplements
SUBMISSION DATE:	9/21/07 and 10/5/07
SPONSOR:	Schwarz Biosciences
REVIEWER:	Veneeta Tandon, Ph.D. Hao Zhu, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
PHARMACOMETRICS TEAM LEADER:	Joga Goburru, Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

Rotigotine (Neupro®), a non-ergolinc dopamine agonist is currently approved in the US for the treatment of signs and symptoms of early-stage, idiopathic Parkinson's disease (PD). It is also approved in the European Union (EU) for the treatment of signs and symptoms of Parkinson's disease (Early and Advanced PD). Schwarz is seeking approval for the indication of the treatment of the signs and symptoms of primary Restless Legs Syndrome (RLS) and for the treatment of the signs and symptoms of advanced stage Parkinson's disease in sNDAs 035 and 036.

The sponsor proposed dosing regimen for RLS is once daily dosing of patches 1, 2 or 3 mg/24 hours (containing 2.25, 4.5 and 6.75 mg rotigotine per transdermal system), with doses being increased at weekly increments of 1mg/24 hours. The proposed dosing regimen for advanced PD is once daily dosing of patches 4, 6 or 8 mg/24 hours (containing 9, 13.5 and 18 mg rotigotine per transdermal system), with doses being increased at weekly increments of 2mg/24 hours.

The currently approved strengths of the rotigotine patches are 2, 4 and 6 mg/24 hour patches. In the original NDA submission of January 2005, the 8 mg patches were evaluated in clinical studies, (b) (4) . The new patch strengths included in these supplements are 1, 3 and 8 mg/24 hours patches. The quantitative composition per area is identical for all strengths, and the nominal delivery per each cm^2 is 0.2mg/24 hours.

The following table shows the strengths of rotigotine transdermal system that have been proposed by the sponsor and also that have been used in the clinical development of both the proposed and the approved indications.

Rotigotine nominal dose/24h (mg)	Rotigotine content per transdermal system (mg)	Patch surface area (cm^2)	Indication
(b) (4)			
1	2.25	5	RLS
2	4.5	10	RLS and Early PD
3	6.75	15	RLS
4	9	20	Early and Advanced PD
6	13.5	30	Early and Advanced PD
8	18	40	(b) (4) Advanced PD

[a] used in clinical development only

From a clinical pharmacology perspective, to support the RLS indication, the supplement contains one Phase I study (SP871) that assesses the relative bioavailability of rotigotine after administration of rotigotine transdermal system 6.75mg (15cm2) compared to combined application of one 2.25mg (5cm2) system plus one 4.5mg (10cm2) system. In addition to this, the sponsor has conducted two drug-drug interaction studies with oral contraceptives and omeprazole. Oral contraceptive study was conducted as the RLS indication has high prevalence in women as well. Omeprazole study was conducted to evaluate the inhibition of CYP2C19 as original NDA had evaluated the inhibition of CYP2C19 using a non specific inhibitor, cimetidine.

To support the Advanced Parkinson's NDA the sponsor conducted a thorough QT/QTc study in patients with Parkinson's disease. This study was evaluated by the IRT team.

Synonymous Terms: Throughout this application the internal codes used for rotigotine are 'N- 0923', and 'SPM 962'. In addition, rotigotine may be referred in study reports as rotigotine continuous delivery system or rotigotine transdermal system.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-1 has reviewed the Clinical Pharmacology information submitted to sNDAs 21-829 (035 and 036) and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert. The following comment regarding the Pharmacometrics review should be conveyed to the sponsor

1. *We recommend in the future, the sponsor perform logistic regression analysis to direct link the exposure and incidence of adverse events for each individual.*

Veneeta Tandon, Ph.D.
Division of Clinical Pharmacology I

Hao Zhu, Ph.D.
Pharmacometrics Reviewer

Team Leaders: Ramana Uppoor, Ph.D._____

Joga Goburru, Ph.D._____

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The following conclusions were drawn from the Clinical Pharmacology section of the supplemental NDA:

Exposure Response for RLS:

The exposure response analysis in RLS patients showed a dose dependent reduction in IRLS scores. An exposure-response relationship between rotigotine plasma concentration and idiopathic restless leg syndrome rating scale was established. Higher rotigotine concentration yields larger reduction of IRLS, with the concentration of half maximal effect at 0.227 ng/mL.

Exposure Response for Advanced Parkinson's Disease:

There did not seem to be a clear dose response in the advanced Parkinson's trials. No formal exposure-response analysis was conducted in this population.

Effect on QTc Prolongation:

A thorough QTc study with doses up to 54 mg was conducted and there was no indication of a QT/QTc prolonging effect with doses up to 24 mg/24 hours (54 mg).

Pharmacokinetics in Patients:

The pharmacokinetics in patients with RLS and Advanced Parkinson's were generally similar to that in healthy subjects.

Drug Interactions:

Oral Contraceptives: Rotigotine (3 mg) has no effect on the pharmacokinetics of ethinyl estradiol and levonorgestrel.

Omeprazole: Omeprazole had no effect on the pharmacokinetics of rotigotine (4 mg or 9 mg/day)

Relative Bioavailability:

Two new strengths of 1 and 3 mg have been added to the approved strengths of rotigotine transdermal patches.

One 6.75mg (15cm^2) patch had similar relative bioavailability to a combined application of one 2.25mg (5cm^2) patch and one 4.5mg (10cm^2) patch. This would be expected because the patches are compositionally proportional.

In addition to this, the sponsor is seeking approval of a 8 mg rotigotine patch, (b) (4) No new clinical pharmacology study has been conducted with the 8 mg patch.

The sponsor is currently experiencing manufacturing problems with the patches and may need to reformulate it. In the event that the reformulation takes place, additional bioavailability/bioequivalence studies may be necessary.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: Transdermal Patches

1, 2, 3mg / 24 hours of rotigotine and patch sizes of 5, 10, and 15cm2, respectively for Restless Legs Syndrome.
Note: 1 and 3 mg patches are new strengths for this indication
4, 6 and 8mg/24 hours of rotigotine and patch sizes of 20, 30, and 40cm2, respectively for Advanced Parkinson's Disease.

Indication: *1. Treatment of signs and symptoms of primary Restless Leg Syndrome (RLS)*

2. Advanced Stage Parkinson 's Disease

Dosage and administration (Sponsor's Proposed):

Restless Leg Syndrome: The patch is to be applied once a day with rotation of the application sites with a recommended starting dose of 1mg / 24hours. Based on the individual patient response, the daily dosage should be increased in weekly increments of 1 mg/24 hours to the individual optimal dose up to 3mg/24 hours. The highest daily dose of rotigotine recommended is 3mg/24 hours in patients with primary Restless Legs Syndrome.

Advanced Stage Parkinson's Disease: The patch is to be applied once a day with rotation of the application sites with a recommended starting dose of 4mg / 24hours. Based on the individual patient response, the daily dosage should be increased in weekly increments of 2mg / 24 hours to the individual optimal dose up to 8mg / 24 hours. The highest daily dose of rotigotine recommended is 8mg / 24 hours in patients with Advanced-stage Parkinson's disease.

Pharmacologic Class: Non-ergolinic dopamine agonists. It shows a close structural analogy to dopamine and apomorphine. It exhibits agonistic activity at all dopamine and some non-dopaminergic receptors. The rank order of affinities towards the different dopamine

receptors is nearly identical to that of dopamine. However, its affinities are much higher than those of dopamine. Thus, rotigotine resembles dopamine in respect to structure, receptor binding and functional activity.

Chemical Name: (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol. Synonymous Terms: Throughout this application the internal codes used for rotigotine are 'N- 0923', 'SPM 936', and 'SPM 962'

Physical Characteristics: Rotigotine is a white to off-white powder.

Mechanism of action: The precise mechanism of action of rotigotine as a treatment for RLS is unknown. It is supposed to directly stimulate post-synaptic dopamine D_3, D_2 and D_1 receptors within the caudate-putamen of the brain as suggested for dopamine agonists in general.

Formulation: For the indication of idiopathic RLS, 3 strengths of rotigotine transdermal system are proposed, containing 2.25, 4.5, or 6.75mg of rotigotine free base (corresponding to nominal doses of 1, 2 or 3mg/24h and patch sizes of 5, 10, and 15cm_2, respectively). The formulation of all patch sizes, including the 2 additional new sizes providing 1 and 3mg/24h, is identical to the currently approved product.

Rotigotine transdermal system is a silicone-based matrix-type patch of drug-in-adhesive design. The adhesive matrix, in which the drug substance is homogenously dispersed, functions as a drug reservoir. It provides for a constant drug concentration gradient at the skin/patch interface and for continuous drug delivery to the skin application site over the intended period of 24 hours. The matrix composition is identical per patch area for all dose strengths, containing (b) (4) rotigotine per area unit (cm^2) of the patch surface. Apparent dose of rotigotine was calculated to be 0.2mg/cm_2/24h based on data collected in a series of Phase 1 trials and is the basis for the nominal dose/24h.

The formulation of all the patches is given in the following Table, with patches of 2.25 and 6.75 being new patch sizes

not previously approved. The table shows that they are all compositionally proportional.

Composition of rotigotine patches

Material	mg/patch (5 cm^2)	mg/patch (10 cm^2)	mg/patch (15 cm^2)	mg/patch (20 cm^2)	mg/patch (30 cm^2)	mg/patch (40 cm^2)	%
Rotigotine							(b) (4)
Silicone adhesive (b) (4)							
Silicone adhesive (b) (4)							
Povidone (b) (4)							
Sodium metabisulfite							
Ascorbyl palmitate							
							(b) (4)

[a] q.s. = Quantum satis, as much as needed [b] Removed during processing, not present in finished product

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

Restless Legs Syndrome:

The sponsor has conducted two pivotal adequate and well controlled efficacy studies (SP 790 in Europe and SP792 in US) in patients with RLS. A tabular listing of all studies along with study design features and durations are summarized in the following Table. The pivotal studies also included open label extensions (SP 791 and SP793) to collect long term safety data:

Trials evaluating efficacy of rotigotine patch in RLS

Protocol number	Trial design	Rotigotine dose	Treatment duration	Total number of unique subject exposures to rotigotine (SS)
Primary efficacy trials				
SP790	Multicenter, DB, PC, fixed-dose	1, 2, or 3mg/24h	Approximately 7 months	341[a]
SP792	Multicenter, DB, PC, fixed-dose	0.5, 1, 2, or 3mg/24h	Approximately 7 months	404
Long-term trials				
SP710	Multicenter, OL	0.5, 1, 2, 3, or 4mg/24h	Up to 5 years	295 (46 new exposures)[b]
SP791	Multicenter, OL	1, 2, or 3mg/24h	Up to 1 year	341 (76 new exposures)[b]
SP793	Multicenter, OL	0.5, 1, 2, or 3mg/24h	Up to 1 year	278 (59 new exposures)[b]
Supporting trials				
SP666	Multicenter, DB, PC, fixed-dose	0.5, 1, or 2mg/24h	7±1 day	49
SP709	Multicenter, DB, PC, fixed-dose	0.5, 1, 2, 3, or 4mg/24h	7 weeks	285
SP794	Multicenter, DB, PC, dose-escalation to optimal dose	1, 2, or 3mg/24h	Up to 8 weeks	46

DB=double-blind; OL=open-label; PC=placebo-controlled; RLS=Restless Legs Syndrome; SS=Safety Set

a Total rotigotine exposure was 344 subjects because 3 subjects randomized to placebo were treated in error with rotigotine

b New exposures include subjects who received placebo in the preceding double-blind trial

Studies SP 666 and SP709 were proof of concept and dose finding studies. Study SP 794 was a Phase 3 sleep lab study.

Advanced Parkinson's Disease:

The sponsor conducted 10 clinical trials that evaluated efficacy of rotigotine in subjects with advanced-stage Parkinson's disease. This includes 3 pivotal double-blind, placebo-controlled efficacy trials (SP511, SP650DB, and SP515). These trials are summarized in the following table.

Trials evaluating efficacy of rotigotine transdermal system in advanced-stage Parkinson's disease

Protocol number	Trial design	Rotigotine dose	Maximum treatment duration	Total number of unique subject exposures to rotigotine
Primary efficacy trials				
SP511	Multicenter, DB, PC	4, 8, and 12mg/24h	12 weeks	224
SP650DB	Multicenter, DB, PC	8 and 12mg/24h	30 weeks	229
SP515	Multicenter, DB, PC	Up to 16mg/24h	24 weeks	205
Long-term extension trials				
SP650OL	Multicenter, OL	Up to 16mg/24h	Until commercially available	92
SP516	Multicenter, OL	Up to 16mg/24h	Until commercially available	232
SP833	Multicenter, OL	Up to 16mg/24h	Until commercially available	0
Other trials				
SP533	Single-center, OL, dose-escalation	Up to 16mg/24h	4 weeks	10
SP591	Multicenter, OL, dose-escalation	Up to 24mg/24h	12 weeks	34
SP824	Multicenter, OL	Up to 8mg/24h	13 weeks	73
SP826	Multicenter, OL	Up to 16mg/24h	18 weeks	52

DB=double-blind; OL=open-label; PC=placebo-controlled

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

Restless Legs Syndrome:

Efficacy was assessed by analyzing changes from Baseline to end of Maintenance Period in mean International Restless Legs Syndrome Study Group Rating Scale (IRLS) and Clinical Global Impression Item 1 (CGI Item 1) scores.

A reduction in IRLS score is considered beneficial to treatment.

Advanced Parkinson's Disease:

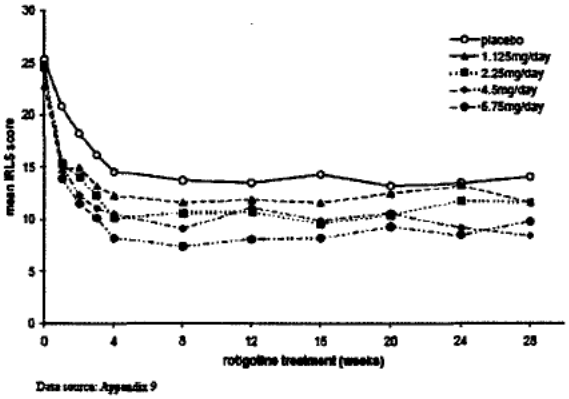
The primary variable evaluated was the absolute change from Baseline to end of treatment in absolute time (hours) spent "off".

2.2.3 What are the characteristics of exposure/effectiveness relationships?

Restless Legs Syndrome:

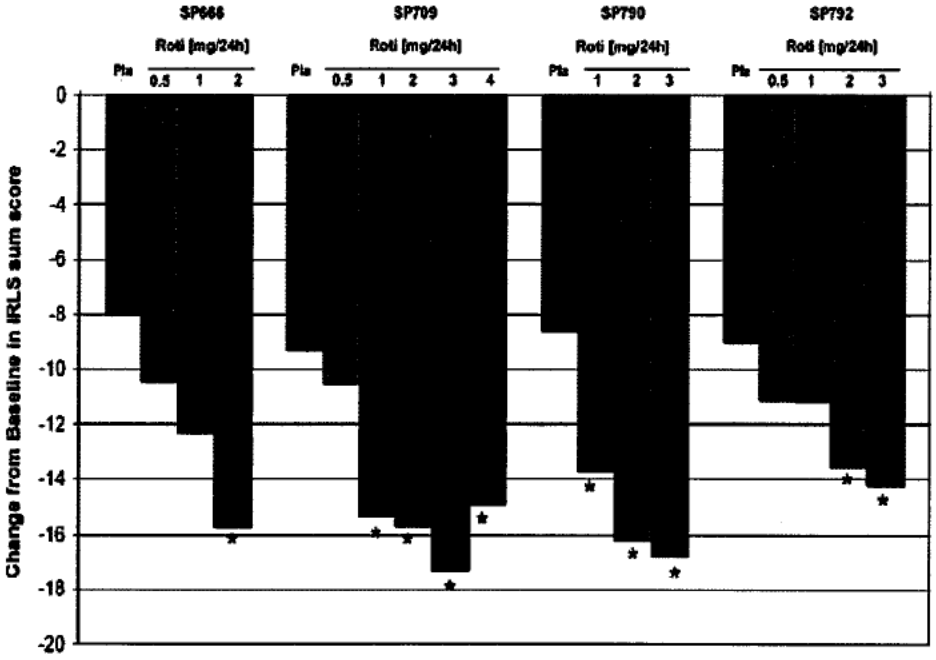
Yes. An exposure-response relationship between rotigotine plasma concentration and idiopathic restless leg syndrome rating scale is established. Following the treatment of placebo or rotigotine, IRLS score reduces rapidly in the first 4 weeks and then it is stabilized (Figure 2). Rotigotine treatment leads to a maximum reduction of 9.32 in IRLS in addition to placebo effect. Higher rotigotine concentration yields larger reduction of IRLS, with the concentration of half maximal effect at 0.227 ng/mL.

Figure 1 Time Course of IRLS Reduction Following the Treatment of Placebo or Rotigotine



Data source: Appendix 9

A dose-response was also observed in the proof of concept and dose finding studies (SP666 and SP709) as well as in the pivotal efficacy studies (SP790 and SP792), as seen in the following bar graph. The absolute change from Baseline at the end of the Maintenance Period in the IRLS sum score was the primary efficacy variable in SP666 and SP709, and was a coprimary variable along with change in the CGI Item 1 (Severity of Illness) score in SP790 and SP792.



h=hours, IRLS=International Restless Legs Syndrome Study Group Rating Scale, Roti=rotigotine

Note: Statistical significance compared to placebo is denoted with an asterisk (*)

The change from baseline IRLS score at the end of maintenance period based on effectiveness analysis is given in the following Tables for the pivotal studies.

IRLS sum score at Baseline and end of Maintenance Period in SP792

Treatment group	n	Mean Baseline IRLS sum score (SD)	Mean IRLS sum score at end of MP (SD)	Mean Change from Baseline at end of MP (SD)
Placebo	99	23.5 (5.1)	14.5 (8.0)	-9.0 (7.7)
Rotigotine 1.125mg/day	98	23.1 (5.0)	12.2 (8.2)	-10.9 (8.9)
Rotigotine 2.25mg/day	99	23.2 (5.3)	12.1 (8.7)	-11.1 (9.3)
Rotigotine 4.5mg/day	95	23.3 (4.6)	9.9 (8.8)	-13.4 (9.2)
Rotigotine 6.75mg/day	103	23.6 (5.0)	9.3 (8.5)	-14.3 (9.4)

IRLS sum score at Baseline and end of Maintenance Period in SP790

Treatment group	n	Mean Baseline IRLS sum score (SD)	Mean IRLS sum score at end of MP (SD)	Mean change from Baseline at end of MP (SD)
Placebo	114	28.1 (6.3)	20.0 (11.2)	-8.0 (9.7)
Rotigotine 2.25mg/day	112	28.1 (6.3)	14.9 (11.1)	-13.2 (10.0)
Rotigotine 4.5mg/day	109	28.2 (6.1)	12.5 (9.6)	-15.6 (9.5)
Rotigotine 6.75mg/day	112	28.0 (5.9)	11.9 (10.9)	-16.1 (10.9)

Advanced Parkinson's Disease:

On the contrary, there does not seem to be a clear dose response in the advanced Parkinson's trials as seen in the following effectiveness analysis by the sponsor for LOCF and without LOCF (observed cases):

Results for change in "off" time from Baseline to the end of the double-blind Maintenance Period by trial and randomized treatment (FAS with LOCF for SP511, SP650, and SP515)

Trial/treatment group	LS means (SE)	Treatment comparison	Result (SE)	P-value	95% CI
SP511					
Placebo (N=81)	-1.81 (0.34)	NA	NA	NA	NA
Rotigotine 4mg/24h (N=77)	-2.13 (0.35)	Rot 4mg/24h - PBO	-0.32 (0.48)	0.5114	(-1.27, 0.63)
Rotigotine 8mg/24h (N=75)	-1.72 (0.36)	Rot 8mg/24h - PBO	0.09 (0.49)	0.8517	(-0.87, 1.05)
Rotigotine 12mg/24h (N=77)	-2.44 (0.35)	Rot 12mg/24h - PBO	-0.63 (0.48)	0.1931	(-1.58, 0.32)
SP650					
Placebo (N=119)	-0.91 (0.30)	NA	NA	NA	NA
Rotigotine 8mg/24h (N=113)	-2.74 (0.32)	Rot 8mg/24h - PBO	-1.83 (0.41)	<0.0001	(-2.64, -1.02)
Rotigotine 12mg/24h (N=109)	-2.14 (0.32)	Rot 12mg/24h - PBO	-1.23 (0.41)	0.0031	(-2.04, -0.42)
SP515					
Placebo (N=100)	-0.88 (0.29)	NA	NA	NA	NA
Rotigotine up to 16mg/24h (N=201)	-2.46 (0.20)	Rotigotine - PBO	-1.58 (0.35)	<0.0001	(-2.27, -0.90)
Pramipexole (N=200)	-2.81 (0.20)	Pramipexole - PBO	-1.94 (0.35)	<0.0001	(-2.63, -1.25)

ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; NA=not applicable; PBO=placebo; Rot=rotigotine; SE=standard error

Results for change in "off" time from Baseline to the end of the double-blind Maintenance Period by trial and randomized treatment (FAS without LOCF [observed cases] for SP511, SP650, and SP515)

Trial/treatment group	LS means (SE)	Treatment comparison	Result (SE)	P-value	95% CI
SP511					
Placebo (N=71)	-2.10 (0.35)	NA	NA	NA	NA
Rotigotine 4mg/24h (N=65)	-2.46 (0.36)	Rot 4mg/24h - PBO	-0.36 (0.50)	0.4711	(-1.34, 0.62)
Rotigotine 8mg/24h (N=63)	-2.17 (0.37)	Rot 8mg/24h - PBO	-0.07 (0.50)	0.8920	(-1.06, 0.92)
Rotigotine 12mg/24h (N=65)	-2.46 (0.36)	Rot 12mg/24h - PBO	-0.36 (0.50)	0.4700	(-1.34, 0.62)
SP650					
Placebo (N=92)	-1.00 (0.33)	NA	NA	NA	NA
Rotigotine 8mg/24h (N=86)	-3.25 (0.35)	Rot 8mg/24h - PBO	-2.24 (0.45)	<0.0001	(-3.13, -1.36)
Rotigotine 12mg/24h (N=80)	-2.66 (0.35)	Rot 12mg/24h - PBO	-1.66 (0.45)	0.0003	(-2.55, -0.76)
SP515					
Placebo (N=74)	-1.17 (0.32)	NA	NA	NA	NA
Rotigotine up to 16mg/24h (N=179)	-2.67 (0.20)	Rotigotine - PBO	-1.51 (0.37)	<0.0001	(-2.24, -0.77)
Pramipexole (N=171)	-3.01 (0.21)	Pramipexole - PBO	-1.84 (0.38)	<0.0001	(-2.58, -1.10)

ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; NA=not applicable; PBO=placebo; Rot=rotigotine; SE=standard error

2.2.4 What are the characteristics of exposure-safety relationships?

The incidence of application and instillation site reactions showed a positive correlation with the estimated plasma concentration for the Titration and Maintenance Periods combined. No concentration-related trends were observed for the incidence of nausea, headache, upper respiratory tract infections, or fatigue for the doses 1-3 mg. However, application and instillation site reactions showed dose dependency (doses 4-12 mg). Adverse events at the higher doses have been extensively evaluated in the original Safety review of the application.

The following Table shows the incidence of common treatment emergent adverse events (TEAE) for doses 1-3 mg for the RLS indication based on the sponsor's analyses.

