

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022399Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022399

SUPPL #

HFD # 120

Trade Name Horizant

Generic Name gabapentin enacarbil

Applicant Name GSK

Approval Date, If Known

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)(2) and a NME

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?

5 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES 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:

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: Susan Daugherty

Title: RPM

Date: 4-4-11

Name of Office/Division Director signing form: Russell Katz, M.D.,

Title: Division Director

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

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
04/06/2011

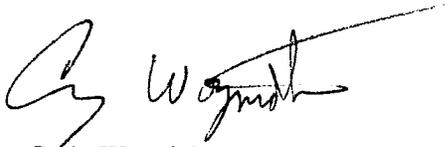
ERIC P BASTINGS on behalf of RUSSELL G KATZ
04/06/2011

CONFIDENTIAL

m1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

GlaxoSmithKline 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 (NDA022399).

A handwritten signature in black ink, appearing to read "Craig Wozniak", with a long horizontal stroke extending to the right.

Craig Wozniak

August 2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 022399 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type: 1
Proprietary Name: Horizant Established/Proper Name: gabapentin enacarbil Dosage Form: Extended-Release Tablets		Applicant: Glaxo Group Limited d/b/a/GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Beverly Conner		Division: Neurology
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p style="padding-left: 40px;">NDA-020235 Neurontin (gabapentin) Capsules</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>NDA 022399 provides for the use of Horizant to treat moderate to severe RLS. HORIZANT is an extended-release formulation of gabapentin enacarbil, a prodrug of gabapentin. HORIZANT provides approximately dose-proportional and extended exposure to gabapentin over the range 300 to 6,000 mg. HORIZANT and gabapentin are not interchangeable because the same daily dose of each results in different plasma concentrations of gabapentin.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p style="text-align: center;"><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 4/5/11</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p>

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	X No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	X No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Patent info Verified 2.1.10 <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	<input checked="" type="checkbox"/> Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 4-6-11 CR – 2-17-10
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.
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❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Patient Package Insert (in January 9, 2009 resubmission) Medication Guide (in October 9, 2009 REMS amendment)
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Carton labels from 10/9/2009 amendment. And 3/15/11
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	April 9, 2009 Ltr: Not Acceptable June 25, 2009 Ltr: Not Acceptable October 20, 2009: Granted <ul style="list-style-type: none"> • April 7, 2009 DMEPA Review “Solzira” – Not Acceptable • June 17, 2009 DMEPA Review “Xubrient” – Not Acceptable • October 15, 2009 DMEPA Review • December 24, 2009 DMEPA Rev “Horizant” – Acceptable • March 28, 2011 DMEPA 90-day Review “Horizant” – Acceptable
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA October 28, 2009, Pt labeling, Med guide January 7, 2010 ; 1/4/11 <input checked="" type="checkbox"/> DRISK 10/20/09; 3/23/11 <input checked="" type="checkbox"/> DDMAC 3/25/11 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	74 day filing letter; date 3/13/2009
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC September 15, 2009; 2/23/11 If PeRC review not necessary, explain: _____ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable February 1, 2010
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	<input checked="" type="checkbox"/> Included
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/> Included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	3/22/11
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg 5/18/10
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> Pre- NDA mtg 12/14/07
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> Yes 12/20/05
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	SPA 11/22/2005
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	

Decisional and Summary Memos

❖ Office Director Decisional Memo:	<input type="checkbox"/> None 2/17/10; 4/6/11
Division Director Summary Review:	<input type="checkbox"/> None 2/15/2010; 4/4/11
Cross-Discipline Team Leader Review,	<input type="checkbox"/> None 2/10/10
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 12

Clinical Information⁵

❖ Clinical Reviews	
• Clinical Team Leader Review(s)	2/10/10; 4/5/11
• Clinical review(s)	2/12/2010; 4/6/11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Financial disclosure included in NDA submission MO review 2-12-10
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None QTIRT 5/7/09; EPI 4/4/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

❖ Risk Management	
<ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo (<i>indicate date</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 8/17/09
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review -	<input checked="" type="checkbox"/> None
Statistical Team Leader Review -	<input checked="" type="checkbox"/> None
Statistical Review -	<input checked="" type="checkbox"/> 10/9/2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review -	<input checked="" type="checkbox"/> None
Clinical Pharmacology review -	<input checked="" type="checkbox"/> 8/11/09,
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> 2/12/2010; 4/5/11 <input checked="" type="checkbox"/> 2/5/2010; 4/5/11 <input checked="" type="checkbox"/> 2/1/10; 4/5/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 1/20/10
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> 5/6/05; 8/4/09
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
<ul style="list-style-type: none"> ONDQA/OBP Division Director Review(s) Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> 2/05/2010 <input checked="" type="checkbox"/> 8/31/09 <input checked="" type="checkbox"/> 8/31/09; 9/30/09; 9/17/09