Incidence of the most common TEAEs by estimated rotigotine plasma concentration at the time of onset (Pool RS1)

MedDRA[a] Preferred Term	n/N (%)								
	Rotigotine plasma concentration (ng/mL)								
	0.00 N=217	>0 to <0.1631 N=460	0.1631 to <0.2634 N=494	0.2634 to <0.3637 N=191	0.3637 to <0.4640 N=223	0.4640 to <0.5644 N=124	0.5644 to <0.6647 N=84	0.6647 to <0.7650 N=38	0.7650 to ≤0.8654 N=12
Nausea	21 (9.7)	54 (11.7)	46 (9.3)	16 (8.4)	22 (9.9)	10 (8.1)	8 (9.5)	3 (7.9)	1 (8.3)
Application and instillation site reactions[b]	8 (3.7)	52 (11.3)	64 (13.0)	38 (19.9)	48 (21.5)	35 (28.2)	27 (32.1)	13 (34.2)	6 (50.0)
Fatigue	17 (7.8)	27 (5.9)	30 (6.1)	10 (5.2)	8 (3.6)	2 (1.6)	2 (2.4)	2 (5.3)	0
Upper respiratory tract infections[b]	31 (14.3)	33 (7.2)	30 (6.1)	13 (6.8)	13 (5.8)	8 (6.5)	9 (10.7)	4 (10.5)	3 (25.0)
Headache	24 (11.1)	45 (9.8)	46 (9.3)	11 (5.8)	18 (8.1)	7 (5.6)	9 (10.7)	3 (7.9)	0

N=number of subjects; n=number of subjects reporting at least 1 TEAE; %=n/N; SS=Safety Set; TEAE=treatment-emergent adverse event

Safety at the higher doses that would be used in the Advanced Parkinson's disease has been evaluated at the time of original NDA review.

2.2.5 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moieties are adequately measured in the new clinical pharmacology studies. Please refer to section 2.6 for further details.

2.2.6 How do the pharmacokinetics of the drug in healthy volunteers compare to that in RLS and Advanced Parkinson's patients?

The plasma levels of unconjugated rotigotine are similar in subjects with RLS (SP666, SP709, SP710, SP790, SP792, and SP794) and healthy subjects. The following table summarizes mean plasma concentrations of unconjugated rotigotine in trials with subjects with RLS.

Mean plasma concentration of unconjugated rotigotine (ng/mL) at end of Maintenance in clinical trials with subjects with RLS - SP666, SP709, SP790, SP792, and SP794 (arithmetic mean [SD])

Trial	Rotigotine dose (mg/day)									
	1.125		2.25		4.5		6.75		9	
	n	Conc.	n	Conc.	n	Conc.	n	Conc.	n	Conc.
SP666[a]	17	0.071 (0.035)	11	0.186 (0.103)	19	0.246 (0.134)	NA	NA	NA	NA
SP709[b]	46	0.088 (0.055)	57	0.179 (0.116)	47	0.322 (0.233)	58	0.533 (0.374)	51	0.691 (0.469)
SP790[c]	NA	NA	21	0.303 (0.377)	19	0.451 (0.381)	18	0.522 (0.333)	NA	NA
SP792[c]	21	0.060 (0.034)	23	0.164 (0.114)	13	0.290 (0.209)	15	0.392 (0.290)	NA	NA
SP794[c]	NA	NA	12	0.144 (0.054)	17	0.322 (0.147)	14	0.383 (0.326)	NA	NA

Conc.=mean plasma concentration of unconjugated rotigotine (SD); n=number of subjects assessed; NA=not applicable; SD=standard deviation

In general, these mean concentrations are similar to those seen in healthy subjects (Cmax's) for the different doses. For example, for the 6.75 mg dose, the concentrations (Cmax) in healthy (Study SP 871) was 0.522 ng/ml. In RLS patients, the mean concentrations across various studies ranged from 0.383-0.533 ng/ml, although high variability is seen across studies and doses in general. For the 4.5 mg dose, the mean Cmax ranged from 0.31-0.51 ng/ml (Studies SP503, 534 and 535 from Dr. Kavanagh's review) in healthy subjects. These values are also similar (0.290-0.451) to the mean concentrations seen in RLS subjects in the Table above.

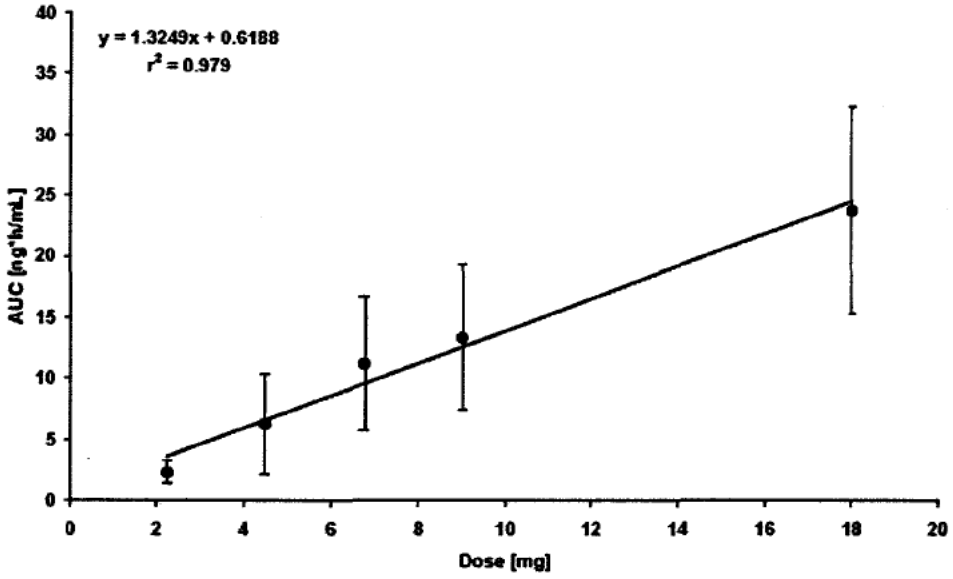
The pharmacokinetics in the Advanced Parkinson's Disease patients is also similar to that seen in the healthy subjects. Please see the following section 2.2.7 that discusses dose proportionality in Advanced Parkinson's Disease patients that follows the same trend as seen in healthy subjects, suggesting similarity of pharmacokinetics in the patient population.

2.2.7 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

No adequate single or multiple dose study was conducted to assess linearity in the original NDA submission. However, several Phase I, II and III studies have shown that rotigotine exhibits linear kinetics in the dose range of (b) (4) Please refer to page 19 of Dr. Kavanagh's review of February 2006.

The sponsor pooled data from healthy subjects and RLS patients to demonstrate dose proportionality as seen in the following Figure:

Linear regression of AUC and applied dose



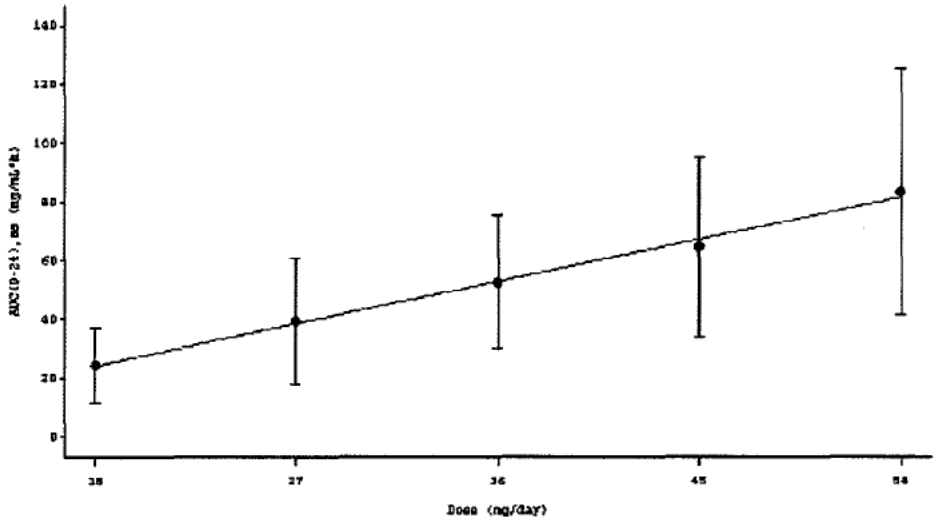
Dose proportionality is also seen at higher doses (up to 54 mg) in advanced Parkinson's patients (Thorough QTc study SP864) and follows the dose proportionality as seen in healthy subjects and RLS patients at lower doses. The following Table shows the AUC and Cmax's in healthy subjects (SP861, SP871, SP862) and advanced Parkinson's patients (SP864):

$AUC_{(0\text{-}24)ss}$ (ng/mL*h) and $C_{max,ss}$ (ng/mL) of unconjugated rotigotine and dose in healthy subjects and in subjects with idiopathic Parkinson's disease (geometric mean and coefficient of variation [%])

Trial	n	Dose (mg/day)	$AUC_{(0\text{-}24)ss}$ (ng/mL*h)	$C_{max,ss}$ (ng/mL)
SP861	36	6.75	10.624 (45.6)	0.581 (38.1)
SP871	40	6.75	9.119 (45.6)	0.522 (45.3)
SP862	37	9	11.628 (49.3)	0.688 (45.9)
SP864[a]	66	18	21.687 (51.3)	1.375 (51.5)
	65	27	34.810 (51.6)	2.055 (46.6)
	65	36	48.106 (44.2)	2.819 (41.8)
	65	45	57.935 (49.9)	3.343 (48.9)
	64	54	74.244 (51.6)	4.344 (50.6)

The dose proportionality assessment from Study SP864 is shown in the following Figure:

Dose of rotigotine (mg/day) vs $AUC_{(0-24)ss}$ (arithmetic mean ±SD) of unconjugated rotigotine– PKS in SP864



The dose proportional increase in AUC and Cmax in the healthy subjects, RLS and Advanced Parkinson's Disease patient populations at doses 2.25-54 mg also suggest similarity in pharmacokinetics in the healthy subjects versus the patient populations.

2.2.8 What is the variability in the PK data?

The variability seen in the pharmacokinetic parameters seen in the clinical pharmacology studies submitted in these supplements is similar (40-60% CV) to that seen in the studies from the original NDA.

2.3 INTRINSIC FACTORS

These have been reviewed during the original submission review.
In addition to the information obtained from the original NDA, the sponsor conducted a population analysis in the RLS patient population, evaluating the effect of covariates such as: age, gender, body weight, height and body mass index. No clinical relevant covariates were identified based on the population PK analysis. In the analysis, demographic information (age, gender, body weight, height, body mass index, and creatinine clearance) and the laboratory values (AST, ALT, GGT, ALK, and total bilirubin) were tested for covariate effect. None of them demonstrated significant covariate effect for the

major pharmacokinetic parameters (i.e., CL and Vd). Please refer to the Population PK review by Dr. Zhu provided in the Appendix II on page 100.

2.4 EXTRINSIC FACTORS

These have been reviewed during the original submission review. Additional extrinsic factors evaluated are a drug interaction with Oral contraceptive as younger women with Restless leg syndrome could be on oral contraceptives.

The sponsor also evaluated the effect of a CYP2C19 inhibitor omeprazole on the pharmacokinetics of rotigotine, since CYP2C19 was found to metabolize rotigotine, along with many other CYPs as well. Another drug interaction study with omeprazole was conducted because in the original NDA submission, the effect of cimetidine, a non specific inhibitor was evaluated.

2.4.1 Are there any other in-vivo drug-drug interaction studies in addition to the ones conducted with the original NDA that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.1.1 Influence of rotigotine on other drugs:

Influence of rotigotine on the pharmacokinetics of concomitant drugs is summarized in the following Table. None of the drugs indicate that exposure in different when co-administered, hence no dosage adjustment is necessary.

Concomitant Medication	Concomitant medication dose	Rotigotine doses evaluated	Cmax Ratio (90% CI) w/wo rotigotine % change	AUC Ratio (90%CI) w/wo rotigotine	Dosage Adjustment
Ethinyl Estradiol (Nordette)	0.03 mg 3 cycles	3 mg/24 hours (6.75 mg patch) for 14 days	1.0491 (0.9264, 1.1882) ↔	1.0493 (0.8993, 1.2243) ↔	none no effect on PD such as progesterone, LH and FSH concentrations as well
levonorgestrel (Nordette)	0.15 mg 3 cycles	3 mg/24 hours (6.75 mg patch) for 14 days	1.0072 (0.9557, 1.0615) ↔	0.9777 (0.9450, 1.0115) ↔	none

2.4.1.2 Influence of other drugs on the pharmacokinetics of rotigotine:

Influence of omeprazole on the pharmacokinetics of rotigotine was evaluated. No dosage adjustment is necessary.

Concomitant Medication	Concomitant medication dose	Rotigotine doses evaluated	Cmax Ratio (90% CI) w/wo rotigotine % change	AUC Ratio (90%CI) w/wo rotigotine	Dosage Adjustment
Omeprazole	40 mg	(4 mg/24 hours) 9 mg patch for 9 days	1.0613 (0.9723; 1.1585 ↔	0.9853 (0.9024; 1.0757 ↔	none

The sponsor has evaluated the ability of omeprazole to inhibit rotigotine as rotigotine is metabolized by CYP2C19. Although, rotigotine also has low inhibition potential for CYP2C19 (based on approved label), hence the effect of rotigotine on omeprazole levels could have been useful as well.

Rotigotine also has low inhibition potential for CYP2D6. In vivo studies to further evaluate this have not been conducted and were not requested during original NDA review.

Although, the Cmax (=I) from Study SP871 was 0.581, The I/Ki ratio for CYP2C19 and 2D6 was below 0.01, suggesting remote potential for in vivo drug interactions with co-administered drugs that are substrates of CYP2C19 and 2D6 at relevant doses for the RLS patients. Similar I/Ki has been established for the therapeutic concentrations for the Parkinson's disease in the original NDA, suggesting remote potential for an in vivo interaction. Hence, although the current approved label for rotigotine mentions that it has low inhibition potential for CYP2C19, an in vivo study is not necessary in this case.

(b) (4)

In addition to this, a drug interaction study with levodopa-carbidopa conducted during the original NDA review demonstrated that co-administration of levodopa/carbidopa (100/25mg bid) with rotigotine (9 mg/day) had no effect on the steady state pharmacokinetics of rotigotine; rotigotine had no effect on the pharmacokinetics of levodopa/carbidopa. This study was conducted at low doses of both drugs. However,

extrapolation of these results for advanced Parkinson's Disease patients where higher doses of both drugs may be co-administered may not be possible.

Dr. Kavanaugh, in his original review had the following comments for the sponsor:

(b) (4)

Even though the magnitude of interaction with higher doses of levodopa/carbidopa cannot be predicted, the clinical trials have used different doses of carbidopa /levodopa. and no drug interaction was observed using a low dose of carbidopa /levodopa.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the bioavailability of the new strengths of 1 (5 cm^2) and 3 mg/24 hours (15 cm^2) transdermal patches and how does it compare to the approved strengths?

The sponsor has conducted a relative bioavailability study of rotigotine 6.75mg/day after application of one 6.75mg (15cm^2) patch (Treatment A) with combined application of one 2.25mg (5cm^2) patch and one 4.5mg (10cm^2) patch (Treatment B) at steady state in 40 healthy subjects.

One 6.75mg (15cm^2) patch had similar relative bioavailability to a combined application of one 2.25mg (5cm^2) patch and one 4.5mg (10cm^2) patch, as would be expected because the patches are compositionally proportional. The pharmacokinetic parameters for the treatment A and B is given in the following Table:

PK parameters of unconjugated rotigotine by treatment (Day 13 to Day 14)

Parameter	Geo mean (geo CV[%])[a]	
	A (n=40)	B (n=40)
$AUC_{(0-24)ss}$ (ng/mL*h)	9.119 (45.6)	9.563 (45.5)
$AUC_{(0-24)ss,norm}$ (ng/mL*h/mg)	2.6658 (40.8)	2.8551 (32.0)
$C_{max,ss}$ (ng/mL)	0.5225 (45.3)	0.5371 (43.5)
$C_{max,ss,norm}$ (ng/mL/mg)	0.1527 (40.8)	0.1604 (33.0)
$t_{max,ss}$ (h)[a]	16.0 (0-24)[a]	16.0 (2-20)[a]

A=one 6.75mg (15cm2) rotigotine patch; B=one 2.25mg (5cm2) + one 4.5mg (10cm2) rotigotine patch
AUC(0-24)ss,norm=area under the concentration versus- time curve during a 24-hour dosing interval at steady state normalized by apparent dose
Cmax,ss,norm=maximum plasma concentration at steady state normalized by apparent dose;

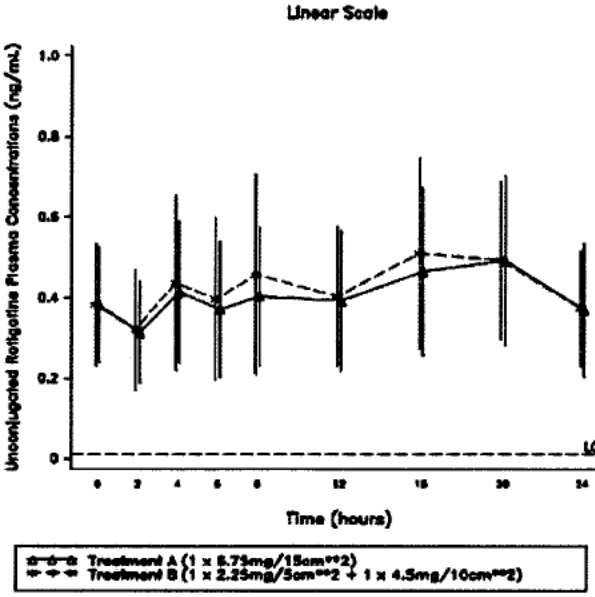
Point estimates for the ratio (A/B) and the respective 90% confidence intervals of the primary PK parameters based on results from the analysis of variance (ANOVA) show that the 90% confidence intervals (CIs) for the ratio A/B are within the acceptance range for bioequivalence (80% to 125%) for all PK parameters (see following table):

ANOVA of PK parameters for unconjugated rotigotine (Day 13 to Day 14)

	$AUC_{(0-24)ss}$	$AUC_{(0-24)ss,norm}$	$C_{max,ss}$	$C_{max,ss,norm}$
Point estimate for ratio A/B (%)	95.36	93.37	97.27	95.24
90% CI	90.51, 100.48	88.24, 98.80	92.11, 102.73	88.91, 102.02
ANOVA CV (%)	13.9	15.1	14.5	18.4

The mean plasma concentration-versus-time courses of unconjugated rotigotine for Treatment A and B throughout the 24-hour patch-on period are shown in the following figure:

Arithmetic mean and SD of unconjugated rotigotine plasma concentrations by treatment on Day 13 and Day 14



Note:

1. While a single dose design is preferred for a BE study, in this case since different strengths are compositionally proportional, the in vivo BE study is not critical
2. The relative bioavailability of 8 mg/24 hour patch versus 2x4 mg/24 hour patches have been evaluated during the original NDA review in Study SP651 in subjects with idiopathic Parkinson's disease and were found to be bioequivalent.

2.5.2 Is the proposed to-be-marketed formulation of rotigotine transdermal patch bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The proposed formulation for the 1 and 3 mg transdermal patches has been used in the pivotal clinical studies and the relative bioavailability study. However, the sponsor is currently experiencing manufacturing problems with the patches and may need to reformulate it. In the event that the reformulation takes place, additional bioavailability/bioequivalence studies may be necessary.

2.5.3 What is the relative bioavailability at the different application sites?

The sponsor evaluated the relative bioavailability at the shoulder, upper arm, abdomen, flank and hip and found in Study SP871 (Doses 1, 2 and 3 mg) that the mean PK parameters varied by application site; the higher mean values for $AUC_{(0\text{-}24),ss}$ and $C_{max,ss}$ were observed at the application sites shoulder, upper arm, and flank compared to

abdomen, hip and thigh. Shoulder, upper arm and flank had similar exposures and abdomen, hip and thigh had similar exposures to each other. Although, after normalizing by apparent dose, mean PK parameters of all application sites were very similar.

The PK parameters by application site are given in the Table below:

PK parameters of unconjugated rotigotine by application site

Parameter	Geometric mean (geometric CV [%])[a]					
	Application site					
	Shoulder	Upper arm	Abdomen	Flank	Hip	Thigh
$AUC_{(0-24),ss}$ (ng/mL*h)	10.6310 (33.7)	10.1153 (37.8)	8.3426 (35.6)	10.7565 (32.5)	8.9794 (39.1)	7.7148 (41.2)
$AUC_{(0-24),ss,norm}$ (ng/mL*h/mg)	2.6683 (29.4)	2.7061 (33.6)	2.4592 (31.2)	2.5969 (26.0)	2.6862 (30.9)	2.4594 (27.3)
$C_{max,ss}$ (ng/mL)	0.59064 (33.6)	0.60033 (48.9)	0.51132 (30.3)	0.58386 (30.6)	0.53676 (39.5)	0.50946 (37.0)
$C_{max,ss,norm}$ (ng/mL/h)	0.14825 (29.9)	0.16060 (48.2)	0.15073 (33.7)	0.14091 (26.2)	0.16057 (31.2)	0.16241 (31.1)
t_{max} (h)[a]	8.0 (0-20)	16.0 (0-24)	14.0 (0-24)	8.0 (0-24)	16.0 (0-24)	18.0 (0-24)

However, the application site difference was also evaluated by the sponsor in Study SP651 (doses 9 and 18 mg) submitted in response to the original NDA approvable letter (See Clinical Pharmacology Review dated 1/30/2007). In this study the shoulder had higher concentration even after normalizing for apparent dose as compared to the abdomen and labeling based on Study SP651 is given in the currently approved label for rotigotine. The sponsor is not seeking any change in the approved label regarding application site differences. The reason for the difference in results of the two studies is not clear.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The validation method (LC-MS/MS) for unconjugated rotigiotine was not changed in the supplement and has been reviewed in the original NDA.
The sponsor amended the assay validation report for the determination of total SPM 962 in human plasma by LC-MS/MS (Amendment JA-010), (b) (4)

(b) (4) The amended assay validation report was acceptable as shown in the following Table of validation parameters:

Validated Parameter	Results total SPM 962
Calibration range	10.0 – 2000 pg/mL
LOQ	(b) (4)
r^2 (overall mean)	
Inter-Day precision [%]*	
Inter-Day accuracy [%]*	
Intra-Day precision [%]*	
Intra-Day accuracy [%]*	
Stability in prepared samples at room temperature	at least 72 hours
Stability in prepared samples in a refrigerator	at least 72 hours
Stability in matrix at room temperature	at least 72 hours
Stability in matrix in a refrigerator	at least 72 hours

* at the lowest QC level

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APPENDIX

REVIEW OF INDIVIDUAL STUDIES

Study SP871: Single-site, randomized, open-label, crossover trial to assess the relative bioavailability of rotigotine after administration of rotigotine transdermal patch 6.75mg/15cm2 compared to combined application of 1x2.25mg/5cm2 plus 1x4.5mg/10cm2 in healthy male subjects

Objectives:

- The primary objective of this trial was to evaluate the relative bioavailability of rotigotine after single dose administration of 1 patch (6.75mg [15cm²], Treatment A) compared to 2 patches (one 2.25mg [5cm²] + one 4.5mg [10cm²], Treatment B) at steady state, in healthy male subjects.
- Secondary objectives of this trial were to evaluate the relative bioavailability of rotigotine after patch application (6.75mg [15cm²]) to 6 different application sites (shoulder, upper arm, flank, abdomen, hip, thigh), to investigate the patch adhesiveness of rotigotine transdermal patches, the local tolerability, and the safety and tolerability of both treatments.