<p>❖ Microbiology Reviews</p> <p><input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)</p> <p><input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)</p>	<p><input checked="" type="checkbox"/> Not needed</p>
<p>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)</p>	<p><input checked="" type="checkbox"/> None</p>
<p>❖ Environmental Assessment (check one) (original and supplemental applications)</p>	
<p><input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</p>	
<p><input checked="" type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)</p>	<p>September 29, 2009</p>
<p><input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)</p>	
<p>❖ Facilities Review/Inspection</p>	
<p><input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</p>	<p>Date completed: 9/24/09</p> <p><input checked="" type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p>
<p><input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)</p>	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p>
<p>❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)</p>	<p><input type="checkbox"/> Completed</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Not yet requested</p> <p>X Not needed</p>

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Neurology Products (DNP) Susan Daugherty 6-0878 (bldg 22 #4350)	
REQUEST DATE 3-11	IND NO.	NDA/BLA NO. 22399	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Horizant (gabapentin enacarbil)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
NAME OF FIRM:		PDUFA Date: 4-6-11	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
		REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission:			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: [Insert Date] Labeling Meetings: [Insert Dates] Wrap-Up Meeting: [Insert Date]			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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/s/

SUSAN B DAUGHERTY
03/22/2011



NDA 022399

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Glaxo Group Limited
d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.
Manager, US Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

We acknowledge receipt, on October 6, 2010, of your October 6, 2010, resubmission of your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Horizant (gabapentin enacarbil) Extended-Release Tablets 600 mg.

We consider this resubmission to be a complete, Class 2 response to our February 17, 2010, action letter. Therefore, the user fee goal date is April 6, 2011.

If you have any questions, call Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

Jacqueline H. Ware, PharmD
Supervisory Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

JACQUELINE H H WARE
11/05/2010

From: [Abate, Richard](#)
To: [CDER OSE CONSULTS:](#)
cc: [Conner, Beverly](#); [Williams, James](#);
Subject: RE: OSE Consult (Except Proprietary Name Reviews) (FRM-CONSULT-06).doc
Date: Tuesday, October 12, 2010 1:27:06 PM

Beverly,

I have forwarded your consult request to the OSE consult inbox

Rick Abate

From: Conner, Beverly
Sent: Tuesday, October 12, 2010 1:18 PM
To: Williams, James; Abate, Richard
Subject: FW: OSE Consult (Except Proprietary Name Reviews) (FRM-CONSULT-06).doc

From: Conner, Beverly
Sent: Thursday, October 07, 2010 10:53 AM
To: Williams, James
Subject: OSE Consult (Except Proprietary Name Reviews) (FRM-CONSULT-06).doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE Attention		From: HFD-120 Division of Neurology Products, Russell Katz, M.D. Call Beverly Conner 61171		
DATE 10/5/10	IND NO.	NDA NO. 22-399	TYPE OF DOCUMENT Review	DATE OF DOCUMENT 10/7/10
NAME OF DRUG Horizon (gabapentin enacarbil)	PRIORITY CONSIDERATION HIGH	CLASSIFICATION OF DRUG Restless Leg Syndrome	DESIRED COMPLETION DATE 11/07/10	
NAME OF FIRM: Glaxo/Smith/Kline				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please Review Epidemiological database for gabapentin NDA 22399

SIGNATURE OF REQUESTER Beverly Conner 6-1171

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER 10/8/2010

SIGNATURE OF DELIVERER

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

/s/

BEVERLY A CONNER

10/13/2010

If you need more time that is OK.

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/s/

BEVERLY A CONNER
10/13/2010



NDA 022399

GENERAL ADVICE

GlaxoSmithKline
Attention: Debra H. Lake
Manager, US Regulatory Affairs
Five Moore Drive
Research Triangle
North Carolina, 27709-13398

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Horizant™ (gabapentin enacarbil) Extended-Release Tablets.

We have reviewed your July 29, 2010, request to amend NDA 022399 from a 505(b)(1) application to a 505(b)(2) application as part of your Resubmission following discussion at the May 18, 2010, meeting. You may amend your 505(b)(1) application to a 505(b)(2) application that relies on published literature and FDA's finding of safety and/or effectiveness for Neurontin (the listed drug described in the published literature) in a Complete Response Resubmission. You should designate the application as a 505(b)(2) application on FDA Form 356h with your Resubmission. Your submission must contain all relevant information needed to support your 505(b)(2) application including:

- Identifying each listed drug(s) (in accordance with the Agency's regulations at 21 CFR 314.54) on which GSK intends to rely on the Agency's finding of safety and/or effectiveness or published literature describing the listed drug(s);
- Establishing that such reliance is scientifically appropriate (e.g., establishing a "bridge" between your proposed drug product and each listed drug(s) upon which you propose to rely);
- Submitting data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s);
- Complying with applicable regulatory requirements, including but not limited to providing an appropriate patent certification or statement for each patent(s) listed in the Orange Book for the listed drug(s) on which GSK intends to rely.

Provided the Resubmission is complete and it meets the requirements for a 505(b)(2) application, the Agency would consider the Resubmission a Class 2 Resubmission with a 6 month PDUFA review clock.

If you have any questions, call Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
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-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	Horizant
NDA-22399	GI-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	Horizant

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/s/

RUSSELL G KATZ
09/13/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22399

MEETING MINUTES

Glaxo/Smith/Kline
Attention: Debra H. Lake
Manager, US Regulatory Affairs

Five Moore Drive
Research Triangle
North Carolina 27709-13398

Dear Ms Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Horizant™ (gabapentin enacarbil) Extended-Release-Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 18, 2010. The purpose of the End of Review Meeting was to discuss the information that is needed to adequately address the review issues presented in the February 17, 2010 Complete Response letter.

A copy of the official minutes of the End of Review Meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beverly Conner, Regulatory Project Manager at (301) -796-1171.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: End of Review Conference

Meeting Date and Time: May 18, 2010, 9:00 am to 10:00 am
Meeting Location: CDER WO 1309 conf rm Bldg 22

Application Number: NDA 22399
Product Name: Horizant™ (gabapentin enacarbil) Extended Release Tablets

Indication: For the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)
Sponsor/Applicant Name: GlaxoSmithKline

Meeting Chair: Russell Katz, MD, Division Director, DNP
Meeting Recorder: Beverly Conner, PharmD, DNP

FDA ATTENDEES

Dr. Russell Katz, Division Director, DNP
Dr. Dave Podskalny, Clinical Team Leader, DNP
Dr. Beverly Conner, DNP
Dr. Ellis Unger, Deputy Director, OND
Dr. Lois Freed, Supervisory Pharmacologist, DNP
Dr. Susanne Goldstein, DNP
Laurie Kelley, PA, OSE
Dr. Kelley Simms, OSE
Dr. Allen Brinker, OSE
Dr. Ju-Ping Lai, OCP
Dr. Venneta Tandon, OCP
Dr. James Williams, Epidemiology
Dr. Solomon Iyasu, Epidemiology
Dr. Simone Pinheiro, Epidemiology

GLAXOSMITH KLINE ATTENDEES

Jeffrey Ambroso, MPH, PhD, DART, Manager Research Toxicologist, Nonclinical Safety Assessment
Cathy Barrow, PhD, Director Analytic Sciences, Neurosciences
Randal Batenhorst, PharmD, Vice President, Vice President, Global Regulatory Affairs, Neurosciences

Ros Cheetham, MSc, Vice President, Medicines Development Leader, Neurosciences Medicines Development Center

Michael C Irizarry, MD, MPH, Director Worldwide Epidemiology, Neurosciences

Debra Lake, MS, Manager, Regulatory Affairs, Neurosciences

John W Logie, PhD, Director, Worldwide Epidemiology, Observational Data Analytics, United Kindgom

Susan Van Meter, MD, Medical Director, Neurosciences Medicines Development Center

XenoPort, Inc.

Ron Barrett, PhD, Chief Executive Officer

Kenneth Cundy, PhD, Senior Vice President, Preclinical Development

Tim McCullough, PhD, Executive Director, Toxicology

External Expert

Daniel S. Longnecker, M.D., Dartmouth College

NDA 022399 Horizant Meeting Questions for Discussion:

1. Does the FDA concur that the evidence described in this meeting package on species differences in acinar cell tumors in conjunction with comparative tissue accumulation data and new data on transporter expression would allow for a conclusion about the relevance of carcinogenicity findings in rats to human cancer risk? (Section 11.3.1.6)

Preliminary FDA Response

The evidence, as described in the meeting package, may provide useful information regarding the relevance to humans of the pancreatic acinar cell tumors detected in rat. Certainly, interspecies differences in tissue exposure will be an important consideration. Whether or not the evidence will be sufficient to allow a conclusion regarding human relevance is a matter for review.

It should be noted, however, that data from the Summary Basis of Approval for Neurontin (1993) cannot be used in support of your application.

Meeting Discussion

The Sponsor asked for clarification on the use of the data in the Neurontin (gabapentin) SBA to support the NDA for gabapentin enacarbil. The Agency stated that any data in the SBA that are not in published literature are proprietary and cannot be used in support of the Sponsor's NDA. Therefore, any comparisons to gabapentin, which would require the use of unpublished data, would need to be based on data generated by the Sponsor.

Regarding the pancreatic acinar cell tumors:

- *The Agency stated that it is assumed that the pancreatic acinar cell tumors produced by gabapentin enacarbil are due to gabapentin.*
- *The Sponsor proposed basing safety margins on pancreatic tissue concentrations, rather than plasma exposures (AUC).*