The study design is as follows:

<table>
<tr><td>Study Site</td><td>(b) (4)</td></tr>
<tr><td>Study Design</td><td>This trial was a randomized, open-label, crossover multiple dose trial with administration of daily rotigotine dose of 4.5mg during the Run-In Period on Days 1-3 followed by a daily dose of 6.75mg on Days 4-12. On Day 1, subjects were randomized to a rotation scheme of application sites (effective on Days 7-12) combined with a treatment sequence (effective on Days 13-14). On Days 13 and 14, subjects consecutively received one 6.75mg (15cm2) patch (Treatment A) and two patches, one 2.25mg (5cm2) + one 4.5mg (10cm2) (Treatment B) in a treatment sequence AB and BA, respectively. The application site on Days 13 and 14 was identical to that on Day 12.
<table>
<tr><th></th><th>Days of trial</th><th>Dose/size of rotigotine patch administered</th></tr>
<tr><td>Titration Period</td><td>1-3</td><td>4.5mg (10cm²)</td></tr>
<tr><td></td><td>4-6</td><td>6.75mg (15cm²)</td></tr>
<tr><td>Maintenance Period</td><td>7-12[a]</td><td>6.75mg (15cm²)</td></tr>
<tr><td></td><td>13-14[b]</td><td>Treatment A:
6.75mg (15cm²)
Treatment B:
2.25mg (5cm²) plus 4.5mg (10cm²)</td></tr>
</table>
a Subjects were randomized to a rotation scheme of 6 application sites (abdomen, shoulder, upper arm, flank, hip, thigh) for Days 7 to 12.
b Subjects were randomized to treatment sequence AB or BA with regard to patch application on Days 13 and 14. On both Days 13 and 14, patch(es) were applied to the same application site as on Day 12.</td></tr>
<tr><td>Study Population</td><td>N=56 Healthy subjects enrolled, 41 completed the study, 40 had full PK data: Fifteen subjects discontinued the trial prematurely, 14 of which</td></tr>
</table>

<table>
<tr><td></td><td>were discontinued due to manufacturing problems with the trial medication. One subject (Subject 81004) randomized to treatment sequence AB) discontinued from the trial due to an AE (preferred term: thrombophlebitis, superficial)

Age: 18-45 years (mean 24.4 years)
Gender: All males
Weight: 58-99 kg (mean 76.6 kg)
Race: All White</td></tr>
<tr><td>Treatment Group</td><td>Treatment A: 1x 6.75mg (15cm2) patch
Treatment B: 1x 2.25mg (5cm2) + 1x4.5mg (10cm2)</td></tr>
<tr><td>Dosage and Administration</td><td>Rotigotine transdermal patches were applied once daily with a 24-hour patch-on period.

The dosage was 4.5mg rotigotine on Days 1-3 and 6.75mg on Days 4-14.
<table>
<tr><th>Day</th><th>Treatment sequence[a]</th><th>Dose [size] of rotigotine transdermal patch applied</th></tr>
<tr><td>1-3[b]</td><td>AB and BA</td><td>1 x 4.5mg (10cm^2)</td></tr>
<tr><td>4-6[b]</td><td>AB and BA</td><td>1 x 6.75mg (15cm^2)</td></tr>
<tr><td>7-12[c]</td><td>AB and BA</td><td>1 x 6.75mg (15cm^2)</td></tr>
<tr><td>13[d]</td><td>AB</td><td>1 x 6.75mg (15cm^2)</td></tr>
<tr><td></td><td>BA</td><td>1 x 2.25mg (5cm^2) + 1 x 4.5mg (10cm^2)</td></tr>
<tr><td>14[d]</td><td>AB</td><td>1 x 2.25mg (5cm^2) + 1 x 4.5mg (10cm^2)</td></tr>
<tr><td></td><td>BA</td><td>1 x 6.75mg (15cm^2)</td></tr>
<tr><td>15</td><td>AB and BA</td><td>none</td></tr>
</table>
a On Day 1 of the trial, subjects were randomly allocated to treatment sequence AB or BA (for Days 13 and 14).
b Patch application sites were rotated between the abdomen, shoulder, upper arm, flank, hip, and thigh.
c Subjects were randomized to a rotation scheme of 6 different application sites (abdomen, shoulder, upper arm, flank, hip, thigh).
d The same application site was used as on Day 12.

Rotigotine patch was supplied by SCHWARZ BIOSCIENCES GmbH; batches 0507260002 (2.25mg [5cm2]),
0506210002 (4.5mg [10cm2]), and
050802001 and 0603310005 (6.75mg [15cm2])

Diet: Subjects were required to fast for at least 10 hours before safety laboratory measurements at EA and on Days -1, 15,
No special food restrictions were necessary.
Alcohol consumption and smoking was not permitted</td></tr>
<tr><td>Sampling: Blood</td><td>For unconjugated rotigotine
Day 1: predose
Day 7-14: predose (ie, immediately prior to patch removal), and
Days 13-14: at 2, 4, 6, 8, 12, 16, 20 hours after patch application,
Day 15: 24 hours after patch application on Day 14</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Method: LC/MS/MS method in plasma</td></tr>
</table>

	Lower Limits of Quantitation: Plasma Unconjugated Rotigotine 10 pg/ml Plasma: Linear Range: 10-2000 pg/ml in plasma Quality control concentrations: 25, 250 and 2000 pg/ml Inter-day precision: < 6.2%CV Inter-day accuracy:95.6-99.1% of the nominal concentration
PK Assessment	Unconjugated Rotigotine in plasma Primary PK parameters were: • AUC(0-24),ss and Cmax,ss Secondary PK parameters were: • plasma concentrations (Days 7-14) • AUC(0-24),ss, Cmax,ss, AUC(0-24),ss,norm, Cmax,ss,norm, and tmax (Days 7- 12) • fAUC (ie, individual ratio of AUC(0-24),ss 15cm2 versus [10cm2+5cm2]) and fCmax (ie, individual ratio of Cmax,ss 15cm2 versus [10cm2+5cm2]) (Days 13 and 14) The plasma concentration-time courses of unconjugated rotigotine were summarized by application site (shoulder, upper arm, flank, hip, thigh, and abdomen) and by Treatment
Safety Assessment	adverse events (AEs), local (skin) tolerability, laboratory parameters and physical examination, and vital parameters (pulse rate, blood pressure [BP], and electrocardiogram [ECG]).
PD Assessment	None
Patch Adhesiveness	Patch adhesiveness was assessed prior to each patch removal according to the score described below on Days 8 to 15. Adhesiveness score: 0= 90% or greater adhered (essentially no lift off of the skin) 1= 75-<90% adhered (some edges only lifting off of the skin) 2= 50-<75% adhered (less than half the system lifting off of the skin) 3= <50% adhered (more than half the system lifting off of the skin without falling off) 4= patch detached (patch completely off the skin) 5= not assessable due to fixation of patch with hypoallergenic tape 6= not assessable due to new patch application

Note: Hypoallergenic tape was allowed for proper fixation during PK sampling days and about 39-42 % of the patches needed this.

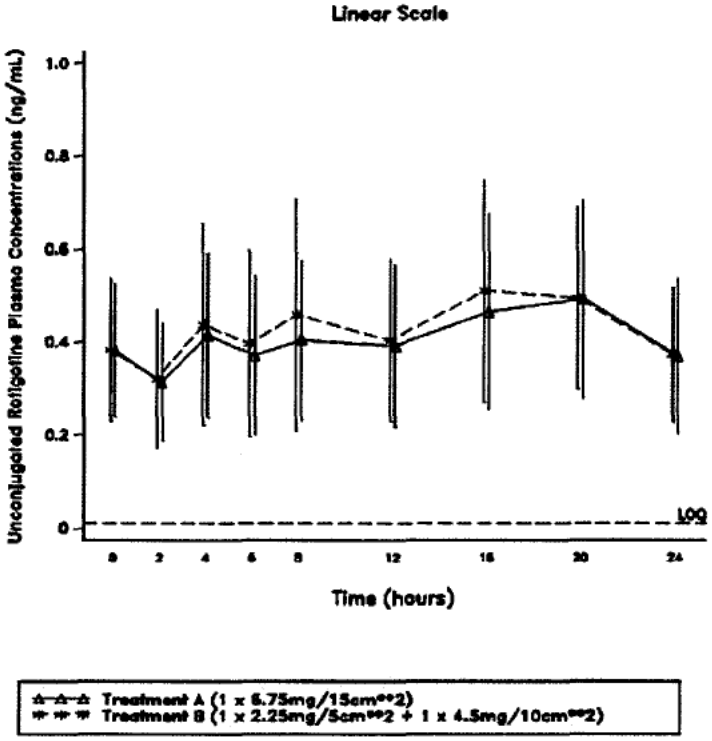
Pharmacokinetic Results:

Pharmacokinetics of unconjugated rotigotine in plasma

A total of 56 subjects were enrolled in this trial. Forty-one of which completed the trial as scheduled in the protocol. Fifteen subjects discontinued the trial prematurely, 14 of which were discontinued due to manufacturing problems with the trial medication. PK data (on Days 13 and 14) were available for 40 subjects due to detachment of rotigotine patch on Day 14 for 1 subject.

The mean plasma concentration vs time courses were similar for Treatment A and B throughout the 24-hour patch-on period and are shown in the following figure

Arithmetic mean and SD of unconjugated rotigotine plasma concentrations by treatment on Days 13 and 14



The following table summarizes the results of descriptive statistics for the PK parameters for Treatments A and B

PK parameters of unconjugated rotigotine by treatment

Parameter	Geo mean (geo CV[%])[a]	
	A (n=40)	B (n=40)
$AUC_{(0-24),ss}$ (ng/mL*h)	9.1194 (45.6)	9.5627 (45.5)
$AUC_{(0-24),ss,norm}$ (ng/mL*h/mg)	2.6658 (40.8)	2.8551 (32.0)
$C_{max,ss}$ (ng/mL)	0.52247 (45.3)	0.53711 (43.5)
$C_{max,ss,norm}$ (ng/mL/mg)	0.15273 (40.8)	0.16036 (33.0)
$t_{max,ss}$ (h)[a]	16.0 (0-24)[a]	16.0 (2-20)[a]

A=one 6.75mg (15cm^2) rotigotine patch, B=one 4.5mg (10cm^2) + one 2.25mg (5cm^2) rotigotine patch, CV=coefficient of variation, geo=geometric, n=number of subjects assessed, PKS=Pharmacokinetic Set

a=median and range for $t_{max,ss}$

The relative bioavailability of rotigotine was compared for Treatment A and B. Point estimates for the ratio (A/B) and the respective 90% confidence intervals of the primary PK parameters based on results from the ANOVA are provided in the following table

Parametric analysis of primary PK parameters for unconjugated rotigotine (Days 13-14)

	$AUC_{(0-24),ss}$ (ng/mL*h)	$AUC_{(0-24),ss,norm}$ (ng/mL*h/mg)	$C_{max,ss}$ (ng/mL)	$C_{max,ss,norm}$ (ng/mL/mg)
Point estimate for ratio A/B (%)	95.36	93.37	97.27	95.24
90% CI	90.51, 100.48	88.24, 98.80	92.11, 102.73	88.91, 102.02
ANOVA CV (%)	13.9	15.1	14.5	18.4

A=one 6.75mg (15cm^2) rotigotine patch, ANOVA=analysis of variance, B=one 2.25mg (5cm^2) + one 4.5mg (10cm^2) rotigotine patch, CI=confidence interval, CV=coefficient of variation, n=number of subjects assessed,

Point estimates (ratio A/B) for the comparison of Treatment A versus B for all PK parameters were between 93-97%. The 90% confidence intervals (CIs) for the ratio A/B are within the acceptance range for bioequivalence (80% to 125%) for all PK parameters.

The apparent dose of rotigotine was determined from the used patches removed on Day 8 to Day 15. The apparent dose of rotigotine was calculated as the difference between the initial drug content and residual drug amounts in the patches.

The mean apparent doses were similar, with 3.503mg±0.760mg during Treatment A and a total of 3.480mg±0.942mg during Treatment B. The total mean apparent dose observed

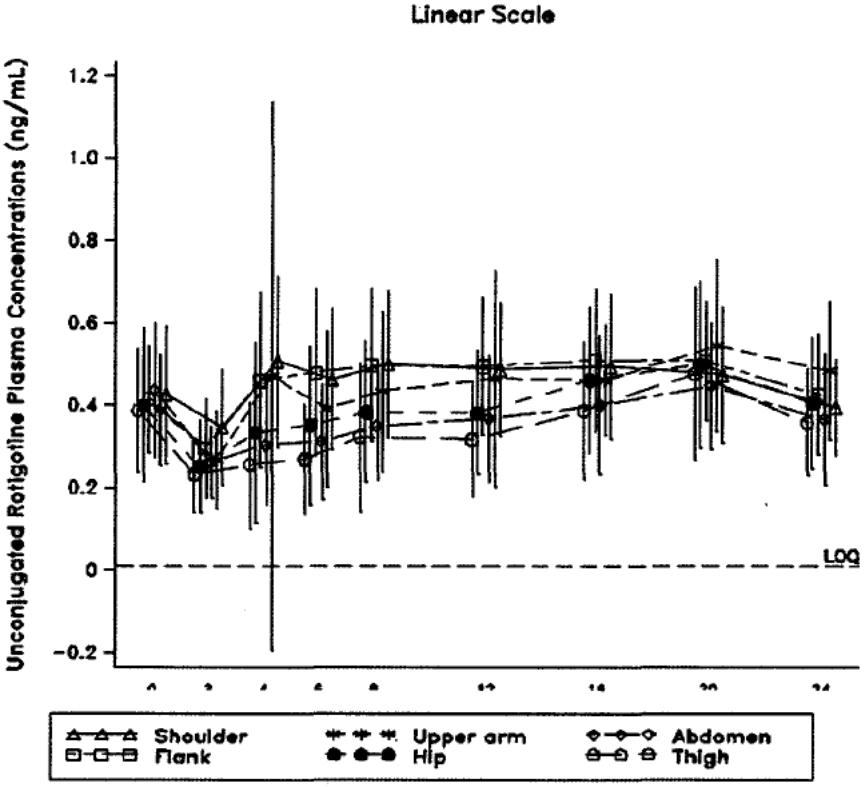
during Treatment B consisted of the mean apparent dose of 2.326mg±0.629mg delivered by the 4.5mg (10cm2) patch and of 1.154mg±0.336mg delivered by the 2.5mg (5cm2) patch.

Approximately 50% of the total drug content (18.1% to 80.4%) of each patch size was delivered to the skin within 24 hours.

Plasma concentrations of unconjugated rotigotine at different application sites

The mean unconjugated rotigotine plasma concentration vs time courses at steady state were similar for all application sites throughout the 24-hour patch-on period and are shown in the following figure:

Arithmetic mean and SD of unconjugated rotigotine plasma concentrations by application site after administration of 6.75mg (15cm2) rotigotine on Days 7 to 12

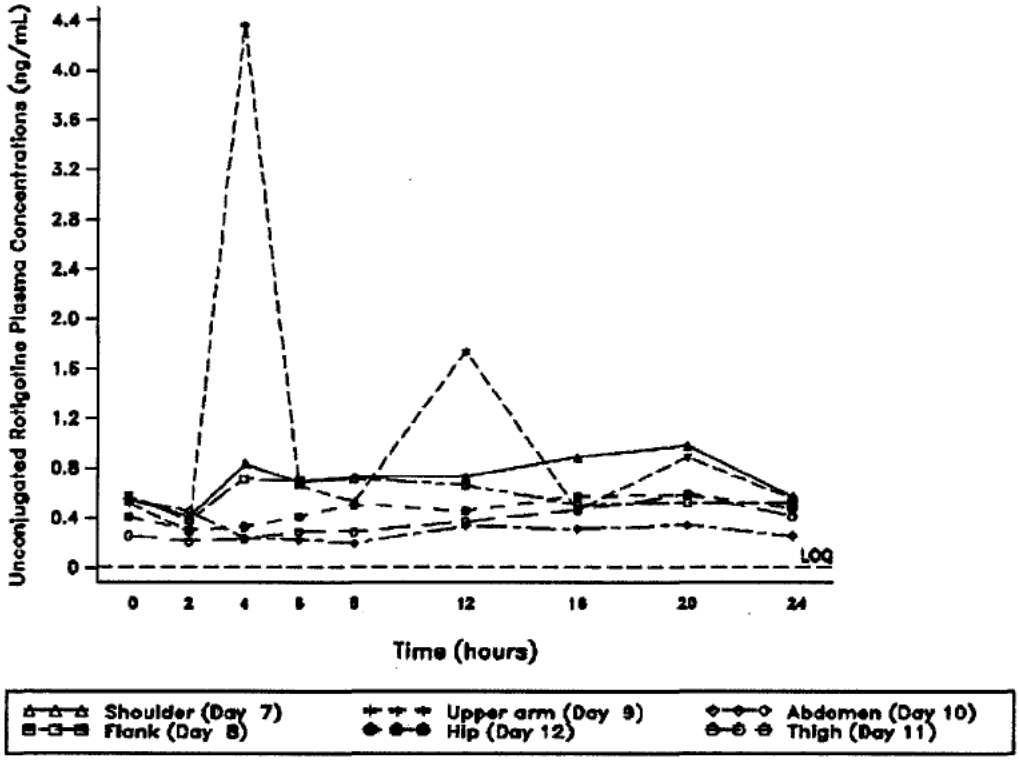


Within 2 hours after patch application, the mean plasma concentrations decreased slightly followed by an increase to plateau plasma concentrations. The highest mean plasma concentrations of approximately 0.3ng/mL to 0.5ng/mL were generally reached approximately 20 hours after patch application. Immediately prior to patch removal, the mean plasma concentrations of unconjugated rotigotine were similar to the corresponding

concentrations at time of patch removal the day before. Highest mean plasma concentrations were observed for the application sites shoulder, upper arm, and flank.

The higher variability at the application site upper arm at 4 hours after patch application was caused by 1 value measured for Subject 81007. For this subject, the plasma concentration of unconjugated rotigotine was 4.3649ng/mL at 4 hours after patch application to the upper arm. All other measurements for this subject were either <1.0ng/mL or 1.7399ng/mL

PK profile of this subject is given below:



The PK parameters by application site is given in the Table below:

PK parameters of unconjugated rotigotine by application site

Parameter	Geometric mean (geometric CV [%])[a]					
	Application site					
	Shoulder	Upper arm	Abdomen	Flank	Hip	Thigh
$AUC_{(0-24),ss}$ (ng/mL*h)	10.6310 (33.7)	10.1153 (37.8)	8.3426 (35.6)	10.7565 (32.5)	8.9794 (39.1)	7.7148 (41.2)
$AUC_{(0-24),ss,norm}$ (ng/mL*h/mg)	2.6683 (29.4)	2.7061 (33.6)	2.4592 (31.2)	2.5969 (26.0)	2.6862 (30.9)	2.4594 (27.3)
$C_{max,ss}$ (ng/mL)	0.59064 (33.6)	0.60033 (48.9)	0.51132 (30.3)	0.58386 (30.6)	0.53676 (39.5)	0.50946 (37.0)
$C_{max,ss,norm}$ (ng/mL/h)	0.14825 (29.9)	0.16060 (48.2)	0.15073 (33.7)	0.14091 (26.2)	0.16057 (31.2)	0.16241 (31.1)
t_{max} (h)[a]	8.0 (0-20)	16.0 (0-24)	14.0 (0-24)	8.0 (0-24)	16.0 (0-24)	18.0 (0-24)

Mean PK parameters varied by application site; the highest mean values for $AUC_{(0-24),ss}$ and $C_{max,ss}$ were observed at the application sites shoulder, upper arm, and flank. Although, after normalizing by apparent dose, mean PK parameters of all application sites were very similar.

The median t_{max} value was 8 hours for the application sites shoulder and flank and 14 to 18 hours for all other application sites.

The relative bioavailability of rotigotine was compared for the 6 different patch application sites. Point estimates (%) for the ratios of the different application sites and the respective 90% CIs of the PK parameters $AUC_{(0-24),ss}$ and $C_{max,ss}$ based on the results from the ANOVA are provided in the following Tables:

Parametric analysis of $AUC_{(0-24),ss}$ (ng/mL*h) by application site

Application site 1		Application site 2		Point estimate for ratio (1/2) (%)	90% CI (%)
Site	LS means	site	LS means		
Shoulder	10.5433	Upper arm	10.0823	104.57	(97.24, 112.46)
		Abdomen	8.2842	127.27	(118.35, 136.87)
		Flank	10.6399	99.09	(92.14, 106.57)
		Hip	8.8715	118.84	(110.53, 127.78)
		Thigh	7.6147	138.46	(128.75, 148.90)
Upper arm	10.0823	Abdomen	8.2842	121.70	(113.19, 130.86)
		Flank	10.6399	94.76	(88.11, 101.90)
		Hip	8.8715	113.65	(105.68, 122.22)
		Thigh	7.6147	132.40	(123.12, 142.39)
Abdomen	8.2842	Flank	10.6399	77.86	(72.40, 83.73)
		Hip	8.8715	93.38	(86.83, 100.42)
		Thigh	7.6147	108.79	(101.16, 117.00)
Flank	10.6399	Hip	8.8715	119.93	(111.52, 128.98)
		Thigh	7.6147	139.73	(129.95, 150.24)
Hip	8.8715	Thigh	7.6147	116.50	(108.33, 125.29)

Pairwise comparisons of $AUC_{(0-24),ss}$ of unconjugated rotigotine for different application sites resulted in point estimates around 100% (ranging from 93.38% to 139.73%). Shoulder, upper arm and flank had similar exposures and abdomen, hip and thigh had similar exposures.

After normalizing by apparent dose, pairwise comparisons of $AUC_{(0-24),ss,norm}$ of unconjugated rotigotine for different application sites resulted in point estimates ranging from 91.84% to 111.01% (Table below). The 90% CIs for all pairwise comparisons of $AUC_{(0-24),ss,norm}$ were within a range of 80% to 125%.

Parametric analysis of $AUC_{(0-24),ss,norm}$ (ng/mL*h/mg) by application site (dose normalized)

Application site 1		Application site 2		Point estimate for ratio (1/2) (%)	90% CI (%)
Site	LS means	site	LS means		
Shoulder	2.6582	Upper arm	2.7041	98.30	(92.42, 104.56)
		Abdomen	2.4521	108.40	(101.92, 115.30)
		Flank	2.5791	103.07	(96.90, 109.63)
		Hip	2.6699	99.56	(93.62, 105.88)
		Thigh	2.4358	109.13	(102.60, 116.07)
Upper arm	2.7041	Abdomen	2.4521	110.28	(103.70, 117.27)
		Flank	2.5791	104.85	(98.57, 111.52)
		Hip	2.6699	101.28	(95.22, 107.73)
		Thigh	2.4358	111.01	(104.37, 118.08)
Abdomen	2.4521	Flank	2.5791	95.08	(89.39, 101.13)
		Hip	2.6699	91.84	(86.35, 97.69)
		Thigh	2.4358	100.67	(94.65, 107.07)
Flank	2.5791	Hip	2.6699	96.60	(90.82, 102.75)
		Thigh	2.4358	105.88	(99.56, 112.60)
Hip	2.6699	Thigh	2.4358	109.61	(103.05, 116.58)

Pairwise comparisons of $C_{max,ss}$ of unconjugated rotigotine for different application sites resulted in point estimates around 100% (ranging from 95.58% to 118.22%)

Parametric analysis of $C_{max,ss}$ (ng/mL) by application site

Application site 1		Application site 2		Point estimate for ratio (1/2) (%)	90% CI (%)
Site	LS means	site	LS means		
Shoulder	0.58437	Upper arm	0.59485	98.24	(89.94, 107.31)
		Abdomen	0.50536	115.64	(105.87, 126.31)
		Flank	0.57710	101.26	(92.70, 110.61)
		Hip	0.52870	110.53	(101.22, 120.70)
		Thigh	0.5315	116.14	(106.33, 126.86)
Upper arm	0.59485	Abdomen	0.50536	117.71	(107.79, 128.54)
		Flank	0.57710	103.08	(94.37, 112.59)
		Hip	0.52870	112.51	(103.01, 122.89)
		Thigh	0.5315	118.22	(108.23, 129.14)
Abdomen	0.50536	Flank	0.57710	87.57	(80.17, 95.65)
		Hip	0.52870	95.58	(87.51, 104.41)
		Thigh	0.5315	100.44	(91.95, 109.71)
Flank	0.57710	Hip	0.52870	109.16	(99.93, 119.23)
		Thigh	0.5315	114.70	(105.03, 125.25)
Hip	0.52870	Thigh	0.5315	105.08	(96.20, 114.78)

After normalizing by apparent dose, pairwise comparisons of $C_{max,ss,norm}$ of unconjugated rotigotine for different application sites resulted in point estimates ranging from 86.91% to 114.05% (Table below). The 90% CIs were within a range of 80% to 125% for 14 of the 15 pairwise comparisons and within the range of 70% to 143% for the comparison flank vs hip (79.65, 94.85).