- *The Agency noted that interspecies differences in gabapentin concentrations in the pancreas following oral administration of gabapentin enacarbil will be taken into consideration, but may not be the sole or most important factor in determining the relevance of the finding to humans. For example, published data suggest that gabapentin may be a mitogen; therefore, neoplasms could potentially develop in any tissue exposed to sufficient concentrations of gabapentin.*
- *It does not appear that any mechanistic studies are planned. The Agency suggested that the Sponsor further investigate potential mechanisms (e.g., stimulation of CCK) for the tumors. It has been reported that gabapentin does not elevate CCK in vivo; however, the Agency noted that it is not clear, based on published literature, that a CCK-mediated effect has been definitively ruled out.*
- *Based on the historical control information provided in the Sponsor's briefing package, the spontaneous incidence of pancreatic acinar cell tumors is similar in female mice and rats. However, pancreatic acinar cell tumors were increased in treated female rats, but not in treated mice. The Agency indicated that this would argue against the Sponsor's assertion that rat is a more sensitive species due to a higher spontaneous incidence of pancreatic acinar cell tumors.*
- *The Sponsor stated that it is presumed that there is a threshold exposure for induction of tumors, given that gabapentin was negative in the standard battery of genetic toxicology studies. The Agency agreed, but noted that it is unclear what that threshold is.*
- *The Agency noted that older published literature suggests that pancreatic acinar cells may transform to give rise to ductal neoplasms, which would potentially increase the human relevance of the findings in rat. The Sponsor stated that more recent published studies confirm that this as a possibility.*

2. Since the extremely low incidence of acinar cell carcinomas and the lack of subtype information in commonly accessible epidemiology databases preclude an epidemiologic study of the risk of gabapentin exposure and this histological subtype, does the FDA accept that a formal epidemiologic study of the incidence of pancreatic cancer (all histological subtypes) associated with gabapentin use will provide sufficient evidence to dissociate the rat findings from humans? (Section 11.4.1)

Preliminary FDA Response:

We agree that an acinar cell carcinoma primary outcome would likely not be feasible given its low incidence rate. Well-designed epidemiologic studies will provide information about the association between gabapentin and more common forms of pancreatic cancer however, they will not be able to specifically rule out an association with pancreatic acinar cell carcinoma. As such, any risk communication generated from a well-designed epidemiologic study would need to acknowledge this limitation.

Meeting Discussion

The sponsor noted that pancreatic tumors are uncommon tumors and pancreatic acinar tumors are uncommon among pancreatic tumors. The FDA acknowledged that pancreatic acinar cell carcinoma has a low incidence rate (see FDA Preliminary Response).

3. Does the FDA agree with the design of the proposed epidemiology study as described in the protocol outline to evaluate the relationship between pancreatic cancer and renal cancer with gabapentin exposure using the United Kingdom GPRD? (Section 11.4.2.1)

Preliminary FDA Response:

DEPI conducted a preliminary review of the submitted study design. In general, we did not find any serious deficiencies with GSK's approach to studying an association between gabapentin and specific cancers in the General Practice Research Database (GPRD). However, we concur with the review Agency's opinion that GSK should broaden their study to include an all-cancer outcome in light of the concern regarding the specificity of animal-based pharmacology and toxicology data in addition to the exploratory nature of the Kaiser study which reported an association between gabapentin and kidney/renal pelvis cancer. Of note, we recommend GSK submit a third-party validation of their proposed all-cancer case definition in GPRD since it will encompass a large number of READ/OXMIS codes.

The submitted protocol is meant to further study the two potential safety signals generated from animal models and the aforementioned Kaiser study (Friedman et al., 2009). However, DEPI feels the outcomes should be further expanded based on a review of supplemental data from the Kaiser study which lists the unadjusted odds ratio for each comparison made between gabapentin exposure and incidence of cancer at specific sites that was provided by GSK.

Overall, we feel the Kaiser study is best characterized as an exploratory or descriptive pharmacovigilance study meant for hypothesis generation rather than a well-designed epidemiologic study meant to serve as the basis for inferential statements (Friedman et al., 2009). The Kaiser study had significant limitations which should prevent one from making any inference based on its results. First, this study did not quantitatively assess the effect of confounding variables on the association between gabapentin exposure and specific types of cancer. Second, this study was very vulnerable to type I error. In total, the authors conducted 17,328 comparisons for 105 drugs with three exposure categories across 55 cancer sites in addition to an all-cancer outcome. Although, the authors did attempt to mitigate type I error by developing a priori criteria for statistical significance (odds ratio > 1.5, p-value < 0.01, etc), it is unlikely that this strategy completely mitigated the type I error associated with 17,328 comparisons. Finally, this study potentially has significant type II error or power issues. At first glance, this study, based on a cohort of (b) (4) subscribers, may look quite large. However, the sample size for each specific comparison was determined by the number of cases identified in the cohort. Therefore, given the low gabapentin exposure rate ((b) (4) subscribers) this study may not have been adequately powered to detect reasonable effect sizes in cancers with a low baseline prevalence.