Parametric analysis of $C_{max,ss,norm}$ (ng/mL/mg) by application site (Dose Normalized)

Application site 1		Application site 2		Point estimate for ratio (1/2) (%)	90% CI (%)
Site	LS mean	site	LS mean		
Shoulder	0.14733	Upper arm	0.15954	92.35	(84.61, 100.80)
		Abdomen	0.14959	98.49	(90.24, 107.51)
		Flank	0.13989	105.32	(96.49, 114.96)
		Hip	0.15911	92.60	(84.86, 101.05)
		Thigh	0.16095	91.54	(83.87, 99.91)
Upper arm	0.15954	Abdomen	0.14959	106.66	(97.74, 116.39)
		Flank	0.13989	114.05	(104.49, 124.48)
		Hip	0.15911	100.27	(91.87, 109.44)
		Thigh	0.16095	99.12	(90.81, 108.20)
Abdomen	0.14959	Flank	0.13989	106.93	(97.97, 116.72)
		Hip	0.15911	94.01	(86.13, 102.62)
		Thigh	0.16095	92.94	(85.15, 101.44)
Flank	0.13989	Hip	0.15911	87.92	(80.55, 95.96)
		Thigh	0.16095	86.91	(79.65, 94.85)
Hip	0.15911	Thigh	0.16095	98.86	(90.57, 107.90)

Apparent dose at different application sites

The apparent daily rotigotine doses that were used to calculate the normalized parameters $AUC_{(0-24),ss,norm}$ and $C_{max,ss,norm}$ are summarized in the table below.

Apparent dose (mg) by application site

Application site	n	Apparent dose Mean (±SD) (mg)	Relative apparent dose (±SD) (%)
Shoulder	40	4.045 (0.686)	59.92 (10.17)
Upper arm	40	3.803 (0.796)	56.35 (11.78)
Abdomen	40	3.526 (0.981)	52.22 (14.53)
Flank	40	4.211 (0.786)	62.40 (11.63)
Hip	40	3.435 (0.818)	50.88 (12.11)
Thigh	40	3.246 (0.885)	48.09 (13.11)

Approximately 50% to 60% of the total drug content was delivered to the skin within 24 hours at each application site.

Conclusions:

- The PK parameters $AUC_{(0-24),ss}$ and $C_{max,ss}$ were similar after application of one 6.75mg (15cm2) rotigotine patch (Treatment A) versus concomitant application of one 4.5mg (10cm2) plus one 2.25mg (5cm2) rotigotine patch (Treatment B) The 90% CIs were within the acceptance range for bioequivalence of 80% to 125%.

- This multiple dose deign is not optimal to detect any performance difference between patches (to assess BA/BE). However, in vivo BE demonstration is not critical since the strengths are compositionally proportional.[In vitro release comparison's will be made by ONDQA].

- Bioavailability of unconjugated rotigotine was compared after application of one 6.75mg (15cm2) patch to 6 different application sites (shoulder, upper arm, abdomen, flank, hip, and thigh) and showed the following results:
  - $AUC_{(0-24),ss}$ and $C_{max,ss}$ varied by application site. Higher values were observed for the application sites shoulder, upper arm, and flank compared to abdomen, hip, and thigh.
  - The differences in relative bioavailability were due to differences in apparent dose at the individual sites, since the exploratory statistical analysis of $AUC_{(0-24),ss,norm}$ resulted in 90%CIs within the range of 80% to 125% for all pairwise comparisons.

- Approximately 50% to 60% of the total drug content was delivered to the skin within 24 hours.

Study SP861: Randomized, double-blind, placebo-controlled, crossover, multiple-dose trial to investigate the influence of 6.75mg rotigotine on the suppression of ovulation by oral hormonal contraception in healthy female subjects.

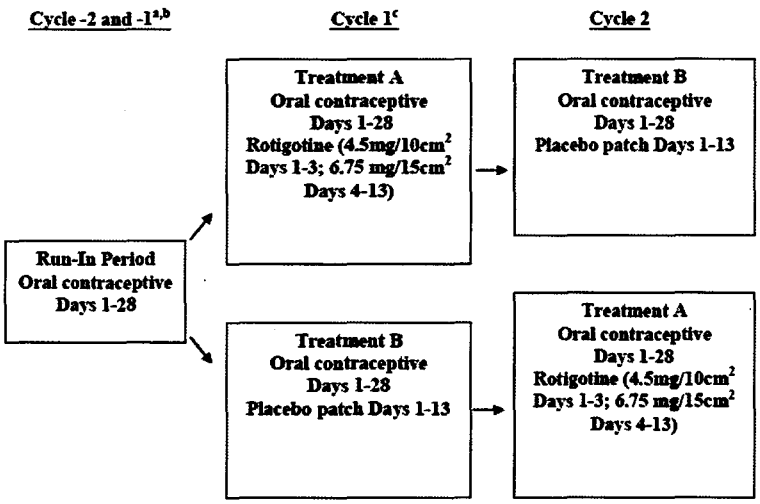
Since RLS may begin early in life and has a higher prevalence in women than in men, it is necessary to offer rotigotine to women of childbearing potential who use oral contraceptives. This trial is designed to investigate the influence of the rotigotine transdermal patch on the suppression of ovulation by oral hormonal contraception in healthy female subjects. This trial investigates the effects of a 6.75mg daily dose of rotigotine (15cm2). This dose represents the highest dose which is currently in development for the RLS indication.

Objectives:

- The primary objective of this trial was to investigate the influence of rotigotine on the suppression of ovulation by oral contraception in healthy female subjects.
- The secondary objective was the investigation of safety, tolerability, and pharmacokinetics of treatment with 6.75mg (15cm2) rotigotine transdermal patch once daily over 10 days in women on oral hormonal contraception.

The study design is as follows:

Study Site	(b) (4)
Study Design	This trial was a randomized, double-blind, placebo-controlled, multiple-dose trial with a crossover design. Following a 2-month Run-In Period on oral hormonal contraception, subjects received rotigotine patch (Treatment A) or placebo patch (Treatment B) in a randomized sequence (AB or BA) for 2 treatment cycles.

	 Each cycle lasted 28 days during which patch medication was administered on Days 1 to 14. Subjects initially received 4.5mg (10cm2) rotigotine daily on Days 1 to 3 under Treatment A. Consecutively, this dose was escalated to 6.75mg (15cm2) rotigotine daily for Days 4 to 13. Under Treatment B, subjects received placebo patches that matched rotigotine patches in appearance and size. Concomitantly, an oral hormonal contraceptive was administered once daily on Days 1 to 28 of each cycle.
Study Population	N=43 Healthy subjects enrolled, 40 completed the study, 36 had full PK data Age: 18-35 years (mean 27.1 years) Gender: All females Weight: 45.2-85 kg (mean 66.41 kg) Race: 37 White, 3 others
Treatment Group	Treatment A: 1x4.5mg (10cm2) patch followed by 6.75mg (15cm2) patch + oral hormonal contraceptive containing 0.03mg ethinylestradiol and 0.15mg levonorgestrel (Nordette®) Treatment B: placebo + oral hormonal contraceptive containing 0.03mg ethinylestradiol and 0.15mg levonorgestrel (Nordette®)
Dosage and Administration	During Run-In Cycles -1 and -2, subjects received the following medication: • Days 1-21: Nordette® active tablet (containing 0.03mg ethinylestradiol and 0.15mg levonorgestrel) • Days 22-28: Nordette® inert tablet During both Cycles 1 and 2, the following trial medication was administered: • Days 1-3: 4.5mg rotigotine patch (10cm2) or matching placebo patch + Nordette® active tablet • Days 4-13: 6.75mg rotigotine patch (15cm2) or matching

	placebo patch + Nordette® active tablet • Days 14-21: Nordette® active tablet • Days 22-28: Nordette® inert tablet Rotigotine transdermal patches were applied once daily in the morning with a 24-hour patch-on period at the right or left lateral abdomen, thigh, hip, flank, shoulder and/or upper arm in accordance to the randomization schedule defining the sequence of the 6 application sites. The oral contraceptive was administered concomitantly each morning together with 200mL of drinking water directly before or after patch application. Rotigotine patch was supplied by SCHWARZ BIOSCIENCES GmbH; • 4.5mg (10cm2): 086106010011 (bulk product batch number: 0506210002) • 6.75mg (15cm2): 086106010012 (bulk product batch number: 0508020001) Nordette® was manufactured by Akromed Products LTD, (b) (4) batch QP218/QP219 Duration of treatment: The expected duration of a subject's participation was approximately 4 months. A 2-month Run-In Period was followed by 2 cycles of 28 days and a Safety Follow-Up Visit at least 7 days after last administration of Nordette®. Diet: Subjects were required to fast for at least 10 hours before all laboratory measurements and before dosing on Day 13 of Cycles 1 and 2. On Day 13 (the day of PK profiling), subjects continued fasting until 4 hours after dosing, after which a lunch was served. On Day 13, subjects were not allowed to drink water 1 hour prior to administration of trial medication or 1 hour after administration of trial medication. Subjects were allowed to consume nonalcoholic and noncaffeinated food and beverages (not containing quinine or grapefruit) throughout the trial. Alcohol consumption was not allowed from Days 1 to 14 of Cycles 1 and 2. Tobacco consumption was not allowed throughout the entire trial. Since this trial investigated the effect of rotigotine on oral hormonal contraception, subjects were required to use an additional contraceptive barrier method during the trial.
Sampling: Blood	Serum Progesterone: Days 19, 20 and 21. Ethinylestradiol and levonorgestrel plasma concentrations: blood sampling at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours on Day 13 of Cycle 1 and 2

<table>
<tr><td></td><td>Rotigotine plasma concentrations: blood sampling at 0 (predose), 4, 6, 9, 16, and 24 hours on Day 13 of Cycle 1 and 2</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Method: LC/MS/MS method in plasma

Lower Limits of Quantitation:
Plasma
Unconjugated Rotigotine 0.01 ng/ml

<u>Plasma:</u>
Linear Range: 0.0100 to 2.00 ng/mL
Quality control concentrations: 0.03, 0.90, 1.50 ng/ml
Inter-day precision: < 8.9%CV
Inter-day accuracy:97.33-103% of the nominal concentration

Summary of calibrators, quality control samples and sample volume for LH<table><tr><th>Item</th><th>Specification</th></tr><tr><td>Calibrators</td><td>(b) (4)</td></tr><tr><td>QCs</td><td></td></tr><tr><td>Sample volume</td><td></td></tr></table>a) at levels Low, Medium and High

Summary of calibrators, quality control samples and sample volume for FSH<table><tr><th>Item</th><th>Specification</th></tr><tr><td>Calibrators</td><td>(b) (4)</td></tr><tr><td>QCs</td><td></td></tr><tr><td>Sample volume</td><td></td></tr></table>a) at levels Low, Medium and High

Summary of calibrators, quality control samples and sample volume for Progesterone<table><tr><th>Item</th><th>Specification</th></tr><tr><td>Calibrators</td><td>(b) (4)</td></tr><tr><td>QCs</td><td></td></tr><tr><td>Sample volume</td><td></td></tr></table>a) at levels Low, Medium and High

Summary of calibrators, quality control samples and sample volume for Estradiol<table><tr><th>Item</th><th>Specification</th></tr><tr><td>Calibrators</td><td>(b) (4)</td></tr><tr><td>QCs</td><td></td></tr><tr><td>Sample volume</td><td></td></tr></table>a) at levels Low, Medium and High, respectively
The accuracy and precision of all these were within the acceptable value of 15%.

<u>Levonorgestrel in plasma:</u> by LC/MS/MS

Linear Range: 50-10000 pg/ml
QC: 150, 750 and 7500 pg/ml</td></tr>
</table>

	Accuracy: 5.9, 5.0, 5.5% CV's respectively Precision: 7.9, 6.3, 4.1% CV, respectively Ethinyl Estradiol in plasma: by LC/MS/MS Linear Range: 3.00 – 600 pg/mL QC: 9.00, 50.0 and 450 pg/mL Accuracy: 1.7, 4.6, 2.4 and 1.2%,CV's respectively Precision: (8.4, 6.1, 6.1% CV, respectively
PK Assessment	On Day 13 the following pharmacokinetics (PK) parameters were additionally measured: • AUC(0-24),ss, Cmax,ss, and tmax,ss for plasma ethinylestradiol and levonorgestrel • AUC(0-24),ss, Cmax,ss, tmax,ss, AUC(0-24),ss,norm and Cmax,ss,norm (normalized by apparent dose), for total and unconjugated plasma rotigotine
Safety Assessment	adverse events (AEs), local (skin) tolerability, laboratory parameters and physical examination, and vital parameters (pulse rate, blood pressure [BP], and electrocardiogram [ECG]) and newly developed pregnancy.
PD Assessment	Primary variable: The primary variable for this trial was progesterone serum concentrations on Days 19 to 21. Progesterone serum concentrations were summarized using descriptive statistics. No influence of rotigotine on the suppression of ovulation was concluded if none of the subjects in the PK group had progesterone serum concentrations ≥2ng/mL at any measurement on Days 19, 20, and 21. Secondary variables: Serum concentrations of estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were determined (estradiol: Days 10, 13, 14, 19-21; LH and FSH: Days 10, 13, and 14).
Patch Adhesiveness	Before patch removal on Days 2-14

Note: Hypoallergenic tape was allowed for proper fixation during PK sampling days and about 39-42 % of the patches needed this.

Pharmacodynamic Results:

Progesterone serum concentrations are summarized in the table below:

Summary of progesterone serum concentrations

Treatment (subjects)	Day	n≥LOQ[a]	Progesterone serum concentration [ng/mL]			
			Mean	SD	Min	Max
A (n=36)	19	27	0.4599	0.2999	0.000	0.999
	20	26	0.4511	0.3231	0.000	1.160
	21	27	0.4606	0.3105	0.000	1.090
B (n=36)	19	27	0.4578	0.2909	0.000	0.969
	20	29	0.4804	0.2818	0.000	1.210
	21	27	0.4587	0.2946	0.000	1.020

A=rotigotine patch, B=placebo patch,
a=Number of subjects with values above the LOQ (LOQ=0.408ng/mL). Values <LOQ were replaced by zero for the statistical analysis.

Mean serum concentrations of progesterone varied between 0.45ng/mL and 0.46ng/mL after treatment with rotigotine, and between 0.46ng/mL and 0.48ng/mL after treatment with placebo patch. The maximum progesterone serum concentration measured was 1.16ng/mL after rotigotine treatment and 1.21ng/mL after treatment with placebo patch. None of the subjects reached a serum concentration of progesterone of ≥2ng/mL during Days 19 to 21 after either treatment. These data indicate sufficient suppression of ovulation, regardless of whether subjects were treated with rotigotine or placebo patch.

Estradiol serum concentrations are summarized in the table below:

Summary of estradiol serum concentrations [pg/mL]

Treatment (subjects)	Statistic	Day 10	Day 13	Day 14	Day 19	Day 20	Day 21
A (n=36)	n≥LOQ[a]	22	20	22	11	13	13
	Median [pg/mL]	14.50	13.95	14.30	0.00	0.00	0.00
	Min	0.0	0.0	0.0	0.0	0.0	0.0
	Max	51.1	20.8	19.9	19.7	20.3	17.6
B (n=36)	n≥LOQ[a]	21	16	17	16	15	13
	Median [pg/mL]	13.95	0.00	0.00	0.00	0.00	0.00
	Min	0.0	0.0	0.0	0.0	0.0	0.0
	Max	32.3	19.7	18.9	20.7	21.0	19.2

LOQ=13.6pg/mL
Median estradiol serum concentrations ranged between 0.00pg/mL and 14.50pg/mL in subjects treated with rotigotine and between 0.00pg/mL and 13.95pg/mL in subjects treated with placebo patch. The highest individual serum concentrations of estradiol reached were 51.10pg/mL in subjects treated with rotigotine and 32.30pg/mL in subjects treated with placebo patch, respectively

LH and FSH serum concentrations are summarized in the table below:

Summary of LH and FSH serum concentrations

Hormone	Treatment (subjects)		Day 10	Day 13	Day 14
LH [U/L]	A (n=36)	n≥LOQ[a]	31	23	21
		Median	2.9300	0.9905	0.9475
		Min	0.000	0.000	0.000
		Max	12.800	7.070	6.530
	B (n=36)	n≥LOQ[a]	26	19	21
		Median	1.9750	0.7190	0.8780
		Min	0.000	0.000	0.000
		Max	7.090	5.240	8.610
FSH [U/L]	A (n=36)	n≥LOQ[a]	28	21	17
		Median	1.760	1.100	0.000
		Min	0.00	0.00	0.00
		Max	5.11	5.09	4.69
	B (n=36)	n≥LOQ[a]	24	18	17
		Median	1.48	0.55	0.00
		Min	0.00	0.00	0.00
		Max	4.80	4.14	4.24

Median LH serum concentrations ranged between 0.95U/L and 2.93U/L in subjects treated with rotigotine and between 0.72U/L and 1.98U/L in subjects treated with placebo patch. The highest individual serum concentrations of LH reached were 12.80U/L in subjects treated with rotigotine and 8.61U/L in subjects treated with placebo patch

Median FSH serum concentrations ranged between 0.00U/L and 1.76U/L in subjects treated with rotigotine and between 0.00U/L and 1.48U/L in subjects treated with placebo patch. The highest individual serum concentrations of FSH reached were 5.11U/L in subjects treated with rotigotine and 4.80U/L in subjects treated with placebo patch

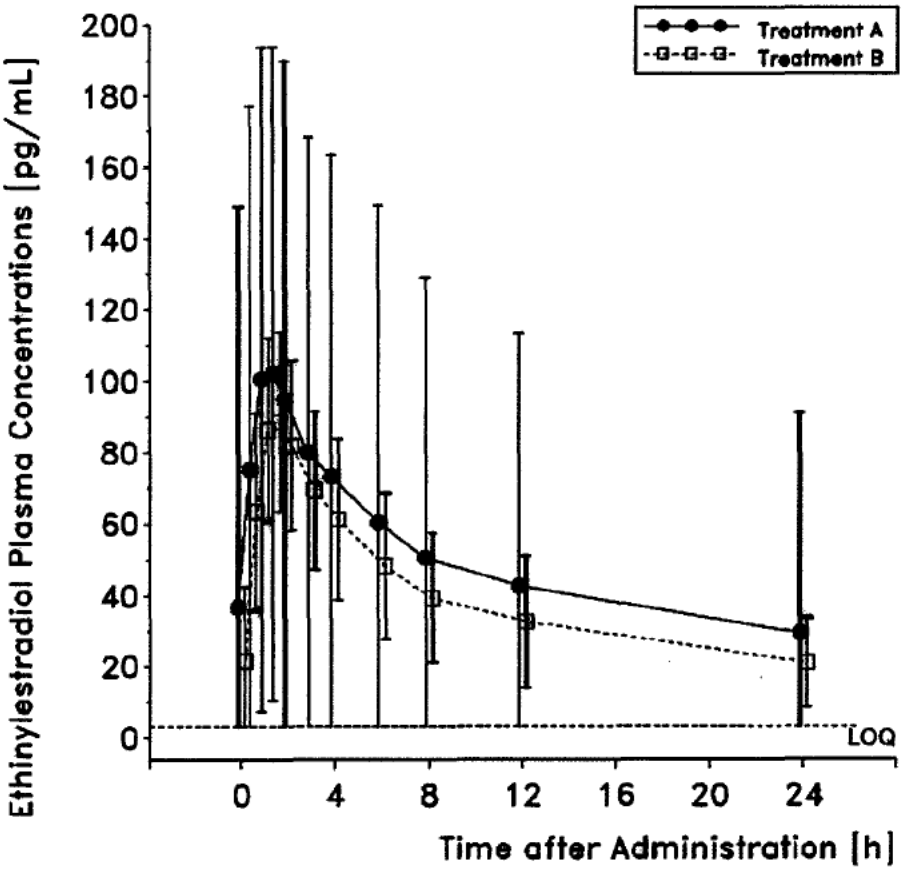
All of the LH and FSH serum concentrations measured fall within the normal range of non-ovulatory female subjects.

Pharmacokinetic Results:

Plasma concentrations of ethinylestradiol

Mean concentration-time profiles of ethinylestradiol separated by treatment are shown in the following figure:

Arithmetic mean and SD of ethinylestradiol plasma concentrations by treatment



The following table summarizes mean plasma concentrations of ethinylestradiol on Day 13:

Ethinylestradiol plasma concentrations over time during concomitant administration of rotigotine or placebo patch with oral hormonal contraceptive (Day 13)

Time after administration of the oral hormonal contraceptive [h]	Ethinylestradiol plasma concentrations [pg/mL]			
	Treatment A (n=36)		Treatment B (n=36)	
	Mean (SD)	Median	Mean (SD)	Median
0	36.77 (112.02)	18.15	21.69 (20.81)	19.30
0.5	75.27 (102.04)	55.10	63.40 (27.61)	59.05
1	100.62 (93.05)	80.50	86.31 (25.64)	85.95
1.5	102.19 (91.68)	86.30	88.63 (25.25)	87.25
2	94.91 (95.12)	74.95	81.94 (23.88)	82.20
3	80.17 (88.25)	62.60	69.37 (22.10)	67.20
4	73.24 (90.32)	56.40	61.23 (22.60)	56.90
6	60.38 (88.95)	41.70	48.24 (20.32)	44.25
8	50.51 (78.51)	35.25	39.27 (18.12)	35.20
12	42.62 (70.82)	31.25	32.68 (18.53)	30.70
24	29.42 (61.70)	20.20	21.03 (12.65)	18.05

A=rotigotine patch, B=placebo patch,

Mean plasma ethinylestradiol concentrations rose till about 1.5 hours after administration of oral hormonal contraceptive. The mean plasma concentrations of ethinylestradiol were slightly higher during concomitant treatment with rotigotine. Inter-individual variability of plasma concentrations was higher under rotigotine treatment than placebo patch as expressed by the higher SD values. Median plasma concentrations were nearly identical underboth treatments. According to the sponsor, these findings indicate a deviation from normal distribution of the individual data, which may be caused by 1 individual subject's ethinylestradiol measurements during rotigotine treatment (Subject 80038). This subject had high concentrations at all time points including Day 1 at predose (102 pg/ml, when all subjects were <LOQ). On Day 13, his predose levels were 689 pg/ml.

Summary statistics of the ethinylestradiol PK values are shown in the following table:

Summary of pharmacokinetic parameters of ethinylestradiol

Treatment (subjects)		$AUC_{(0-24),ss}$ [pg/mL*h]	$C_{max,ss}$ [pg/mL]		$t_{max,ss}$ [h]
A	Geo mean	925.99	93.31	Median	1.50
(n=36)	Geo CV (%)	56.9	45.1	Range	0.0 – 2.0
B	Geo mean	882.51	88.93	Median	1.25
(n=36)	Geo CV (%)	38.6	28.3	Range	0.5 – 4.0

For Subject 80038, values of 11658 pg/mL*h and 689.0pg/mL were determined for $AUC_{max,ss}$ and $C_{max,ss}$ for ethinylestradiol during rotigotine treatment. These values are approximately 12- and 7-fold, respectively, higher than those of all other subjects. This subject was included in the calculation of the above mean and also in the calculation of the 90% confidence intervals.