In the context of the three issues highlighted above, it is hard to interpret the eleven other positive associations between gabapentin exposure and cancer subtypes which had a p-value less than 0.05, but did not meet the author's a priori criteria either because the effect

size was less than 1.5 or the p-value was not less than 0.01. Given the questionable risk/benefit trade-offs identified by the review agency, we feel it is prudent to err on the side of caution in interpreting these supplemental results. As such, we recommend GSK also study the relationship between gabapentin and

cancer at the following sites which had an odds ratio greater than one and a p-value less than 0.05 in the supplemental Kaiser results: 1) stomach, 2) anus, anal canal, and anorectum, 3) other digestive organs, 4) lung and bronchus, 5) bones and joints, 6) breast, 7) penis, 8) urinary and bladder, 9) other nervous system, and 10) all-cancer sites. It is not necessary to explore the positive association between gabapentin and cancers of an unspecified site, as we interpret this as a catch-all category for patients who could not be classified due to missing data. We recognize that it may not be feasible to design an epidemiological study to explore the relationship between gabapentin and more rare cancers such as bone cancer. However, excluding large effect sizes in these rarer cancers may be informative. As such, we encourage GSK to explore the feasibility of conducting such studies and report back the effect sizes which could be detectable at an $(1-\beta)=0.80$.

Meeting Discussion

See discussion in question 5.

4. Are the pancreatic cancer results from the Kaiser study acceptable evidence to further address the lack of a relationship between pancreatic cancer and gabapentin exposure? (Section 11.4.2.2)

Preliminary FDA Response

No, the Friedman et al (2009) study cannot be interpreted as evidence for a null association between pancreatic cancer and gabapentin exposure. As stated above, this study cannot be classified as a well-designed epidemiologic study meant to serve as the basis for inferential statements.

Meeting Discussion

The sponsor contends the Friedman study was adequately designed and it supports the conclusion that there is no association between gabapentin use and an increased risk for pancreatic carcinoma in humans.

The Agency considers the major methodological flaw of the Friedman study is the large number of multiple comparisons that increase the risk of Type I error. The Agency considers the results as more signal generating because of the numerous comparisons.

5. The proposed GPRD study is powered to detect an odds ratio (OR) of 1.5-1.8 for pancreatic cancer and renal cancer with gabapentin exposure. If the GPRD study detects no significant association of gabapentin exposure with these cancers, is the GPRD study (in conjunction with the Kaiser study and the FDA's assessment of the AERS data) sufficient to support a conclusion that the risk is sufficiently low as to be acceptable in patients with RLS? (Section 11.4.2.2)

Preliminary FDA Response

The results of the proposed GPRD study, by itself, may not provide sufficient evidence to support a conclusion that the risk is sufficiently low as to be acceptable in patients with RLS. Furthermore, as previously stated, the Kaiser study cannot be used as evidence for no association between gabapentin and pancreatic cancer (Friedman et al., 2009).

A null finding from a well-designed and executed GPRD study would provide some evidence that would inform the risk-benefit discussion. However, null findings from other well-designed and executed epidemiologic studies in independent samples would provide additional confirmatory evidence.

Meeting Discussion

The sponsor believes that in conjunction with the other arguments (Pharm Tox, Epi) GPRD is the best database to use.

The Agency believes that a third party case definition or one proposed by an experienced 3rd party is preferred. The sponsor proposed using a case definition defined by the GPRD.

If the argument for no association between gabapentin and pancreatic cancer is solely based on Epidemiology studies then one study cannot stand alone. However, in the context of supporting evidence in other disciplines, a single epidemiology study using the GPRD may be sufficient; however the final conclusion regarding the strength of the evidence for or against the association of gabapentin with human carcinoma will be a matter for review.

The Agency asked the sponsor whether the exposure to gabapentin among patients in the GPRD is long enough to answer the question of gabapentin and association with pancreatic cancer.

The sponsor believes that most subjects in GPRD who were prescribed gabapentin remained on the drug for at least 6 months. Approximately 2/1000 patients were exposed for at least a year and 1/1000 exposed for 2 years, with the overall exposure rate estimated to be 1% of the GPRD.

The Agency raised the issue of whether any useful conclusions could be drawn from the currently designed Epidemiology study given the low number of subjects exposed to gabapentin for a relatively short time. The sponsor acknowledged that there will be limits to the conclusions that can be made using the GPRD data.

Considering the sponsor's estimate of the limited number of patients with long-term exposure to gabapentin in the GPRD, the Agency raised the concern that the epidemiology study may not be able to provide reliable information to allow the Agency to conclude there is no association between gabapentin and pancreatic carcinoma in humans. The Agency strongly encouraged the sponsor to submit data using multiple approaches (preclinical and epidemiological) to support their belief that the pancreatic carcinoma signal reported in rats, is irrelevant to humans taking gabapentin.

6. Does the FDA concur with our proposal to utilize all available rat pancreatic acinar cell carcinogenicity information for gabapentin and gabapentin enacarbil in order to better define the safety margin for humans? (Section 11.5.6)

Preliminary FDA Response:

Please see Preliminary Response to Question 1

Meeting Discussion

See Meeting Discussion under Question 1.

The Agency stated that the Sponsor may use data from published studies of gabapentin to address potential mechanism(s). Copies of all published literature cited in support of the sponsor's submission should be provided. The Sponsor may not rely on proprietary data belonging to another company unless a Letter of Authorization is provided that allows the Agency to access those data on the Sponsor's behalf.

The Sponsor asked if information in the Neurontin label could be included in the gabapentin enacarbil label. The Agency stated that the NDA for gabapentin enacarbil is a 505(b)(1) application, and is expected to contain all data necessary to support an action.

[Note added: this issue is currently under internal discussion. When a final determination is made, we will communicate it to you in a separate letter.]

7. Based on preliminary review of the information provided in this meeting package, does the FDA concur that a 600 mg clinical dose of gabapentin enacarbil provides at least a 24-fold margin of safety compared to the No Observed Effect Level (NOEL) for occurrence of carcinomas, and at least a 36-fold margin for a threshold effect for carcinomas? (Section 11.5.6)

Preliminary FDA Response:

Please see Preliminary Response to Question 1

Meeting Discussion

The Sponsor asked if there is a specific safety margin that would be acceptable. The Agency stated that the only guidance available on this issue is the 25 fold margin used to justify high dose selection in 2-year carcinogenicity studies.

(Also, see Meeting Discussion under Question 1.)

8. Based on a weight of evidence assessment, does the FDA agree that the data presented in this meeting package and the proposed epidemiology study support a revised conclusion on the benefit/risk of gabapentin enacarbil in the treatment of primary RLS, sufficient to support approval? (Section 11.7.2)

Preliminary FDA Response:

Please see Preliminary Response to Question 1

Meeting Discussion

The Agency believes the Friedman study should only be interpreted as a descriptive or exploratory study (Friedman et al., 2009). With respect to the proposed GPRD study, one well-designed epidemiologic study may not provide sufficient epidemiological evidence to infer no association between gabapentin and cancer.

9. To address FDA's request to include a more detailed accounting for subjects who discontinued trial participation for the reasons listed as "withdrew consent" or "lost to follow-up" in the pivotal efficacy, long-term safety, and long-term maintenance of effect trials, GSK will provide tabular summaries of demographic data, AE data, and time in study for subjects who withdrew for either of these two reasons from the RLS studies XP052, XP053, XP055, XP060, and XP081. Will this data presentation provide sufficient additional detail to address the FDA's request for a more detailed accounting for these subjects? (Section 11.8.1.2.2)

Preliminary FDA Response:

No, your complete response must include detailed information regarding subjects who "Withdrew Consent" or were listed as "Lost to Follow-Up". The information for each classification (Lost to Follow-Up vs. Withdrawn Consent) must be presented individually, not combined under a single heading". GSK must provide, detailed descriptions including case narratives describing the circumstances surrounding the subject's decision to withdraw consent or why the subjects were classified as lost to follow-up. The Agency must be able to review the relevant information and independently reach conclusions regarding the reason for each subject's departure from the study.

In addition, present updated tables listing the reasons patients prematurely discontinued trial participation from all newly completed or ongoing trials regardless of indication. Update your analysis and describe any trends or patterns identified from your analysis of the new data alone and the new data combined with those previous submitted to the NDA.

You should include updated reports and narratives for all SAEs, deaths, pregnancies and AEs leading to withdrawal.

Meeting Discussion

In reference to case narratives on subjects lost to follow-up and/or withdrawal of consent, there were limitations to data capture. Xenoport provided a checkbox in the CRF for final visit that did not require further explanation. In addition, there are no source documents available at some sites.

The Agency wishes to receive as much information as possible to support the conclusion that subjects did not withdraw for reasons such as adverse event or lack of efficacy.

10. Safety data from the completed Phase IIIb RLS-associated sleep disturbance polysomnography study (RXP110908) will be presented separately within the FSU. This study evaluated treatment of sleep maintenance in subjects with RLS-associated sleep disturbance. Safety data will include disposition, exposure, demography, race, adverse events (AEs), deaths, serious AEs (SAEs), and pregnancies. Does FDA agree with this proposal? (Section 11.8.1.3)

Preliminary FDA Response:

Exposure data must be presented in days (not only subject-years, subject-days). Exposure should be tabulated by dose, including modal dose and duration for all flexible dose trials of XP13512.

Meeting Discussion

The sponsor asked if they could email questions regarding safety issues and exposure data to the clinical team, since there was insufficient time to address the issues during the meeting.

The Agency agreed to review the sponsor's questions, sent by email to the Project Manager, who will distribute them to the clinical team.

11. For the completed studies evaluating post-herpetic neuralgia (PXN110527 and PXN110748) and pain associated with diabetic peripheral neuropathy (PXN110448), safety data will be presented by individual study due to the differing study populations and study designs. Safety data will include disposition, exposure, demography, race, AEs, deaths, SAEs, and pregnancies. Does FDA agree with these proposed data presentations? (Section 11.8.1.4)

Preliminary FDA Response:

Data presented for exposure should be in days (not only subject days or subject years). Exposure should be tabulated by dose, including modal dose and duration for all flexible dose trials of XP13512. AE data must include a listing of the dose the patient was taking when the AE was first reported.

Narratives should be provided for all SAEs, deaths, pregnancies, and AEs leading to withdrawal.

Meeting Discussion

No further discussion.