The following table summarizes the results of the parametric analyses:

Parametric analysis of PK parameters for ethinylestradiol

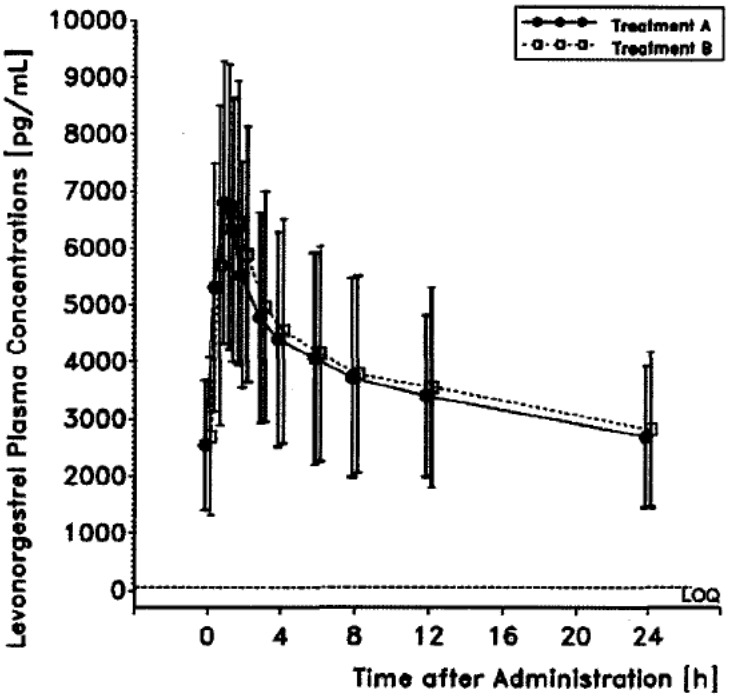
	$AUC_{(0-24),ss}$	$C_{max,ss}$
Point estimate for ratio A/B	1.0493	1.0491
90% CI	0.8993, 1.2243	0.9264, 1.1882
ANOVA CV (%)	40.2	32.0

The 90% CIs for the ratio A/B are within the acceptance range for bioequivalence of 0.8 to 1.25 for both PK parameters.

Plasma concentrations of levonorgestrel

Mean concentration-time profiles of levonorgestrel separated by treatment are shown in the following figure:

Arithmetic mean and SD of levonorgestrel plasma concentrations by treatment



The following table summarizes mean plasma concentrations of levonorgestrel on Day 13:

Levonorgestrel plasma concentrations over time during concomitant administration of rotigotine or placebo with oral hormonal contraceptive (Day 13)

Time after administration of the oral hormonal contraceptive [h]	Mean levonorgestrel plasma concentrations [pg/mL]	
	Treatment A (n=36)	Treatment B (n=36)
	Mean (SD)	Mean (SD)
0	2544.6 (1137.2)	2695.6 (1375.8)
0.5	5311.4 (2180.5)	5695.0 (2801.5)
1	6796.7 (2482.9)	6717.8 (2495.3)
1.5	6313.3 (2312.4)	6447.5 (2482.1)
2	5522.5 (1980.3)	5888.3 (2239.4)
3	4779.2 (1848.7)	4962.5 (2022.2)
4	4400.6 (1877.5)	4545.6 (1966.5)
6	4060.3 (1849.8)	4145.8 (1888.5)
8	3721.7 (1742.2)	3779.7 (1718.1)
12	3403.6 (1413.0)	3555.8 (1747.3)
24	2690.9 (1239.8)	2812.4 (1360.8)

Maximum levonorgestrel levels were reached in an hour. Mean plasma concentrations versus time profiles of levonorgestrel exhibited a similar pattern with or without concomitant administration of rotigotine. Moreover, interindividual variability of plasma concentrations, as expressed by SD values, was comparable in both Treatments A and B (ie, rotigotine and placebo patch). These data indicate that rotigotine has no impact on the plasma concentrations over time of levonorgestrel.

The summary statistics of the levonorgestrel PK values are summarized in the table below:

Summary of pharmacokinetic parameters of levonorgestrel

Treatment (subjects)		$AUC_{(0\text{-}24),ss}$ [pg/mL*h]	$C_{max,ss}$ [pg/mL]		$t_{max,ss}$ [h]
A	Geo mean	81799.1	6762.9	Median	1.00
(n=36)	Geo CV (%)	39.7	33.2	Range	0.5 – 3.0
B	Geo mean	83664.9	6714.2	Median	1.00
(n=36)	Geo CV (%)	43.6	35.5	Range	0.5 – 2.0

Point estimates and exploratory 90% confidence intervals for the ratio "A/B" (ie, rotigotine/placebo patch) are shown in the Table below:

Parametric analysis of PK parameters for levonorgestrel

	$AUC_{(0-24),ss}$	$C_{max,ss}$
Point estimate for ratio A/B	0.9777	1.0072
90% CI	0.9450, 1.0115	0.9557, 1.0615
ANOVA CV (%)	8.6	13.2

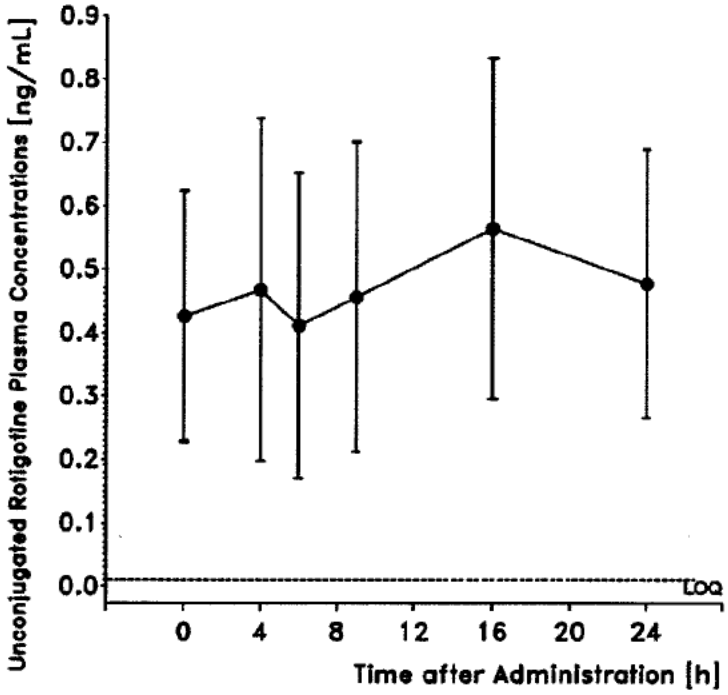
The 90% CIs for the ratios A/B are within the acceptance range for bioequivalence of 0.8 to 1.25 for both PK parameters.

Plasma concentrations of rotigotine

Unconjugated rotigotine

Mean concentration-time profiles of unconjugated rotigotine are shown in the following figure:

Arithmetic mean and SD of unconjugated rotigotine plasma concentration



Mean plasma concentrations of unconjugated rotigotine remained stable throughout the patch-on period on Day 13 and ranged from 0.41±0.24ng/mL to 0.56±0.27ng/mL.

The following table summarizes the results of descriptive statistics for the PK parameters of unconjugated rotigotine:

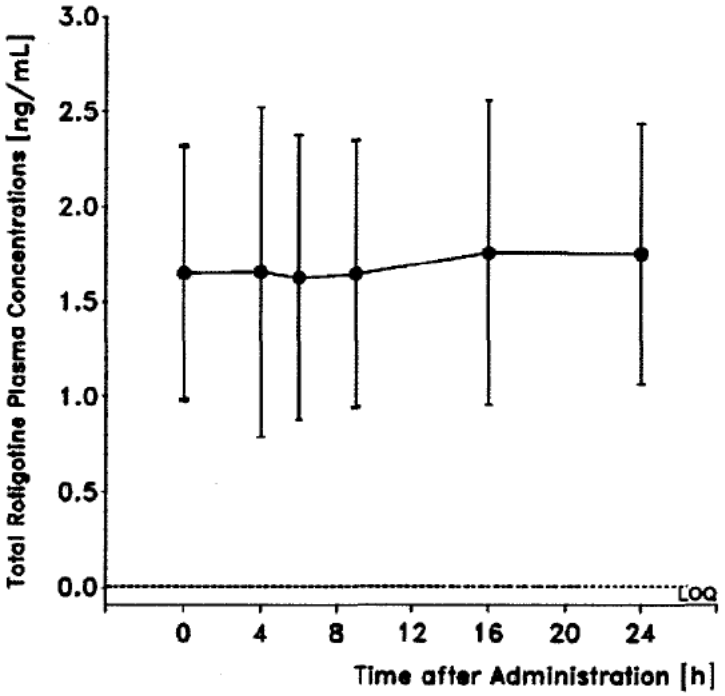
Pharmacokinetic parameters of unconjugated rotigotine (Day 13)

Parameter (n=36)	Unconjugated rotigotine	
	Geo mean	Geo CV (%)
$AUC_{(0\text{-}24),ss}$ [ng/mL*h]	10.624	45.6
$AUC_{(0\text{-}24),ss,norm}$ [ng/mL*h/mg]	2.9799	34.8
$C_{max,ss}$ [ng/mL]	0.5814	38.1
$C_{max,ss,norm}$ [ng/mL/mg]	0.16308	31.6
	Median	**Range**
$t_{max,ss}$ [h]	16.00	0.0 – 24.0

Total rotigotine

Mean concentration-time profiles of total rotigotine are shown in the following figure

Arithmetic mean and SD of total rotigotine plasma concentration



Mean plasma concentrations of total rotigotine remained stable throughout the patch-on period on Day 13 and ranged from 1.63±0.75ng/mL to 1.75±0.69ng/mL.

The following table summarizes the results of descriptive statistics for the PK parameters of total rotigotine:

Pharmacokinetic parameters of total rotigotine (Day 13)

Parameter (n=36)	Unconjugated rotigotine	
	Geo mean	Geo CV (%)
$AUC_{(0-24),ss}$ [ng/mL*h]	37.687	44.0
$AUC_{(0-24),ss,norm}$ [ng/mL*h/mg]	10.5704	36.3
$C_{max,ss}$ [ng/mL]	2.0095	37.9
$C_{max,ss,norm}$ [ng/mL/mg]	0.56361	33.7
	Median	**Range**
$t_{max,ss}$ [h]	6.00	0.0 – 24.0

Apparent dose

Apparent doses of rotigotine (assessed by measuring the residual amount of rotigotine remaining in the used patches removed on Day 14) are summarized by application site in the following table:

Apparent dose of rotigotine by application site

Application site (subjects)	Mean (SD) apparent dose of rotigotine [mg]	Mean (SD) apparent dose of rotigotine [%]
Shoulder (n=6)	3.848 (0.951)	57.03 (14.12)
Upper arm (n=5)	3.510 (1.007)	51.98 (14.92)
Abdomen (n=6)	3.337 (0.607)	49.45 (9.03)
Flank (n=6)	4.137 (0.503)	61.28 (7.43)
Hip (n=8)	3.545 (0.625)	52.49 (9.29)
Thigh (n=7)	3.226 (0.628)	47.81 (9.31)
Total (n=38)	3.590 (0.742)	53.19 (10.99)

Depending on the application site, apparent dose of rotigotine ranged from 3.23±0.63mg (47.81±9.31%) (application to the thigh) to 4.14±0.50mg (61.28±7.43%) (application to the flank). Similar values for apparent dose were observed for all of the application sites when taking into account the comparatively small population sizes per site. Overall, a mean apparent dose of 53.19±10.99% was determined which is comparable to values observed in previous clinical trials.

Patch adhesiveness

Summary of patch adhesiveness prior to patch removal by patch size

Patch size	Trt.	Patch adhesiveness n (%)							
		0	1	2	3	4	5	6	Total
$10cm^2$	A	75 (64.1)	22 (18.8)	1 (0.9)	2 (1.7)	0	15 (12.8)	2 (1.7)	117 (100.0)
	B	88 (77.2)	15 (13.2)	2 (1.8)	0	0	9 (7.9)	0	114 (100.0)
$15cm^2$	A	172 (44.2)	87 (22.4)	23 (5.9)	6 (1.5)	0	86 (22.1)	15 (3.9)	389 (100.0)
	B	289 (76.1)	39 (10.3)	4 (1.1)	0	0	40 (10.5)	8 (2.1)	380 (100.0)

Patch adhesiveness score: 0 = ≥90% adhered, 1 = 75-<90% adhered, 2 = 50-<75% adhered, 3 = <50% adhered, 4 = Patch detached completely, 5 = Not assessable due to fixation with hypoallergenic tape, 6 = Not assessable due to new patch application

Conclusions

- The results of this trial show that rotigotine does not influence the suppression of ovulation by oral hormonal contraception in healthy female subjects. On Days 19 to 21, progesterone serum concentrations of all subjects were clearly <2ng/mL during treatment with rotigotine and placebo patch.
- The pituitary gonadotropins LH and FSH as well as the ovarian steroid estradiol showed no difference during either treatment with rotigotine or placebo patch.
- No relevant differences in rate and extent of absorption of ethinylestradiol and levonorgestrel at steady-state, as expressed by values of $C_{max,ss}$ and $AUC_{(0\ 24),ss}$, were observed when the oral hormonal contraceptive was coadministered with either rotigotine or placebo patch. These similarities are supported by exploratory statistical analysis since the limits of the 90% CIs for the ratio of geometric means of $C_{max,ss}$ and $AUC_{(0\ 24),ss}$ were within the acceptance range for bioequivalence (0.80 to 1.25).
- In summary, concomitant administration of rotigotine had no impact on the pharmacokinetics and pharmacodynamics of the oral hormonal contraceptive.
- Mean rotigotine plasma concentrations at steady-state remained stable over 24 hours. The plasma concentrations and PK parameters are in accordance with data determined in other clinical trials. Approximately 50% of the total drug content was delivered to the skin within 24 hours.

Study SP862: Open-label, multiple dose trial to investigate the effects of omeprazole (40mg) on steady-state pharmacokinetics (PK) and safety and tolerability of rotigotine transdermal patch (9mg/20cm2) in 40 healthy male subjects

Rotigotine is extensively metabolized. The 2 major biotransformation routes are conjugation of the parent compound and N-dealkylation with subsequent conjugation. The major cytochrome P-450 (CYP) isoenzyme involved in the N-dealkylation of rotigotine was found to be CYP2C19. However, multiple CYP isoforms appear to be capable of metabolizing rotigotine. In vitro, the inhibition of specific CYP isoforms did not show an extensive inhibition of rotigotine biotransformation. This was confirmed by a Phase 1 clinical trial (SP627) demonstrating no effect of the non-specific CYP inhibitor cimetidine on the PK of rotigotine. This trial was performed to confirm that CYP2C19 selective inhibition via omeprazole has no effect on rotigotine pharmacokinetics.

Objectives:

- The primary objective of this trial was to investigate the effects of omeprazole (40mg/day) on steady-state PK of rotigotine and its metabolites.
- The secondary objective was to investigate safety and tolerability of rotigotine transdermal patch alone (either 4.5mg/10cm2 or 9.0mg/20mg2) and omeprazole treatment combined with rotigotine transdermal patch (9.0mg/20cm2).

The study design is as follows:

Study Site	(b) (4)
Study Design	This was an open-label, multiple-dose trial. Day -1 marked the beginning of the Treatment Period. Trial medication was administered on Days 1 to 14. Subjects received rotigotine 4.5mg/day (10cm2) on Days 1, 2, 3, and 13 and 14 and rotigotine 9.0mg/day (20cm2) on Days 4 to 12. Subjects received omeprazole capsules (40mg) once daily in the mornings of Days 7 to 12 within 1 minute after patch administration. For each subject, the trial ended with the Safety Follow-Up Visit at least 1 week after the last administration of the rotigotine patch.
Study Population	N=40 subjects were planned and 54 enrolled in this trial. All subjects were extensive metabolizers of CYP2C19. Due to manufacturing defects in the investigational product patch originally provided to the site, the first group of 14 subjects had to be discontinued after Day 8. Data for all 54 subjects were analyzed in the Safety Set; data for 37 subjects were in the Pharmacokinetic Set

<table>
<tr><td></td><td>Age: 18-44 years (mean 24.5 years)
Gender: All males
Weight: 62-105.5kg (mean 78.09 kg)
Race: All White</td></tr>
<tr><td>Treatment Group</td><td>none</td></tr>
<tr><td>Dosage and Administration</td><td>
Treatments administered
<table>
<tr><td></td><td colspan="14">Day</td></tr>
<tr><td>Treatment</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td><td>14</td></tr>
<tr><td>Rotigotine 4.5mg/day (10cm^2 patch)</td><td>x</td><td>x</td><td>x</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>x</td><td>x</td></tr>
<tr><td>Rotigotine 9.0mg/day (20cm^2 patch)</td><td></td><td></td><td></td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td></td><td></td></tr>
<tr><td>Omeprazole (40mg/day)[a]</td><td></td><td></td><td></td><td></td><td></td><td></td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td></td><td></td></tr>
</table>
a administration of omeprazole within 1 minute after patch application

Patches were applied to the right or left abdomen for a period of 24 hours. The application site of the patches was rotated on a daily basis. Concomitant omeprazole capsules were taken with 240mL tap water and within 1 minute following the patch application.

Medication initially provided; only used for first 14 subjects due to manufacturing defects in the patch:
10cm2 Batch number: 0506210002; expiration 31 Mar 2007
20cm2 Batch number: 0502040001; expiration 30 Nov 2006

Replacement medication provided:
10cm2 Batch number: 0506210002; expiration 31 Mar 2007
20cm2 Batch number: 0506210003; expiration 31 Mar 2007

Omeprazole, 40mg capsule
Batch number: 086205120001; expiration 30 Nov 2006

Replacement medication provided:
Batch number: 086206030003; expiration 31 Dec 2007

Duration of treatment: The total duration of the trial for each subject was approximately 3.5 to 6 weeks, including the Eligibility Assessment and Safety Follow-Up Visit.
</td></tr>
<tr><td>Sampling: Blood</td><td>For rotigotine and metabolites:
Day 6 and 12: : 0 (predose), 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours;
For omeprazole:
Day 6 and 12: at 0 (predose) and at 2, 4, and 8 hours</td></tr>
<tr><td>Urine</td><td>Day 6 and 12: Urine over 24 hours</td></tr>
</table>

Feces	none
Analysis	Method: LC/MS/MS method in plasma Lower Limits of Quantitation: Plasma Unconjugated Rotigotine 10 pg/ml Rotigotine in Plasma: Linear Range: 10-2000 ng/ml in plasma Quality control concentrations: 30, 300 and 1500 pg/ml Inter-day precision: < 9.4%CV Inter-day accuracy:% bias -4.4 to 0.2%CV Within study assay validation for the metabolites of rotigitine were also submitted and found acceptable. Omeprazole in plasma: method by LC/MS/MS Linear Range: 20.898 – 9677.240 µg/L LOQ: 20.898 µg/L QCs: 43.602, 4361.549 and 8720.487 Inter-Day precision: <15% CV Inter-day accuracy: <8% CV
PK Assessment	The primary PK parameters were: • $AUC_{(0\text{-}24h),ss}$ and $C_{max,ss}$ of unconjugated rotigotine The secondary PK parameters were: • $AUC_{(0\text{-}24h),ss,norm}$, $C_{max,ss,norm}$, $t_{max,ss}$, Ae_{ss} of unconjugated rotigotine • $AUC_{(0\text{-}24h),ss}$, $C_{max,ss}$, $t_{max,ss}$, Ae_{ss} of total rotigotine • $AUC_{(0\text{-}24h),ss}$, $C_{max,ss}$, $t_{max,ss}$, Ae_{ss} of total despropyl-rotigotine and total desthienylethylrotigotine In addition, unconjugated and total rotigotine plasma concentrations, total despropylrotigotine and desthienylethyl-rotigotine, and omeprazole plasma concentrations were determined at specified time points.
Safety Assessment	adverse events (AEs), local (skin) tolerability, laboratory parameters and physical examination, and vital parameters (pulse rate, blood pressure [BP], and electrocardiogram [ECG])
PD Assessment	none

Pharmacokinetic Results:

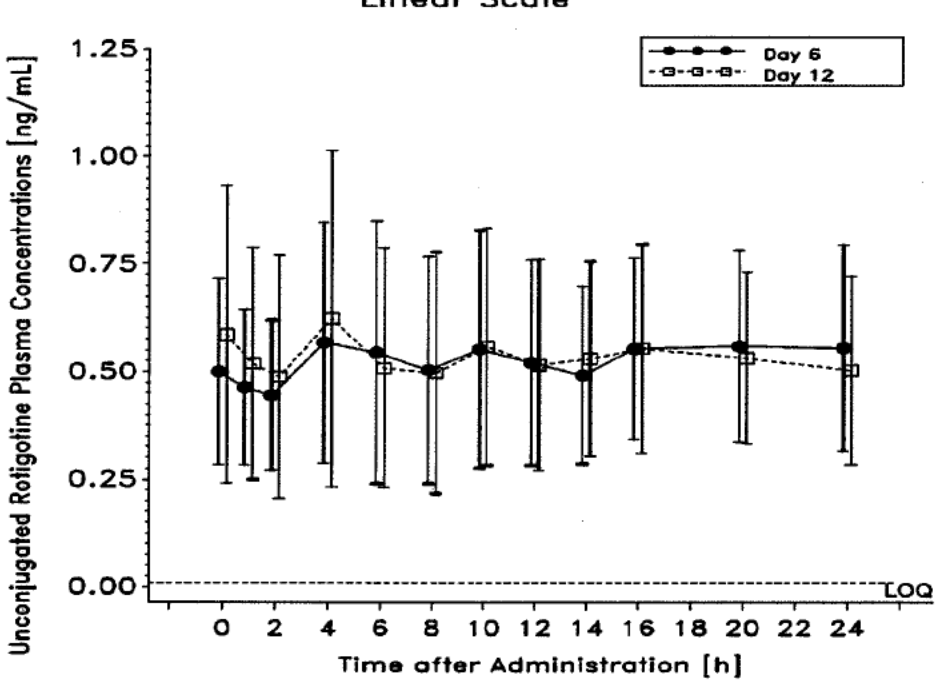
Full PK profiles were determined on Day 6 (rotigotine alone) and on Day 12 (rotigotine + omeprazole).

Unconjugated rotigotine

The mean plasma concentrations of unconjugated rotigotine over time is shown in the following figure:

As shown in the figure below, the mean plasma concentration-time curves of unconjugated rotigotine at steady-state slightly decreased due to lag time of absorption for up to 2 hours after patch application and then increased within the next 2 hours.

Mean plasma concentrations of unconjugated rotigotine over time



Descriptive statistics for PK parameters of unconjugated rotigotine are summarized below:

Pharmacokinetic parameters of unconjugated rotigotine

Parameter	n	Statistic	Rotigotine Day 6	Rotigotine + Omeprazole Day 12
$C_{max,ss}$ (ng/mL)	37	Geometric mean (CV [%])	0.6879 (45.9)	0.7300 (45.5)
$C_{max,ss,norm}$ (ng/mL/mg)	25		0.16873 (35.6)	0.19520 (40.8)
$AUC_{(0-24),ss}$ (ng/mL*h)	37		11.6284 (49.3)	11.4570 (55.0)
$AUC_{(0-24),ss,norm}$ (ng/mL*h/mg)	25		2.81570 (38.9)	3.02199 (37.9)
$t_{max,ss}$ (h)	37	Median (Min, Max)	10.0 (0, 24)	4.0 (0, 24)
Ae_{ss} (µg)	37	Mean±SD	1.7180±1.1754	1.8286±1.1987

Note: Apparent dose was only available for 25 subjects; apparent dose values were missing for Day 7 and Day 13 for 12 subjects in the PK data set.

An ANOVA was performed on log-transformed data of $AUC_{(0-24h),ss}$ and $C_{max,ss}$ of unconjugated rotigotine to derive 90% CIs for the comparison "rotigotine + omeprazole"/"rotigotine alone." The respective 90% CI were within the acceptance range of bioequivalence (0.8;1.25). These ANOVA results shows the similarity of the 2 treatments.