12. For the ongoing study in migraine headache prophylaxis (MPX111381), blinded safety data will be presented for disposition, demography, race, AEs (summarized), and a listing of AEs leading to withdrawal and deaths. Blinded SAEs and pregnancies will be identified from narratives. Does FDA agree with this proposal? (Section 11.8.1.5)

Preliminary FDA Response

Yes, also include narratives and a tabulated summary with your report. Please list patients who withdrew consent separate from patients who were lost to follow-up. Provide narratives for all patients who withdrew consent or were lost to follow-up in addition to the events you have listed in question 12.

Meeting Discussion

No further discussion.

13. Narratives for all SAEs, deaths, pregnancies and AEs leading to withdrawal in Study XP055 will be provided for events reported or updated after the January 16, 2009 120-Day Safety Update submission cut-off date. Additionally, narratives for all SAEs, deaths and pregnancies will be provided for events reported or updated between the January 16, 2009 120-Day Safety Update submission cut-off date and the March 10, 2010 FSU submission cut-off date for GSK-sponsored completed studies (Phase Iamb RLS-associated sleep disturbance [RXP110908], neuropathic pain [PXN110448, PXN110527, PXN110748]) and the ongoing (blinded) study (migraine headache prophylaxis [MPX111381]), as well as Astellas-sponsored completed/terminated studies. Is this acceptable to FDA? (Section 11.8.4)

Preliminary FDA Response:

As stated in the CR letter:

- **Present new all new safety data supporting the RLS indication using the same format as the original NDA submission**
- **Present tabulations of the original safety data contained in the NDA submission, 120-day update, the 120-day update plus the data in the original NDA, safety data since the 120-day update and a combined total of all the safety data collected to the final reporting date.**
- **Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated 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.**

In addition, describe any information that suggests a substantial change in the incidence of deaths, SAEs and non-serious adverse events between the newly submitted data and the original NDA data. Also, provide an updated estimate of use for drug marketed in other countries as well as English translations of current approved foreign labeling not previously submitted.

Meeting Discussion

No further discussion.

14. Case Report Forms (CRF) for all SAEs, deaths, pregnancies and AEs leading to withdrawal in Study XP055 will be provided for events reported or updated after the January 16, 2009 120-Day Safety Update submission cut-off date. Additionally, CRFs for all SAEs, deaths and pregnancies will be provided for events reported or updated between the January 16, 2009 120-Day Safety Update submission cut-off date and the March 10, 2010 FSU submission cut-off date for GSK-sponsored completed studies (Phase IIIb RLS-associated sleep disturbance [RXP110908], neuropathic pain [PXN110448, PXN110527, PXN110748]) and the ongoing (blinded) study (migraine headache prophylaxis [MPX111381]). Is this acceptable to FDA? (Section 11.8.4)

Preliminary FDA Response

Yes, also include narratives and a tabulated summary with your report. Please list patients who withdrew consent separate from patients who were lost to follow-up. Provide narratives for all patients who withdrew consent or were lost to follow-up in addition to the events you have listed in question 14.

Meeting Discussion

No further discussion.

15. Based upon FDA's assessment of the information provided in the meeting package, is the proposed REMS (submitted January 28, 2010, Sequence Number 0036) sufficient to mitigate any potential risk associated with the use of gabapentin enacarbil? (Section 11.9)

Preliminary FDA Response:

Presentation and review of new safety information may result in the Agency requesting changes to the REM, as stated in the Agency's action letter.

"We will continue discussion of your proposed REMS and will notify you about the elements that will be required in the REMS, after your complete response to this action letter has been submitted. Our review of any additional data that you submit in response to this letter may necessitate changes to your proposed REMS."

Meeting Discussion

The sponsor would like to finalize the review of their proposed REMS while they are waiting for results of Epidemiology and Pharmacology Toxicology studies.

REMS discussion will continue as new data is reviewed; the REMS will need to be revised to include updated safety data and changes to the product label.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	GI-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	Horizant

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/s/

BEVERLY A CONNER
07/20/2010

RUSSELL G KATZ
07/21/2010

From: [Conner, Beverly](#)
To: ["Debra Lake";](#)
Subject: GSK Epidemiology Study
Date: Monday, March 29, 2010 3:55:48 PM

The Medical reviewer has read the Epidemiology Study that GSK proposes to conduct and he has briefly discussed it with the safety and Pharm-Tox people involved with the review. Here are our preliminary comments. GSK should expand the focus of the Epidemiology Study to first, look for an increase in any cancer associated with gabapentin then focus on pancreatic, GYN and any other cancers that show an increased association with gabapentin use. The recommendation to broaden the search for a cancer signal in humans addresses our concern that the cancer signal reported in animal studies may not be expressed in exactly the same way in humans. In addition, the study should consider the possibility that pancreatic carcinoma may not be the only carcinoma associated with gabapentin in humans. The Agency's Epidemiology review division will be involved with the formal review of the Epidemiology Study once the final draft is submitted to the agency.