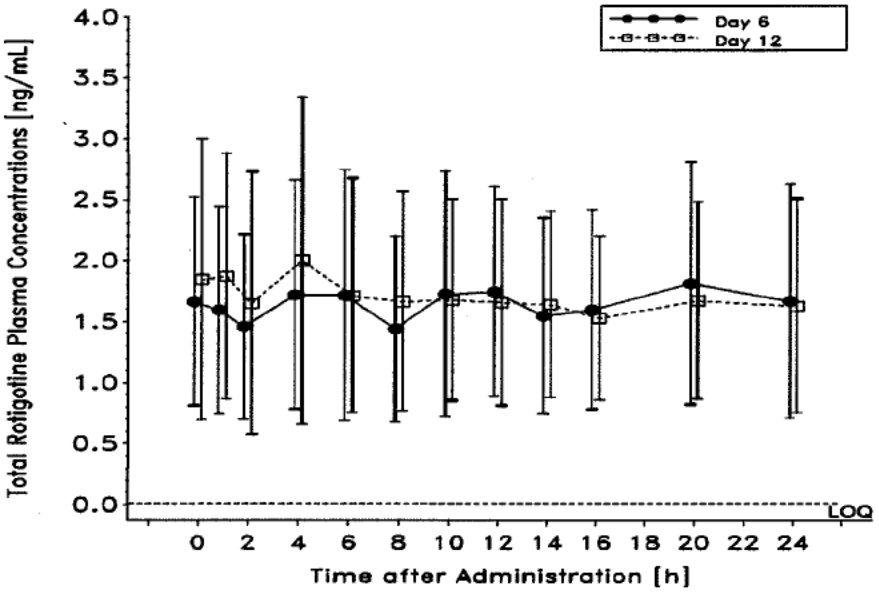
ANOVA for primary PK parameters of unconjugated rotigotine

Parameter	Ratio	Estimate	90% CI	ANOVA-CV (%)
$AUC_{(0-24h),ss}$	rotigotine + omeprazole/ rotigotine alone	0.9853	(0.9024, 1.0757)	22.7
$C_{max,ss}$		1.0613	(0.9723, 1.1585)	22.6

Total rotigotine

The mean plasma concentration of total rotigotine over time is shown in the figure below:

Mean plasma concentrations of total rotigotine over time



The plasma concentrations of rotigotine (unconjugated and total) are similar with and without omeprazole.

Descriptive statistics for PK parameters of total rotigotine are summarized in the table below.

Pharmacokinetic parameters of total rotigotine

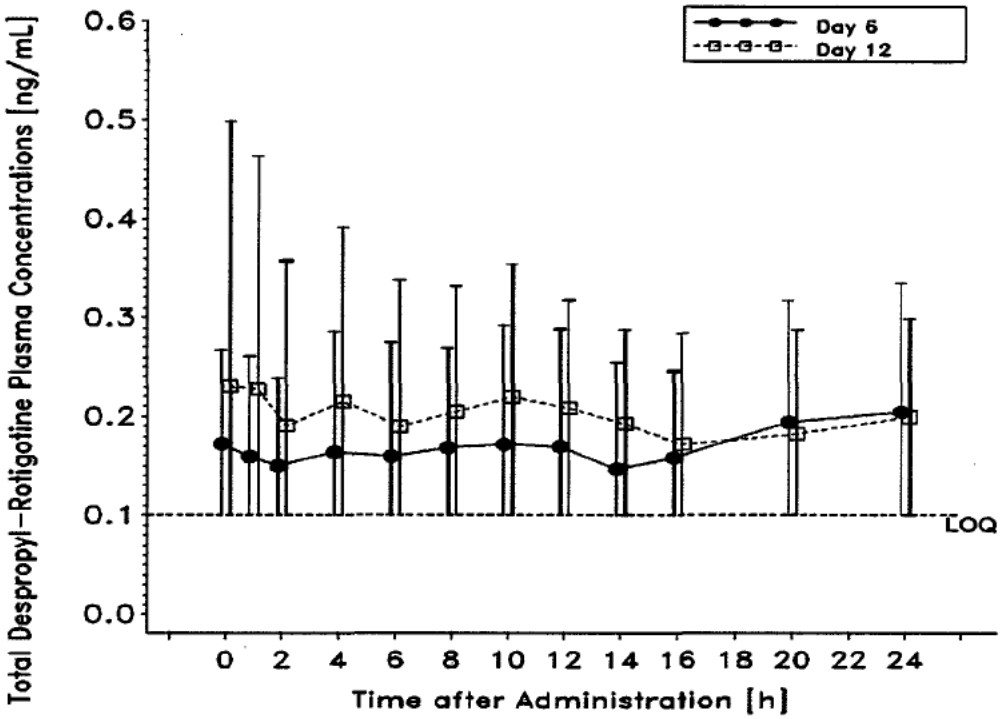
Parameter	n	Statistic	Rotigotine Day 6	Rotigotine + Omeprazole Day 12
$C_{max,ss}$ (ng/mL)	37	Geometric mean (CV [%])	2.0720 (59.1)	2.1995 (58.6)
$AUC_{(0-24h),ss}$ (ng/mL*h)	37		34.9972 (58.6)	35.7698 (59.6)
$t_{max,ss}$ (h)	37	Median (Min, Max)	8.0 (0, 24)	4.0 (0, 24)
Ae_{ss} (µg)	37	Mean±SD	545.4849±179.1088	541.2297±231.1339

As shown in the table above, geometric mean $C_{max,ss}$ and $AUC_{(0-24h),ss}$ values of total rotigotine were similar during administration of rotigotine + omeprazole compared with rotigotine alone.

Total despropyl-rotigotine

The mean plasma concentration of total despropyl-rotigotine over time is shown in the figure below

Mean plasma concentrations of total despropyl-rotigotine over time



As seen in the figure above, the mean plasma concentrations were low (near LOQ) and there was a high variability for these values (CV ranged from 54.8 to 74.2 with rotigotine alone and from 49.3 to 116.3 with rotigotine + omeprazole). The mean plasma concentrations tended to be slightly higher after co-administration with omeprazole when compared to the values of rotigotine treatment alone. Since the plasma concentrations were near the LOQ, the differences seen due to variability may not be meaningful.

Descriptive statistics for PK parameters of total despropyl-rotigotine are summarized in the table below.

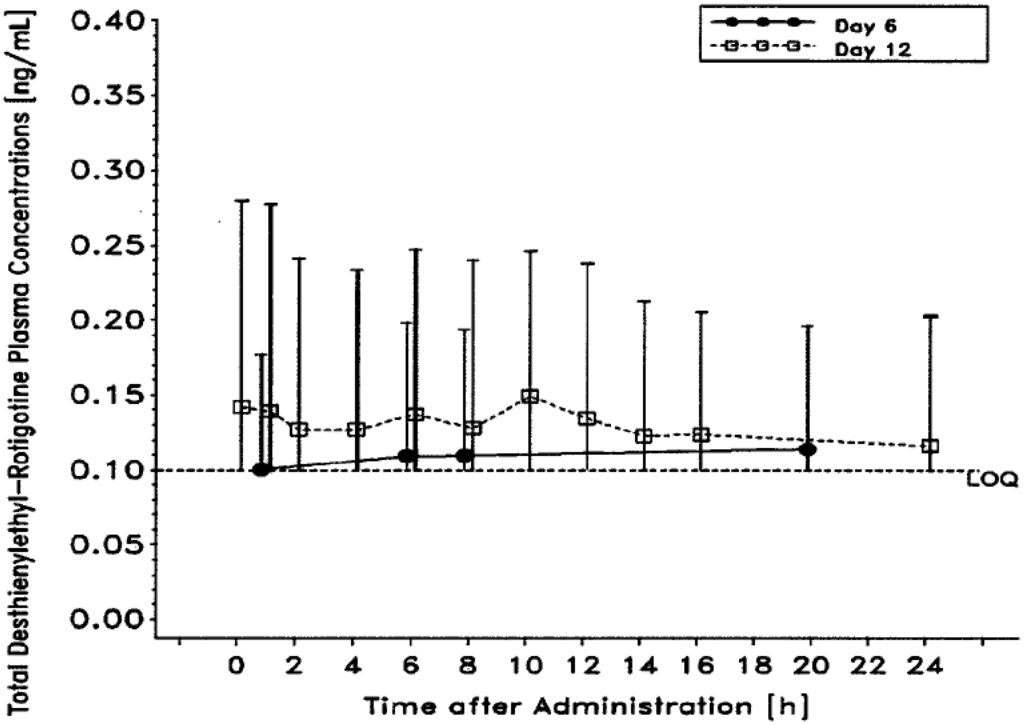
Pharmacokinetic parameters of total despropyl-rotigotine

Parameter	n	Statistic	Rotigotine Day 6	Rotigotine + Omeprazole Day 12
$C_{max,ss}$ (ng/mL)	37	Geometric mean (CV [%])	0.2361 (43.3)	0.2683 (49.3)
$AUC_{(0\text{-}24h),ss}$ (ng/mL*h)	37		2.8316 (172.5)	3.6631 (86.5)
$t_{max,ss}$ (h)	37	Median (Min, Max)	12.0 (0, 24)[a]	10.0 (0, 24)
Ae_{ss} (µg)	37	Mean±SD	15.7226±8.2040	18.2519±12.8340

Total desthienylethyl-rotigotine

Results obtained for total desthienylethyl-rotigotine were similar to those seen with total despropyl-rotigotine

Mean plasma concentrations of total desthienylethyl-rotigotine over time



Descriptive statistics for PK parameters of total desthienylethylrotigotine are summarized in the table below.

Pharmacokinetic parameters of total desthienylethyl-rotigotine

Parameter	n	Statistic	Rotigotine Day 6	Rotigotine + Omeprazole Day 12
$C_{max,ss}$ (ng/mL)	37	Geometric mean (CV [%])	0.1872 (31.0)	0.1961 (42.5)
$AUC_{(0-24h),ss}$ (ng/mL*h)	37		1.7784 (147.4)	1.8410 (209.7)
$t_{max,ss}$ (h)	34	Median (Min, Max)	10.0 (0, 24)[a]	6.0 (0, 24)
Ae_{ss} (µg)	37	Mean±SD	10.8217±6.2646	12.4005±9.4908

Apparent dose of rotigotine

The mean apparent dose was similar with rotigotine alone (4.486mg or 49.84%) compared with rotigotine + omeprazole (4.314mg or 47.93%). Apparent dose data are presented in the table below.

Apparent dose of rotigotine

Statistic	Absolute apparent dose (mg)		Apparent dose relative to total drug content (%)	
Treatment	Rotigotine Day 6	Rotigotine + Omeprazole Day 12	Rotigotine Day 6	Rotigotine + Omeprazole Day 12
n	25	25	25	25
Mean±SD	4.486±0.832	4.314±1.013	49.84±9.24	47.93±11.25
Median	4.370	4.450	48.60	49.40
Min, Max	3.09, 6.02	0.93, 5.93	34.4, 66.9	10.3, 65.8

Pharmacokinetic conclusions

- Omeprazole co-administration did not change steady state plasma concentrations time course and primary PK parameters $AUC_{(0\text{-}24h),ss}$ and $C_{max,ss}$ of unconjugated rotigotine. The point estimate for the ratio "rotigotine + omeprazole"/ "rotigotine alone" was close to 1 for both $AUC_{(0\text{-}24h),ss}$ and $C_{max,ss}$. The respective 90% CIs were within the acceptance range of bioequivalence (0.8;1.25).
- Omeprazole co-administration did not alter steady-state pharmacokinetics of total rotigotine.
- There was no relevant change in plasma concentrations and PK parameters of N-desalkyl metabolites. It has to be taken into account that the plasma concentrations of both metabolites were rather low and near or below LOQ and there was a high variability for these values.
- The amount of excreted unconjugated rotigotine, total rotigotine as well as N-desalkyl metabolites was not altered by omeprazole co-administration.
- In conclusion, these data demonstrate that selective inhibition of CYP2C19 does not alter steady state pharmacokinetics of rotigotine and its metabolites.

APPENDIX II

PHARMACOMETRICS REVIEW
Dr. Hao Zhu

Office of Clinical Pharmacology:
Pharmacometrics review

Summary of Findings

Key Review Questions

The following key questions are addressed in the review.

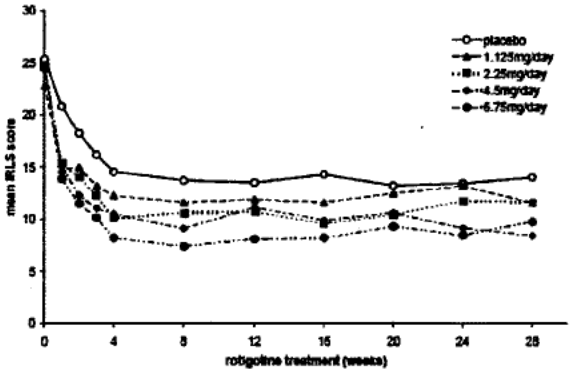
Are there any clinically relevant covariates based on population PK analysis?

No clinical relevant covariates were identified based on the population PK analysis. In the analysis, demographic information (age, gender, body weight, height, body mass index, and creatinine clearance) and the laboratory values (AST, ALT, GGT, ALK, and total bilirubin) were tested for covariate effect. None of them demonstrated significant covariate effect for the major pharmacokinetic parameters (i.e., CL and Vd).

Is there an exposure-response relationship between rotigotine plasma concentration versus idiopathic restless leg syndrome rating scale?

Yes. An exposure-response relationship between rotigotine plasma concentration and idiopathic restless leg syndrome rating scale is established. Following the treatment of placebo or rotigotine, IRLS score reduces rapidly in the first 4 weeks and then it is stabilized (Figure 2). Rotigotine treatment leads to a maximum reduction of 9.32 in IRLS in addition to placebo effect. Higher rotigotine concentration yields larger reduction of IRLS, with the concentration of half maximal effect at 0.227 ng/mL.

Figure 2 Time Course of IRLS Reduction Following the Treatment of Placebo or Rotigotine



Data source: Appendix 9

Is there an exposure-response relationship between rotigotine plasma concentration versus the incidence of common adverse events (>10% of subjects)?

There is a positive correlation between rotigotine exposure and the incidence of application and instillation site reactions. No concentration-related trends were observed for the incidence of nausea, headache, upper respiratory tract infections, or fatigue (Table 1).

Table 1. Incidence of the Common Adverse Events by Estimated Rotigotine Plasma Concentration at the Time of Onset

MedDRA[a] Preferred Term	n/N (%)								
	Rotigotine plasma concentration (ng/mL)								
	0.00 N=217	>0 to <0.1631 N=460	0.1631 to <0.2634 N=494	0.2634 to <0.3637 N=191	0.3637 to <0.4640 N=223	0.4640 to <0.5644 N=124	0.5644 to <0.6647 N=84	0.6647 to <0.7650 N=38	0.7650 to ≤0.8654 N=12
Nausea	21 (9.7)	54 (11.7)	46 (9.3)	16 (8.4)	22 (9.9)	10 (8.1)	8 (9.5)	3 (7.9)	1 (8.3)
Application and instillation site reactions[b]	8 (3.7)	52 (11.3)	64 (13.0)	38 (19.9)	48 (21.5)	35 (28.2)	27 (32.1)	13 (34.2)	6 (50.0)
Fatigue	17 (7.8)	27 (5.9)	30 (6.1)	10 (5.2)	8 (3.6)	2 (1.6)	2 (2.4)	2 (5.3)	0
Upper respiratory tract infections[b]	31 (14.3)	33 (7.2)	30 (6.1)	13 (6.8)	13 (5.8)	8 (6.5)	9 (10.7)	4 (10.5)	3 (25.0)
Headache	24 (11.1)	45 (9.8)	46 (9.3)	11 (5.8)	18 (8.1)	7 (5.6)	9 (10.7)	3 (7.9)	0

N=number of subjects; n=number of subjects reporting at least 1 TEAE; %=n/N; SS=Safety Set; TEAE=treatment-emergent adverse event

a Medical Dictionary for Regulatory Activities (MedDRA®) version 9.1

b MedDRA® High Level Term

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

Pertinent regulatory background

In this supplement NDA submission, the sponsor seeks the market approval of the rotigotine for the treatment of the signs and symptoms of moderate to severe primary restless legs syndrome (RLS).

Results of Sponsor's Analysis

The sponsor submitted one population pharmacokinetics analysis report and two exposure-response analysis report. They are summarized in Table 2.

Table 2 Summary of the Sponsor Submitted Population PK and Exposure-Response Report

Population PK Report	Population Pharmacokinetics of Rotigotine in Subjects with Restless Legs Syndrome
Exposure - Response Report	Exposure-Response Analysis for Efficacy for Rotigotine Treatment in Subjects with Idiopathic Restless Legs Syndrome Exposure-Response Analysis of Safety for Rotigotine Treatment in Subjects with Idiopathic Restless Legs Syndrome

Population Pharmacokinetics Analysis

The sponsor performed population PK analysis in order to: 1.) describe the population PK characteristics of rotigotine and to characterize the inter- and intra- individual variability of the PK parameters of rotigotine in subjects with restless leg syndrome (RLS), and 2.) quantify the relationship between different subject-specific factors and PK parameters. Plasma concentrations of rotigotine obtained prior to the removal of the old patch during the maintenance phase of the two pivotal trials (SP790 and SP792) were included in the population pharmacokinetics analysis (Table 3). Modeling approach is summarized in Table 4. Demographic information (age, gender, body weight, height, body mass index, and creatinine clearance) and the laboratory values (AST, ALT, GGT, ALK, and total bilirubin) were tested for covariate effect.

Table 3 Summary of PK Data in the Pop-PK Analysis

Trial	Observations	Subjects
SP790	168	68
SP792	196	86
Total	364	154

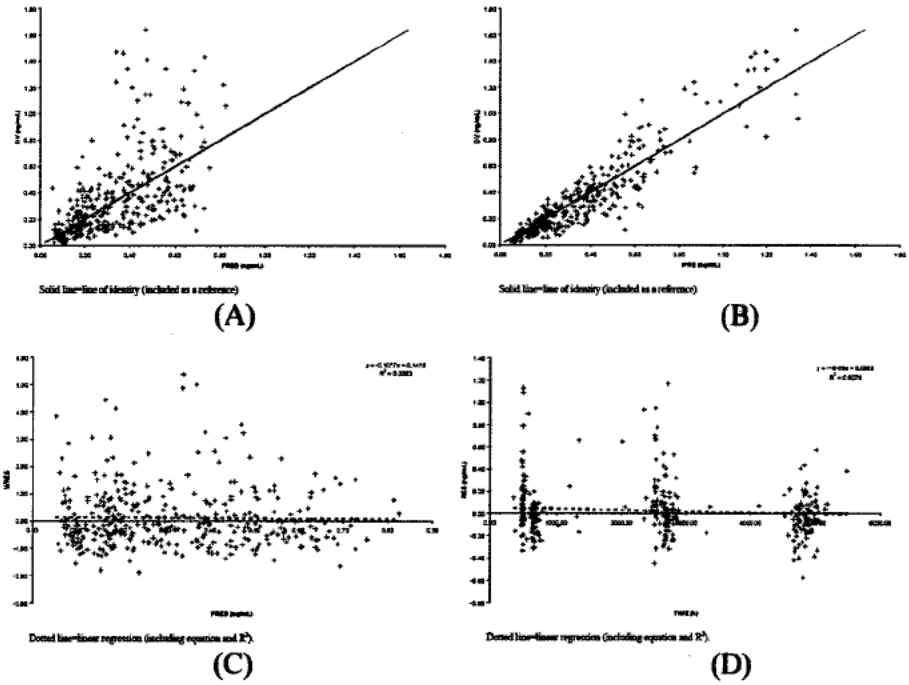
Note: 1.) Records with no reported concentration values, 2.) concentration records < LOQ, 3.) doses were not constant for 7 days prior to the sampling visit were excluded from analysis

Table 4 Summary of the Modeling Approach

Software	NONMEM VI
Analysis Method	FOCE
Covariate Selection	1.) Backward elimination 2.) Forward Inclusion and Backward Elimination
Model Evaluation	Data splitting

A one-compartment model with zero-order absorption and first-order elimination was chosen as the base model (Table 5). This model was also determined as the final model, because inclusion of covariates did not explain additional interindividual variability of PK parameters (i.e. V/F and CL/F). Major diagnostic plots were shown in Figure 3. Based on the Population PK analysis, the sponsor concluded: 1.) Rotigotine plasma concentrations were adequately described by a 1-compartment model with zero-order absorption and first-order elimination. 2.) Overall, it can be concluded that rotigotine plasma concentrations are predictable adequately in the currently evaluated target population. 3.) Body weight was identified to be an appropriate scaling factor for the prediction of CL/f and V/f. 4.) According to the criteria specified for covariate selection, none of the tested potential covariates was identified as covariate on CL/f or V/f. 5.) Based on the final model results, the major determinant for CL/f and V/f was the subjects' body weight. This means that CL/f, V/f and therefore rotigotine plasma concentrations can be best predicted based on subjects' body weight.

Figure 3 Diagnostic Plots for Base Model



Note: (A) = PRED vs. DV, (B) = IPRE vs. DV,
(C) = WRES vs. PRED, (E) = WRES vs. TIME

Table 5 Base Model Structure and Model Parameter Estimates

Parameter	Final Estimate	RSE (%)
CL/F (L/h)	TVCL = θ_1 x (WT /78)	
	502	4.5
V/F (L)	TVV = θ_2 x (WT /78)	
	1.21E+05	18.5

Parameter	IIV (%)	RSE (%)
CL/F (L/h)	CL = TVCL x exp(η_1)	
	44.3	14.6
V/F (L)	V = TVVx(1+ η_2)	
	75.3	35.3
Residual Error	**Final Estimate**	**RSE (%)**
Proportional	42.10%	10.8

(Source: Table on P-28 of the Pop-PK Report)

Reviewer's Comments:

1. The population PK modeling approach that the sponsor used is acceptable. The zero order absorption assumption appears to be reasonable because based on intensive sampling, the mean concentration is between 0.7 – 1.1 ng/mL in a dosing interval of 24 hours (
Figure 4), with no identifiable decline over time.

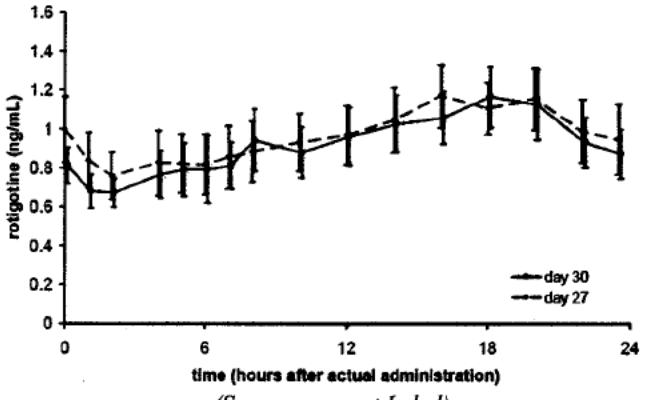
2. The PK data appears to be adequately described by the current Pop-PK model.

3. Rotigotine's label indicates that a lag time of 3 hr is expected when the rotigotine patch is applied on trunk. Because all the samples were taken prior to the removal of the old patch, it is not feasible to reliably evaluate the t_{lag} from current Population PK analysis.

4. Due to the small sample size, the major covariate effects may not be adequately identified.

*5. The unit for clearance and volume of distribution does not appear to be correct. The concentration unit is ng/mL and the unit for dose is mg (***Table 9***). In the sponsor provided control file, the scaling factor is V (i.e. S1=V) (Section 4.2). Therefore, the final unit for volume of distribution and clearance should not be L or L/hr (***Table 5***).*

Figure 4 Average (±95% CI) Neupro Plasma Concentration in Patients with Early-stage Parkinson's Disease After Application of 8 mg/24 hours to 1 of 6 Application Sites (Shoulder, Upper Arm, Flank, Hip, Abdomen, or thigh) on 2 Different Days During the Maintenance Phase.



(Source: current Label)

Exposure-Effectiveness Analysis

The sponsor conducted exposure-effectiveness analysis in order to characterize changes in the International RLS Study Group Rating Scale (IRLS®) sum score in relation to changes in the exposure. The sponsor applied the results to identify the supportive information about the therapeutic doses and the maximum achievable effect. Exposure-efficacy analysis is conducted based on observations in two pivotal studies, study 790 and 792. The exposure is defined as steady state concentration of rotigotine. Because the concentration time profile following the administration of rotigotine patch is almost flat in a dosing interval (
Figure *4*), the steady state concentration is calculated as average concentration using equation 1. The response variable is defined as IRLS score, ranging from 0 (no RLS symptoms present) to 40 (maximum severity in all symptoms), by each visit (without the taper period) (Table 6). A total of 8391 IRLS sum score records from 962 subjects were used for analysis. The modeling process, including the evaluation of two placebo models and three exposure-response models, is summarized in Table 7. Demographic information (Age, Gender, Body weight, Height, Body mass index, Baseline IRLS score, study number) was evaluated for covariate effect.

$$C_{ss} = \frac{Dose}{\tau \times CL/F} = \frac{Dose}{\tau \times TVCL \times Weight/78} \qquad \text{(Equation 1)}$$

Table 6 IRLS Score Change by Visit

	Treatment Period											
Visit	Titration Period[a] (21/28 ± 3 days)				Maintenance Period[a] (180 ± 7 days)							Taper Period[a]
SP790	V2	V3	V4	-	V5	V6	V7	V8	V9	V10	V11[b]	V12
SP792	V2 Base-line	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 End of MP/ With-drawal[b]	V13 End of Taper Period
Week/ Month	W1	W2	W3	W4	M1	M2	M3	M4	M5	M6	End of M6	+1W
IRLS	X[c]	X	X	(X)	X	X	X	X	X	X	X	X

IRLS=International Restless Legs Syndrome Study Group Rating Scale; M=month; MP=Maintenance Period; V=visit; W=week

(Source: Exposure-Efficacy Report, P-12)

Table 7 Summary of Exposure-Efficacy Modeling Approach

Software	NONMEM VI
Analysis Method	FOCEI
Placebo Model Evaluated	$\Delta IRLS\ (t) = \frac{E_{max,\ p} \times t}{t_{50} + t}$ $\Delta IRLS\,(t) = E_{max,\ p} \times (1 - e^{-K \times t})$
E-R Model Evaluated	$E(x) = E_0 - \frac{E_{max} \times x}{EX_{50} + x}$ $E(x) = E_0 - S \times x$ $E(x) = E_0 - S \times \ln x$

Covariate Selection	Backward elimination Forward Inclusion and Backward Elimination
Model Evaluation	Data splitting

The final model is selected as the following (Equation 2), with the pharmacokinetic parameters summarized in the Table 8. The major diagnostic plots are shown in Figure 5.

$$E(t)=(\theta_3+0.322\times(Baseline-25)+\eta_3)\times(1-e^{-(\theta_4\times e^{\eta_4})\times t})+\frac{((\theta_1+\theta_5\times(Baseline-25))+\eta_1)\times c_{ss}}{(\theta_2\times e^{\eta_2})+c_{ss}}+\varepsilon$$

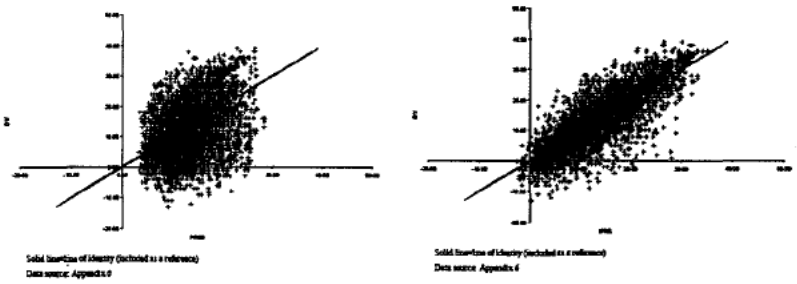
(Equation 2)

Table 8 Rotigotine Final ER Model Parameter Estimates

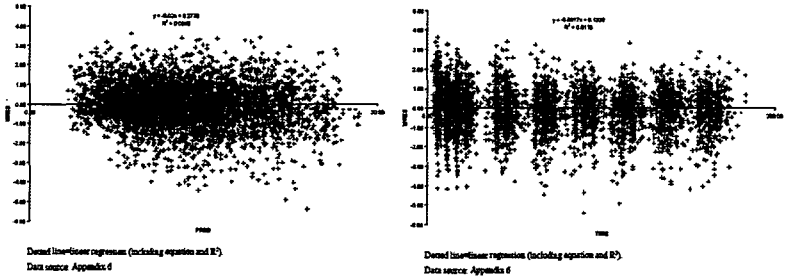
Parameter	Final estimate	RSE (%)
EV	TVEV= θ1 + θ5×(E0-25)	n.a.
θ1	9.32	3.29
θ5	0.603	8.11
C50	0.227	13.0
EP	9.95 +0.322×(E0-25)	–
TK	0.0790[a]	–
Parameter	**IIV**	**RSE (%)**
EV	0.001 SD	64900
C50	348%	22.0%
EP	4.57 SD	12.5
TK	140%	9.2
Residual error	**Final estimate**	**RSE (%)**
Additive	4.91 SD	4.56

C50=time to reach half maximal verum effect; E0=baseline IRLS score; EP=maximum placebo effect; ER=exposure-response; EV=maximum placebo effect; IIV(%)=Inter-individual variability in percent; n.a.=not applicable; RSE(%)=the percent relative standard error of the estimate resp. variance estimate for IIV; θ1=typical value of EV without effect of covariate; θ5=slope of the effect of covariate E0; TK=rate constant of placebo effect; TVEV=typical value of EV
Data source: Appendix 3, Appendix 7

Figure 5 Diagnostic Plots for the Final Model



(A) (B)



(C) (D)

Note: (A) = DV vs. PRED, (B) = DV vs. IPRE, (C) = WRES vs. PRED, (D) = WRES vs. Time

Based on exposure-effectiveness analysis, the sponsor concluded: 1.) The exposure-response relationship for efficacy in subjects with idiopathic RLS receiving different transdermal doses of rotigotine was adequately described by a exposure-response model consisting of a placebo and a verum model, 2.) The placebo effect could be described as a function of time using an exponential model with a rapid onset and a mean maximum placebo effect of 9.95 points, 3.) In addition to the placebo model, the final ER model included the verum effect (reduction of IRLS score by rotigotine treatment), which could be described as a function of the rotigotine concentration by an E_{max} model with a mean maximum verum effect of 9.32 points in addition to the placebo effect. The corresponding rotigotine plasma concentration to achieve the half maximal verum effect is 0.227 ng/mL, corresponding to a rotigotine dose level between 2.25 mg/day (nominal dose 1mg/24h) and 4.5 mg/day (nominal dose 2mg/24h), 4.) According to the criteria specified for covariate selection, E0 was identified as covariate on EV and EP. E0 is the most prominent factor to explain the IIV in the final ER model and an important determinant for the maximal achievable effect, 5.) None of the other tested covariates (age, gender, body weight, height, BMI and study number) were identified as additional covariate on EP, TK, EV and C50. 6.) The results of this ER analysis and the results of the population PK analysis show that differences in rotigotine plasma concentration caused by differences in body weight have only minor influence on the response (reduction of IRLS score), 6.) Overall, it can be concluded that the extent and time course of reduction of IRLS score by rotigotine are predictable adequately in the currently evaluated target population.

Reviewer's Comments:

1. *The exposure-response analysis is acceptable.*
2. *The sponsor modeled the placebo and the treatment group separately. The modeling approach is acceptable. We recommend that the sponsor model both placebo and drug treatment group simultaneously and compare the results from the two approaches.*

Exposure-Safety Analysis

The sponsor demonstrated a positive correlation between the drug exposure and the incidence of application and instillation site reactions (HLT). No concentration-related

trends were observed for the incidence of nausea, headache, upper respiratory tract infections, or fatigue. The exposure-safety analysis was conducted by the sponsor in order to characterize the incidence of common adverse events (reported in > 10% of subjects) in relation to the individual rotigotine exposure at the time of adverse event onset in two pivotal studies, study 790 and 792. The exposure is defined as steady state concentration of rotigotine (equation 1). The analysis results can be seen in Table 1.

Reviewer's Comments:

2. *The sponsor's analysis relates the incidence of common adverse events with the binned rotigotine plasma concentration at the time of onset. This approach is acceptable.*
3. *We recommend in the future, the sponsor perform logistic regression analysis to direct link the exposure and incidence of adverse events fort each individual.*

Listing of Analyses Codes and Output Files

Dataset Definition

Table 9 Definition of Columns in the Dataset

Variable in analysis file	Explanation (unit)
ID	subject no.
TIME	time after administration (hours)
DV	rotigotine plasma concentration (ng/mL)
EVID	event ID: EVID=1 for dosing record; EVID=0 for plasma concentration record
PCMT	no. to characterize compartment
AMT	administered dose (mg)
ADDL	additional identical doses given
II	dosing interval
RATE	rate of zero order input
TOFF	time of end of zero order input
WRT	Scaling factor for body weight

(Source: Appendix 1 of Population PK Report)

Base Model / Final Model Control File

```
;Model Desc: base model, prop. RE, prop. ETA on V
;Project Name: sp790_sp792
;Project ID: NO PROJECT DESCRIPTION
$PROB RUN# run004 (evaluation with simulated rotigotine data)
$INPUT ID TIME DV EVID PCMT AMT ADDL II RATE TOFF WTR BMI WT HM
AGE
```

```
SEX;
$DATA sp790nm_sp792nm_2.xxx
$SUBROUTINES ADVAN1 TRANS2
$PK
TVCL=THETA(1)*WT/78
CL=TVCL*EXP(ETA(1))
TVV=THETA(2)*WT/78
V=TVV*(1+ETA(2))
S1=V
$ERROR
DEL=0
W=0
IF(F.EQ.0) DEL=1
IF(F.NE.0) W=1/F
IPRED=F
IRES=DV-IPRED
IWRES=IRES/(W+DEL)
$THETA
(70, 500) ;[CL]
(1000, 80000) ;[V]
$OMEGA
0.05 ;[P] INTERIND VAR IN CL
0.05 ;[P] INTERIND VAR IN V
$SIGMA
0.2 ;[P] PROPORTIONAL RES. ERROR
$EST PRINT=1 MAXEVAL=9999 NOABORT POSTHOC METHOD=1
$COVARIANCE
$TABLE ID AMT IPRED IRES IWRES TIME ETA1 ETA2
CL V BMI WT HM AGE SEX NOPRINT ONEHEADER FILE=run004.TAB
```

(Source

APPENDIX III

OCP FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-829 (035 and 036)**	**Brand Name**	**Neupro®**
OCPB Division (I, II, III)	**DCP-I**	**Generic Name**	**Rotigotine transdermal system**
Medical Division	**HFD-120**	**Drug Class**	**Non-ergolinic dopamine agonist**
OCPB Reviewer	**Ta-Chen Wu, PhD**	**Indication(s)**	**(1) Treatment of primary Restless Legs Syndrome; (2) Treatment of advanced Parkinson's disease**
OCPB Team Leader	**Ramana S. Uppoor, PhD**	**Dosage Form**	**Transdermal delivery system 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h, 8mg/24h (0.45 mg/cm^2)**
		Dosing Regimen	**RLS: Starting dose is 1mg/24h and should be increased in weekly increments of 1mg/24h up to the highest 3 mg/24h dose, based on individual patient response** **Early-stage PD: Initial dose 2 mg/24h with an weekly increase by 2 mg/24h, with highest recommended dose 6 mg/24h** **Advanced-stage PD: Starting dose 4 mg/24h with an weekly increase by 2 mg/24h, with highest recommended dose 8 mg/24h**
Date of Submission	**035: September 21, 2007 036: October 05, 2007**	**Route of Administration**	**Transdermal**
Estimated Due Date of OCPB Review	**6/23/08**	**Sponsor**	**Schwarz Pharma**
PDUFA Due Date	**8/11/08**	**Priority Classification**	**S**
Division Due Date	**7/10/08**		

Clin. Pharm. And Biopharm. Information

Summary:

Neupro® (rotigotine transdermal system) is currently approved for the treatment of early-stage Parkinson's disease in [redacted]: 2, 4, 6, [redacted]. The sponsor submits 2 sNDAs simultaneously for 2 indications for: (1) treatment of signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS) (Submission 035), and (2) advanced Parkinson's disease (Submission 036).

Rotigotine transdermal system, a silicone-based matrix-type patch of drug-in-adhesive design, provides a constant drug concentration gradient at the skin/patch interface and for continuous drug delivery to the skin application site over the intended period of 24 hours. The matrix composition is identical per patch area for all dose strengths, containing 0.45mg rotigotine per cm^2 of the patch surface. The drug release rate is proportional to the surface area size of the patch in vitro and in vivo. The formulation of all patch sizes, including 2 additional sizes providing 1 and 3mg/24h, is identical to the currently approved product. No changes were made to the formulation (clinical trials vs. TBM).

For RLS indication:

- The sponsor seeks approval for 3 doses (1 mg, 2 mg, and 3 mg/24 h), and hence 2 new dose strengths (1 mg and 3 mg/24 h). These strengths were studied in efficacy trials.
- Newly submitted studies include SP871 (BA study), SP861 and SP862 (both extrinsic factor PK studies), 5 controlled clinical trials (2 Phase-2, 3 Phase-3), 4 uncontrolled trials, and 1 other trial (poc using nasal spray)
- SP871: To assess relative BA of rotigotine transdermal patches 6.75mg/15cm^2 (or 3mg/24h) vs. 1x2.25mg/5cm^2 (or 1mg/24h) + 1x4.5mg/10cm^2 (or 2mg/24h).
- SP790 and SP792: Two pivotal Phase 3 efficacy trials, SP790 and SP792 (both included open-label extensions), to assess efficacy, safety, and tolerability of rotigotine for the treatment of idiopathic RLS. SP790 and SP792 had similar trial design (multicenter, randomized, double-blind, parallel-group), but differ in geographic regions (SP790 was conducted in Europe, SP792 in the US). SP792 includes an additional 0.5mg/24h dose cohort of rotigotine at the request of FDA to further explore the lowest effective dose.
- Exposure-response analyses for efficacy and safety were performed based on data from SP790 and SP792
- Population PK analysis was performed to describe population PK characteristics, inter- and intra-individual variability, and impact of covariates on PK.

For Advanced-stage Parkinson's disease indication:

- The sponsor is seeking approval for 1 new dose (8 mg/24 h).
- Newly submitted studies include SP864 (thorough QT/QTc trial, up to 54mg/patch, moxifloxacin as positive control), 3 controlled clinical trials (SP511, SP515, SP650), and 6 uncontrolled trials.
- All strengths of rotigotine transdermal system that have been used during clinical development

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			• Annotated PDF file

Reference Bioanalytical and Analytical Methods	X		[redacted]	
I. Clinical Pharmacology	-	-	-	
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	SP862: Effect of oral omeprazole (40mg) on steady-state PK of rotigotine
In-vivo effects of primary drug:	X	1	1	SP861: Effect of repeat-dose rotigotine 4.5mg and 6.75mg/15cm^2 on oral hormonal OC
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	X	4	-	RLS: Controlled trials: SP666 and SP709 Other trial: SP879 Advance PD: Controlled trials: SP511
Phase 3:	X	14	-	RLS: Controlled trials: SP790, 792, 794 Uncontrolled trials: SP710, 791, 793 Advanced PD: Controlled trials: SP515, 650 Uncontrolled trials: SP512, 513, 516, 833, 715, 788
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	SP864: thorough QT/QTc trial
Phase 3 clinical trial:	X	1	-	Exposure-response for efficacy and safety (SP790, SP792)
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	X	1	1	RLS: SP790, SP792
II. Biopharmaceutics			-	

Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	SP871: • 6.75mg/15cm^2 (or 3mg/24h) vs. 1x2.25mg/5cm^2 (or 1mg/24h) + 1x4.5mg/10cm^2 (or 2mg/24h). • Electronic files for Raw data and PK results were not provided
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	-	-	-	
Dissolution:	-			
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	**170**	-	
Total Number of Studies		**21**	**3 PK** **1 Assay** **1 Pop PK** **1 PK-PD**	

Filability and QBR comments				
I.	**"X" if yes**	Comments		
II. Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
III. Comments sent to firm ? **IV.**	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward to Sponsor: 1. Please provide the annotated Word file of the proposed labeling. 2. Please provide electronic datasets for PK as SAS transport files (.XPT) for all newly submitted studies in which PK data were collected, in particularly the Studies SP864, SP871, SP861, SP862, SP666, SP709, SP794, and SP511.		
QBR questions (key issues to be considered)	• BE of various strengths of the TBM formulation • Adequate assessment for extrinsic factors • Characteristics of the exposure-response relationships for efficacy and safety • PK in RLS and advanced Parkinson's patients • Sources of inter-subject variability based on population PK analysis on Phase 3 data • Adequate PK/PD assessment for drug effect on QT • Adequately and appropriately validated bioanalytical methods			
Other comments or information not included above	Comments (difficulty to navigate): 1. Inadequate hyperlinking in individual study reports and summaries to individual bioanalytical reports and electronic PK data sets. 2. Bioanalytical reports for individual studies are included in various folders in eCTD in Sequence 0000~0039, as indicated by the sponsor upon request. Submission 0039 is not available in eCTD as of 12/03/07. 3. One bioanalytical report (PA535) for SP864 is being replaced in lifecycle submission 0039. OCP request sent to the sponsor: • Please provide the individual bioanalytical report for all newly submitted studies (in which plasma levels and PK data were collected) in Submissions 035 and 036. [Note: this request has been conveyed to the sponsor. The sponsor responded on 12/03/07 in emails and stated that one report for SP864 is being replaced in lifecycle submission 0039 due to a technical issue observed in the report.].			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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

/s/

Veneeta Tandon
10/15/2008 02:22:57 PM
BIOPHARMACEUTICS

Hao Zhu
10/15/2008 02:30:39 PM
BIOPHARMACEUTICS

Jogarao Gobburu
10/16/2008 02:52:45 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
10/17/2008 12:55:40 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

OTHER REVIEW(S)

SEALD Director Sign Off of End-of-Cycle Format Review of the Prescribing Information
Outstanding Format Deficiencies

Product Title	**Neupro (rotigotine) transdermal system**
Applicant	UCB
Application/Supplement Number	NDA 21,829/S1 and S2
Type of Application	Efficacy Supplements
Indication(s)	• Signs and symptoms of Parkinson's disease (1.1) • Moderate-to-severe primary Restless Legs Syndrome (RLS)
Established Pharmacologic Class[1]	dopamine agonist
Office/Division	ODEI/DNP
Division Project Manager	Stacy Metz
Receipt Date	December 2, 2011
PDUFA Goal Date	April 2, 2012
SEALD Review Date	April 2, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

A Study Endpoints and Labeling Development (SEALD) review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI)-Revised Checklist:
For each SRPI item, one of the following 3 response options is selected:

- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. HL is one-half page or less than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If longer than one-half page:

- Filing Period (Regulatory Project Manager Physicians' Labeling Rule (PLR) Format Review): RPM has notified the Cross-Discipline Team Leader (CDTL).
- End-of Cycle Period: A waiver has been or will be granted by the review division.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *There Is No Cross Reference To The First Bullet Under Adverse Reactions Heading In The HL.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present**
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* See Recent Major Changes section below.

** Virtually all product labeling should include at least one Warning and Precaution.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment:

HIGHLIGHT DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."
Comment:

Product Title

YES 10. Product title in HL must be **bolded.**
Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.
Comment:

Boxed Warning

N/A 12. All text must be **bolded**.
Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").
Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.
Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")
Comment:

N/A 16. Should use sentence case for summary (combination of uppercase and lowercase letters typical in a sentence).
Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Recent Major Changes (RMC)

YES 17. Other than these five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions, there are no other sections noted in RMC.

Comment:

YES 18. Must be listed in same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and if appropriate subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010".

Comment:

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**". Only includes a U.S. phone number.

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Patient Counseling Information Statement

YES 26. Must include one of the following **bolded** verbatim statements:

Product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

Product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: .

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *TOC states "1.1 Parkinson's Disease" whereas the FPI states "1.1 Parkinson's Disease (PD)." TOC states "1.2 Restless Legs Syndrome" whereas the FPI states "1.2 Restless Legs Syndrome (RLS)."*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded and in title case.

Comment:

NO 34. When a section or subsection is omitted, the numbering does not change.

Comment: *Section 12.4 Is Reserved For Microbiology And Section 12.5 Is Reserved For Pharmacolgenomics. Thus, "Pharmacokinetics In Special Populations" Should Be 12.6 And "Adhesion" Should Be 12.7.*

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk

and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Section 9.2 Is Titled "Abuse And Dependence"; But There Is No Such Title. The Information In Section 9.2 Is About Dependence. Recommend Using Section 9.3 For This Information And To Use The Title "Dependence". Section 6.2 Should Be "Postmarketing Experience"; Section 12.5 Is Reserved For "Pharmacogenomics". See SRPI Item #34.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI at approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.1)*].

Comment: *Section 2 And Section 5.2 Have The Incorrect Presentation For Cross-Referencing.*

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Should use sentence case (combination of uppercase and lowercase letters typical in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

(b) (4)

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

(b) (4)

Comment: *If There Are No New Postmarketing Signals, Suggest Complete Removal Of This Subsection.*

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

ERIC R BRODSKY
04/02/2012

LAURIE B BURKE
04/02/2012

SEALD End-of-Cycle Format Review of the Prescribing Information
Outstanding Format Deficiencies

Product Title	**Neupro (rotigotine) transdermal system**
Applicant	UCB
Application/Supplement Number	NDA 21,829/S1 and S2
Type of Application	Efficacy Supplements
Indication(s)	• Signs and symptoms of Parkinson's disease (1.1) • Moderate-to-severe primary Restless Legs Syndrome (RLS)
Established Pharmacologic Class[1]	dopamine agonist
Office/Division	ODEI/DNP
Division Project Manager	Stacy Metz
Receipt Date	December 2, 2011
PDUFA Goal Date	April 2, 2012
SEALD Review Date	March 23, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

A Study Endpoints and Labeling Development (SEALD) review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI)-Revised Checklist:
For each SRPI item, one of the following 3 response options is selected:

- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. HL is one-half page or less than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If longer than one-half page:

- Filing Period (Regulatory Project Manager Physicians' Labeling Rule (PLR) Format Review): RPM has notified the Cross-Discipline Team Leader (CDTL).
- End-of Cycle Period: A waiver has been or will be granted by the review division.

Comment: *The HL Will Be Greater Than One-Half Of A Page When The Most Common Adverse Reactions Are Added. This Does Not Count The Note To The Applicant..*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *There Is No Cross Reference To The Last Statement In The Warnings And Precautions Heading In The HL.*

NO 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present**
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* See Recent Major Changes section below.

** Virtually all product labeling should include at least one Warning and Precaution.

Comment: *The Adverse Reactions Limitations Statement Is In The Wrong Place (It Should Be Under The Adverse Reactions Heading; Not The Use In Specific Population Heading.*

YES 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment:

HIGHLIGHT DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The Name Of The Drug Should Be Capitalized In The HL Limitation Statement "NEUPRO."*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Include the four digit year "2012."*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Should use sentence case for summary (combination of uppercase and lowercase letters typical in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Other than these five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions, there are no other sections noted in RMC.

Comment:

YES 18. Must be listed in same order in HL as they appear in FPI.

Comment:

NO 19. Includes heading(s) and if appropriate subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010".

Comment: *Include The Date For The Change (E.G., 3/2012).*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

(insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch". Only includes a U.S. phone number.

Comment: *This Statement Should Be Moved To Under The Adverse Reaction Heading.*

Patient Counseling Information Statement

YES 26. Must include one of the following **bolded** verbatim statements:

Product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

Product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Include This Date (This Date Can Be Changed Again When The Final PI Is Approved).*

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Multiple Headings Do Not Match.*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded and in title case.

Comment:

NO 34. When a section or subsection is omitted, the numbering does not change.

Comment: *The Pediatric Use Subsection Should Be 8.4; Not 8.5*

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *Include A Period After This Statement.*

Full Prescribing Information (FPI)

GENERAL FORMAT

NO 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES

Selected Requirements of Prescribing Information (SRPI) Revised

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Section 6.1 Should Be "Clinical Trials Experience"; Section 6.2 Should Be Postmarketing Experience; Section 8.1 Should Be "Pregnancy"; Section 8.4 Should Be "Pediatric Use"; Section 12.5 Is Reserved For Pharmacogenomics. There Should Not Be A Section 12.6 Called "Drug Interactions" Because There Is Already A Section 7 Called "Drug Interactions." This Information Is Typically Included In Section 12.3 As A Subheader "Drug Interaction Studies." There Should Never A Three-Digit Section (E.G., 12.6.1). Section 14 Is Called "Clinical Studies" Not "Clinical Studie." Section 17 Should Be "Patient Counseling Information."*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI at approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.1)*].

Comment: *Multiple Places Have The Incorrect Presentation For Cross-Referencing.*

NO 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Should use sentence case (combination of uppercase and lowercase letters typical in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

(b) (4)

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

(b) (4)

Comment: *If There Are No New Postmarketing Signals, Suggest Complete Removal Of This Subsection.*

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

ERIC R BRODSKY
03/23/2012

ANN M TRENTACOSTI
03/23/2012
Signing for Laurie Burke

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: October 29, 2008

TO: Susan Daugherty, Regulatory Health Project Manager
Leonard Kapcala, M. D., Medical Officer
Division of Neurology Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-829 SE1 001

APPLICANT: UCB, Inc.

DRUG: Neupro (rotigotine) Transdermal Patch

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of subjects with advanced-stage, idiopathic Parkinson's disease

CONSULTATION REQUEST DATE: September 14, 2008

DIVISION ACTION GOAL DATE: November 11, 2008

PDUFA DATE: November 11, 2008

I. BACKGROUND:

Neupro (rotigotine) is approved for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease. UCB, Inc. has submitted a supplemental new drug application for marketing approval of Neupro to expand the label and indication for a more severely affected population with advanced Parkinson's disease.

The review division requested inspection of protocol SP650: **"**A multi-center, multinational, phase 3, randomized, double-blind, parallel group, placebo-controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced-stage, idiopathic Parkinson's disease who are not well controlled on levodopa." The sponsor submitted results from protocol SP650 in support of NDA 21-829 SE1 001.

The primary objective of study protocol SP650 was to show that rotigotine is efficacious in advanced-stage disease patients as an adjuvant therapy. A secondary objective was to demonstrate the tolerability and safety of rotigotine. The inspection targeted three domestic clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Paul A.Nausieda, M.D Wisconsin Institute for Neurologic and Sleep Disorders 945 12th Street, Suite # 4602 Milwaukee, WI 53233 Site # 56	Protocol SP650 27 subjects	9/15-17/08	Pending (preliminary classification NAI)
Enrico Fazzini, D.O., Ph.D. New York University Medical Center 345 East 37th Street, Suite 317C New York, NY 10016 Site # 62	Protocol SP650 23 subjects	9/22-24/08	Pending (Preliminary classification NAI)
Daniel Truong, M.D. 9940 Talbert Avenue, Suite 204 Fountain Valley, CA92708 And 701 East 28th Street, #401 Long Beach, CA 90806 Site # 30	Protocol SP650 20 subjects	10/7-9/08	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol SP650

1. Paul A. Nausieda, M.D.
   Wisconsin Institute for Neurologic and Sleep Disorders
   945 N. 12th Street, Suite 4602
   Milwaukee, WI 53233

   Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR

   At this site, a total of 31 subjects were screened; 4 subjects were reported as screen failures; 27 subjects were randomized; 23 subjects completed the double-blind portion of the study and entered the open-label. 15 subjects completed the open-label portion of the study. Informed consent for all subjects was verified to be signed by subjects prior to enrollment. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

   The medical records/source data for 27 subjects were reviewed in depth, and the source data were compared to case report forms, data listings and primary efficacy measures and adverse events. Adverse events experienced by subjects were reported to the IRB and the sponsor within the required time frames. The records reviewed were accurate and no regulatory violations were found that would impact the results. There were no limitations to this inspection.

   The data appear acceptable in support of the pending application.

2. Enrico Fazzini, D.O., Ph.D
New York University Medical Center
345 East 37th Street, Suite 317C
New York, NY 10016

Observations noted below are based on an e-mail summary statement from the field investigator; the EIR for this inspection is currently pending. An inspection addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

At this site, a total of 26 subjects were screened; 3 subjects were reported as screen failures; 23 subjects were randomized and 2 subjects were discontinued and the reason(s) were documented. 21 subjects entered the open-label portion of the study. Informed consent for all subjects was verified.

The medical records/source data for 23 subjects were reviewed in depth including drug accountability records, and source documents were compared to data listings, primary efficacy endpoints and adverse events.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

3. Daniel Truong, M.D.
The Parkinson's and Movement Disorder Institute
9940 Talbert Avenue, Suite 204
Fountain Valley, CA 92708
And
701 East 28th Street, #401
Long Beach, CA 90806

Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site, a total of 31 subjects were screened, and 1 subject was prematurely discontinued and the reason was documented. 30 subjects were randomized and 19 subjects completed the study. Informed consent for all subjects was verified.

The medical records/source documents for 19 subjects were reviewed in depth including drug accountability records, and source documents were compared to

data listings, primary efficacy endpoints and adverse events. Adverse events experienced by study subjects were reported to the sponsor and IRB in a timely manner. Our investigation found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Nausieda, Fazzini and Truong revealed no significant problems that would adversely impact data acceptability. Observations noted for these investigators are based on e-mail summary statements from the FDA field investigators; the EIRs for these inspections are currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIRs.

The data submitted from the inspected sites are acceptable in support of the pending application.

{*See appended electronic signature page}*

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{*See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Constance Lewin
10/29/2008 04:24:23 PM
MEDICAL OFFICER
Entered into DFS by branch chief on behalf of
primary reviewer Dr. Antoine El-Hage.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-829 Supplement # 1 and 2 Efficacy Supplement Type SE- 1

Proprietary Name: Neupro Transdermal Patch
Established Name: rotigotine
Strengths: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, and 8 mg

Applicant: Schwarz Pharma
Agent for Applicant (if applicable):

Date of Application: September 21, 2007 and October 5, 2007
Date of Receipt: October 11, 2007
Date clock started after UN:
Date of Filing Meeting:
Filing Date: December 5, 2007
Action Goal Date (optional): User Fee Goal Date: August 11, 2008

Indication(s) requested: Supplemental application 001 proposes an added indication to treat "the signs and symptoms of advanced Parkinson's disease" and supplemental application 002 proposes an added indication to treat "the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS)."

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
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 or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 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 any approved (b)(1) or (b)(2) application? YES ☐ NO ☐

If yes, explain: NEUPRO is covered by a five-year period of new chemical entity exclusivity that is currently scheduled to expire on May 9, 2012.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☒ 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)]?

  YES ☐ NO ☐

  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)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☒ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 3 years Years 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 ☒ NO ☐
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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 47,852; 63,902; 76,205
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) PD 6/14/01 RLS 10/18/04 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) PD 11/9/06 RLS 4/19/07 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐

If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 5, 2008

NDA #: 21-829/ S-001 and 002

DRUG NAMES: Neupro (rotigotine transdermal patch)

APPLICANT: Schwarz Pharma

BACKGROUND: NDA 21-829 was approved for idiopathic Parkinson's disease on May 9, 2007. Supplemental application 001 proposes an added indication to treat "the signs and symptoms of advanced Parkinson's disease" and supplemental application 002 proposes an added indication to treat "the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS)."

ATTENDEES: Katz, Russell G; Kapcala, Leonard P; Freed, Lois M; Jin, Kun; Uppoor, Ramana S; Yan, Sharon; Chidambaram, Nallaperum; Wu, Ta-Chen; Podskalny, Gerald; Hershkowitz, Norman

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical S-001:	Kapcala
Medical S-002:	Podskalny
Statistical:	Yan
Pharmacology:	
Statistical Pharmacology:	N/A
Chemistry:	Pinto
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Wu
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
OPS:	
Regulatory Project Management:	Daugherty
Other Consults:	

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☐
  If no, explain:

- Advisory Committee Meeting needed? YES, date if known _____ 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 ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: Some parts of the application are difficult to locate and some of the links to not go to the appropriate place.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ 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. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ 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.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Susan Daugherty
Regulatory Project Manager

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

/s/

Susan B. Daugherty
10/15/2008 05:07:50 PM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: August 13, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Leonard Kapcala, M.D., Medical Officer, Division of Neurology Products/HFD-120
Norman Hershkowitz, M.D., Acting Medical Team Leader, Division of Neurology Products/HFD-120

From: Susan Daugherty, Regulatory Health Project Manager Division of Neurology Products/HFD-120

Subject: **Request for Clinical Site Inspections**

I. General Information

UCB, Inc.
Attention: Deborah Hogerman
Regulatory Affairs Manager
1950 Lake Park Drive, Building 2100
Smyrna, GA 30080
Email: Deborah.hogerman@ucb-group.com
Office phone: 770-970-2680
Mobile phone: 585-350-4858

Drug: Neupro (rotigotine) Transdermal Patch
NME: No
Standard or Priority: S
Study Population < 17 years of age: no
Pediatric exclusivity: no

Proposed New Indication(s): to treat the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS)

PDUFA: 11/11/08
Action Goal Date: 11/11/08
Inspection Summary Goal Date: 11/1/08

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
#56 Paul A. Nausieda,M.D. Wisconsin Institute for Neurologic and Sleep Dsicorders 945 12th Street, Suite #4602 Milwaukee, WI 53233	SPM 962	N=27	Advanced Parkinson's disease
#62 Enrico Fazzini, DO, PhD New York University Medical Center 345 East 37th Street, Suite 317C NY, NY 10016	SPM 962	N=23	Advanced Parkinson's disease
#30 Daniel Truong, MD The Parkinson's and Movement Disorder Institute 9940 Talbert Avenue, Suite 204 Fountain Valley, CA 92708 AND 701 East 28th Street, #401 Long Beach, CA 90806	SPM962	N=20	Advanced Parkinson's disease

III. Site Selection/Rationale

Site #56
High enrolling site
Site #62
High enrolling site
Site #30
High enrolling site

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): the NDA involves a significant expansion of the label and indication for a more severely affected population of patients with advanced Parkinson's disease

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Name of RPM* at *301-796-xxxx or Name of Medical Officer* at 301-796-XXXX.

Concurrence: (as needed)

_____ Medical Team Leader

_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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

/s/

Susan B. Daugherty
8/13/2008 07:15:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021-829/S-001/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-829

NAME OF APPLICANT / NDA HOLDER
Schwarz Biosciences, Inc.
(wholly-owned subsidiary of Schwarz Pharma AG)

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)	STRENGTH(S)	
ROTIGOTINE	1 MG / 24 HR	6 MG / 24 HR
	2 MG / 24 HR	8 MG / 24 HR
	3 MG / 24 HR	
	4 MG / 24 HR	

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 submit 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	b. Issue Date of Patent	c. Expiration Date of Patent
6,884,434	04/26/2005	03/18/2119

d. Name of Patent Owner	Address *(of Patent Owner)*	
Joint Owners are: *LTS Lohman Therapie-Systeme AG *Schwarz Pharma Limited (wholly-owned subsidiary of Schwarz Pharma AG)	*See Attachment 1	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

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) ☞ LTS Lohmann address of services: Frommer Lawrence & Haug LLP * Additional information in Attachment 1	Address *(of agent or representative named in 1.e.)*	
	745 Fifth Avenue	
	City/State	
	New York , NY	
	ZIP Code	FAX Number *(if available)*
	10151	(212) 588-0800
	Telephone Number	E-Mail Address *(if available)*
	(212) 588-0500	

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

PSC Media Arts (301) 443-1090 EF

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.**		
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 Claim Number (*as listed in the patent*) | 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 proposed labeling.)*		

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
David Dobrowski	09-21-2007

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 David Dobrowski, Regulatory Affairs, Schwarz Biosciences, Inc., (wholly-owned subsidiary of Schwarz Pharma AG)	
Address P.O. Box 110167	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number (919) 767-3227
FAX Number *(if available)* (919) 767-3139	E-Mail Address *(if available)* david.dobrowski@ucb-group.com

Attachment "1"

ADDENDUM TO FORM FDA 3542a

Section 1 – General

1(d) Joint Owners of U.S. Patent #6,884,434

LTS Lohmann Therapie-Systeme AG
Lohmannstrasse 2
Andernach
Germany
D-56626

Schwarz Pharma Limited
(a wholly-owned subsidiary of Schwarz Pharma AG)
Industrial Estate
Shannon, County Clare, Repulblic of Ireland

1(e) Name of US Agent or Representative

UCB Legal Department
1950 Lake Park Drive
Smyrna, GA 30080

DEBARMENT CERTIFICATION

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.

12 JUL 2007
Signature/Date

Townsend N. Barnett, Jr.

Assoc. Director, Lead GCP QA Manager

R&D Quality Management

SCHWARZ BIOSCIENCES, INC.

DEBARMENT CERTIFICATION

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.

Townsend N. Barnett Jr. 15 AUG 2007

Signature/Date

Townsend N. Barnett, Jr.

Assoc. Director, Quality Assurance, Lead GCP QA Manager

R&D Quality Management

SCHWARZ BIOSCIENCES, INC.

EXCLUSIVITY SUMMARY

NDA # 21829 SUPPL # S-002 HFD # 120

Trade Name Neupro

Generic Name rotigotine

Applicant Name UCB

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

505(b)(1)

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# 21829 Neupro Transdermal Patch Approved May 9, 2007

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:

1. Trial SP650 NDA 21829
2. Trial SP515 NDA 21829

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 ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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 ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Trial SP650 NDA 21829
2. Trial SP515 NDA 21829

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

IND # 47,852	YES ☒	NO ☐ Explain:
Investigation #2		
IND # 47,852	YES ☒	NO ☐ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES ☐ Explain:	NO ☐ Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: Stacy Metz, PharmD
Title: RPM
Date: April 2, 2012

Name of Office/Division Director signing form: Russell Katz, MD
Title: Division Director

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

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/s/

STACY M METZ
04/02/2012

RUSSELL G KATZ
04/02/2012

EXCLUSIVITY SUMMARY

NDA # 21829 SUPPL # S-001 HFD # 120

Trade Name Neupro

Generic Name rotigotine

Applicant Name UCB

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

505(b)(1)

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# 21829 Neupro Transdermal Patch Approved May 9, 2007

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:

1. Trial SP790 NDA 21829
2. Trial SP792 NDA 21829

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 ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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 ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Trial SP790 NDA 21829
2. Trial SP792 NDA 21829

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

IND # 63,902 YES ☒ ! NO ☐
! Explain:

IND # 63,902 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: Stacy Metz, PharmD
Title: RPM
Date: April 2, 2012

Name of Office/Division Director signing form: Russell Katz, MD
Title: Division Director

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

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/s/

STACY M METZ
04/02/2012

RUSSELL G KATZ
04/02/2012

From:	Metz, Stacy
To:	"Ellery.Mangas@ucb.com"
Subject:	rotigotineN21829 DNP request for Revised Peds Clin Development Plan
Date:	Monday, March 05, 2012 12:20:00 PM
Attachments:	rotigotineN21829 DNP request for Revised Peds Clin Development Plan 3112 (3).doc
Importance:	High

Hi Ellery,

I have a request from DNP regarding the Peds Clinical Development Plan. Please note the following excerpt from this document:

Please submit your revised Pediatric Clinical Development Plan within 5 business days so that we can present this plan at our Pediatric Review Committee in March.

Also, I contacted the PeRC coordinator and we were able to reschedule our PeRC meeting for March 28th. We request a quick turnaround on this request so that we can complete and submit our documents for PeRC that are due next week. We would like to submit them to PeRC this coming Monday.

Please let me know if you have any questions.

Best Regards,
Stacy

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/s/

STACY M METZ
03/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Stacy Metz, PharmD, DNP 301-796-2139

Russell Katz, MD, DNP

REQUEST DATE: 1/12/12

NDA/BLA NO.: 021829

TYPE OF DOCUMENTS: Efficacy Supplements (S-001 and S-002)
(PLEASE CHECK OFF BELOW)

NAME OF DRUG: Neupro

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

March 2012

SPONSOR: UCB

PDUFA Date: April 2, 2012

The two efficacy supplements are grouped with a chemistry supplement with a goal date of 4/2/12 so DNP plans to finalize all supplements at that time. Labeling meetings are scheduled for February and early March.

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA021829\021829.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: [Insert Date(s)]

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: [Insert Dates] 2/14/12, 2/29/12 and 3/8/12

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER
Stacy Metz, PharmD, Regulatory Project Manager
301-796-2139

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

	☐ eMAIL (BLAs Only) ☐ DARRTS

Version: 12/9/2011

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/s/

STACY M METZ
01/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021829/S-001 and S-002

PDUFA GOAL DATE EXTENSION

UCB, Inc.
Attention: Deborah A. Hogerman
Senior Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Hogerman:

Please refer to your June 30, 2009 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro (rotigotine transdermal system).

On January 8, 2010, we received your January 7, 2010, major amendment to each of these applications. The receipt date is within three months of the user fee goal dates. Therefore, we are extending the goal dates by three months to provide time for a full review of these submissions. The extended user fee goal dates are April 21, 2010.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS

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/s/

RUSSELL G KATZ
01/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-829

ACKNOWLEDGE CLASS 2 RESPONSE

UCB, Inc.
Attention: Deborah A. Hogerman
Senior Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Hogerman:

We acknowledge receipt on July 21, 2009 of your July 17, 2009 resubmission to your new drug application for Neupro (rotigotine transdermal system).

We consider this a complete, class 2 response to our December 15, 2008 action letter. Therefore, the user fee goal date is January 21, 2010.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Stacy Metz, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS
NDA-21829	SUPPL-1	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS
NDA-21829	SUPPL-2	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS
NDA-21829	SUPPL-2	SCHWARZ BIOSCIENCES INC	NEUPRO(ROTIGOTINE PATCH)2/4/6/8 MG/24HRS

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/s/

STACY M METZ
09/16/2009

MEMO TO FILE

Application Number: N 21829 SE1-001 and 002
Submission Date: October 5, 2007

Background:

Neupro (rotigotine) transdermal patches were approved on May 9, 2007 for the treatment of early stage Parkinson's disease. The applicant submitted the above two supplements for two new indications (Restless Leg Syndrome and Parkinson's Disease). The above submissions also contain CMC information for the marketing of three new patch strengths: 2.25mg, 6.75 mg and 8mg patches. During the course of the review of these supplements, the Agency was notified, via correspondence of March 21, 2008, of the voluntary withdrawal of the Neupro® Patches from the market due to crystallization of drug substance on the surface of the patch. Pending resolution of the crystallization issue, Supplements 001 and 002 were recommended as Not Approval from our perspective (Please refer to my review dated November 6, 2008). A reformulation is strongly recommended for approval of these submissions. The following CMC information will be required for approval of the reformulated product:

Drug Substance
1). Physical and chemical Characterization of the (b) (4) used
2) Data to support any revisions to the manufacturing process and in process controls,
3) Specifications with justification for any new specifications proposed
4) Batch release data,
5) Stability data from three production scale batches, stored under long term (marketed) conditions through retest period and six months under accelerated conditions .

Drug Product
1) Components and composition
2) Unit and batch formula
3) Batch release data,
4) Data to support any revisions to the manufacturing process, In process controls,
5) Specifications with justification for any new specifications proposed
6) Stability data from three production scale batches, stored under long term (marketed) conditions through retest period and six months under accelerated conditions .

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/s/

Julia Pinto
11/24/2008 12:00:35 PM
CHEMIST

Jim Vidra
11/24/2008 01:17:48 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 21-829/S-001
NDA 21-829/S-002

UCB, Inc.
Attention: Deborah Hogerman
Senior Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Ms. Hogerman:

Please refer to your September 21, 2007 and October 5, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro (rotigotine) Transdermal Patch.

On July 17, 2008, we received your July 15, 2008, major amendment to this application. The receipt date is within three 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 November 11, 2008.

If you have questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
7/25/2008 09:37:29 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-829\S-001 and 002

INFORMATION REQUEST LETTER

UCB, Inc.
Attention: Deborah Hogerman
Senior Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Ms. Hogerman:

Please refer to your September 21, 2007 and October 5, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro (rotigotine) patch.

We are reviewing 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.

1. Please ensure that any table of contents for any pivotal study (e.g., studies # 511, 515, 650 for advanced Parkinson's Disease and studies # 790 and 792 for RLS), and for the ISS and ISE shows the page location for any and all tables, figures, and listings and that this page location corresponds to the actual page location of the table, figure, or listing. Consequently, when a page location for a table shown in the table of contents is specified to be printed, the pages printed should correspond to that table location outlined in the table of contents.

2. Please ensure that when a reviewer wants to refer to a specific pivotal study report (e.g., studies # 511, 515, 650 for advanced Parkinson's Disease and/or studies # 790 and 792 for RLS), there is an icon/folder that links the reviewer to the specific final study report. The folder containing studies # 511, 515, 650 should be in a folder for advanced Parkinson's disease and the folder for studies # 790 and 792 should be in a folder for RLS. When the reviewer clicks the specific study # in the folder, the reviewer should be linked and taken directly to the final study report.

3. Please relocate the RLS pooled safety data (RS1-4) to a folder labeled Primary RLS pooled safety data; they are currently listed in a folder labeled advanced Parkinson's disease.

4. Please ensure that all dataset folders containing XPT files appear when the submission is opened in Global Submit Review. Currently, when the submission is opened in Global Submit Review folders labeled “DATASETS” do not appear in the folder tree listing the contents.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

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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/s/

Russell Katz

7/8/2008 05:54:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-829/S-001 and 002

Schwarz Pharma
Attention: David Dobrowski
Director, U.S. Regulatory Affairs
P.O. Box 110167
Research Triangle Park
Raleigh, NC 27709

Dear Mr. Dobrowski:

Please refer to your October 5 and September 21, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neupro® (rotigotine) Transdermal System.

We also refer to your submissions dated October 17, 2007.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications have been filed under section 505(b) of the Act on December 10, 2007 in accordance with 21 CFR 314.101(a).

We also request that you submit the following information:

1. Please add a column indicating treatment group assignment to your analysis data sets for the adverse event (AE) and efficacy (EFFPAR) data sets for supplement 002.

2. We can not find tabulation data sets in your submission. If you plan to send them, please add treatment group to the same data sets for supplement 002.

3. Please provide an annotated Word file of the proposed labeling.

4. Please provide the electronic datasets for PK as SAS transport files (.XPT) for all newly submitted studies in which PK data were collected, in particular for Studies SP864, SP871, SP861, SP862, SP666, SP709, SP794, and SP511.

Please respond only to the above requests for additional information. 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 Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

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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/s/

Russell Katz

12/21/2007 03:03:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-829/S-001 and 002 **PRIOR APPROVAL SUPPLEMENT**

Schwarz Pharma
Attention: David Dobrowski
Director, U.S. Regulatory Affairs
P.O. Box 110167
Research Triangle Park
Raleigh, NC 27709

Dear Mr. Dobrowski:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Neupro® (rotigotine) Transdermal System

NDA Number: 21-829

Supplement number: 001 AND 002

Review Priority Classification: Standard (S)

Date of supplement: October 5, 2007 and September 21, 2007 respectively

Date of receipt: October 11, 2007

Supplemental application 001 proposes an added indication to treat "the signs and symptoms of advanced Parkinson's disease" and supplemental application 002 proposes an added indication to treat "the signs and symptoms of moderate to very severe primary Restless Legs Syndrome (RLS)."

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 December 10, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 11, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty

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