Beverly Conner, Regulatory Project Manager
301-796-1171

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

BEVERLY A CONNER
03/29/2010

From: [Conner, Beverly](#)
To: ["debra.h.lake@gsk.com";](mailto:debra.h.lake@gsk.com)
Subject: RE: Data request from GSK re: NDA 22399 study XP055
Date: Sunday, January 31, 2010 3:04:15 PM
Attachments: [XP055 revised exposure table.xls](#)

Dear Debra,

Please [send](#) GSK to send a revised exposure table for open-label study XP055. Please use that data that includes all randomized patients included in the final study report now that it is complete. Please list the duration of exposure by modal dose (not mean modal dose) ***in days not patient years.*** The shell table is attached. Thank you. [Beverly Conner](#).

Conner, Beverly

From: Conner, Beverly
Sent: Sunday, January 31, 2010 3:04 PM
To: 'debra.h.lake@gsk.com'
Subject: RE: Data request from GSK re: NDA 22399 study XP055

Attachments: XP055 revised exposure table.xls

Dear Debra,

Please send GSK to send a revised exposure table for open-label study XP055. Please use that data that includes all randomized patients included in the final study report now that it is complete. Please list the duration of exposure by modal dose (not mean modal dose) **in days not patient years.** The shell table is attached. Thank you. Beverly Conner.



XP055 revised
exposure table.x...

Study 055 Modal Dose

600 mg 1200 mg 1800 mg Total XP13512

Exposure in Days

0-30 days (1 month)

31-90 days (3 months)

91-180 days (6 months)

181-366 days (12 months)

>365 days (>12 months)

PLEASE GIVE EXPOSURES IN DAYS NOT PATIENT YEARS

CREATE A SECOND TABLE FOR DOSE IN NAÏVE VERSUS NONNAIVE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA
NDA-22399	GI-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

BEVERLY A CONNER
03/26/2010



NDA 22-399

INFORMATION REQUEST

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.,
Manager, Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil extended release tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The manufacturing process description in section m3.2.P.3.3 is not complete and therefore not acceptable. It does not include the design space, including the Quality Process Parameters ranges described in your Pharmaceutical Development section m3.2.P.2 and the description of the manufacturing equipment, including scale. Update the manufacturing section with adequate details or submit commercial master batch records to comply with 21 CFR 314.50 (d)(1)(ii)(c).
2. The agency does not currently have a mechanism for site change by Annual Report. Modify your comparability protocols provided in sections m3.2.S. 2.1 and m3.2.S.2.2 for the post approval site changes for drug substance manufacture, release testing, and stability testing with the proposed data package to be submitted as a CBE-30 supplement.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

RAMESH K SOOD
12/28/2009



NDA 22-399

INFORMATION REQUEST

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.,
Manager, Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil extended release tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.  (b) (4)

2. The following dissolution specification is recommended for gabapentin enacarbil ER tablets:

USP Apparatus	Spindle Rotation Speed	Media volume	Temperature	Medium	Specifications
II	50 rpm	900 mL	37°C	10 mM potassium phosphate monobasic buffer at pH 7.4 with 1% SLS	4 hours: (b) (4) 8 hours: (b) (4) 12 hours: (b) (4) 24 hour: (b) (4)

- a) Your proposed dissolution method appears to be over-discriminating and not clinically relevant. The method discriminates between two batches that have equal in vivo performance. Consider developing a more clinically relevant dissolution method that is not over-discriminating.
- b) Provide stability data from the three primary batches to support the dissolution specification at the recommended time intervals.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

RAMESH K SOOD
10/02/2009



NDA 022399

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Glaxo Group Limited
d/b/a GlaxoSmithKline
PO Box 13398, Five Moore Drive
Research Triangle Park, North Carolina 27709

ATTENTION: Debra H. Lake, M.S.
Manager, Regulatory Affairs

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) dated September 15, 2008, received September 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Enacarbil Extended-release Tablets, 600 mg.

We also refer to your July 23, 2009, correspondence, received July 23, 2009, requesting review of your proposed proprietary name, Horizant. We have completed our review of the proposed proprietary name, Horizant and have concluded that it is acceptable.

The proposed proprietary name, Horizant, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 23, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Beverly Conner at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

CAROL A HOLQUIST
10/20/2009



PDUFA GOAL DATE EXTENSION

NDA 022399

Glaxo Group Limited
d/b/a GlaxoSmithKline
Attention: Debra Lake, M.S.
Manager, U.S. Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Horizant (gabapentin enacarbil) Extended-Release Tablets, 600 mg.

On October 9, 2009, we received your October 9, 2009 major amendment (solicited) to this application, which was a Risk Evaluation Mitigation Strategy (REMS) Proposal. 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 February 9, 2010.

In addition, we are establishing a new timeline for communication of feedback on proposed labeling and postmarketing commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES - FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 7, 2010.

If you have any questions, call Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

Sincerely yours,

{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-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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/s/

JACQUELINE H H WARE on behalf of RUSSELL G KATZ
11/06/2009



NDA 22-399

INFORMATION REQUEST

Glaxo Group Limited
d/b/a GlaxoSmithKline
Attention: Debra Lake, M.S.
Manager, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, N.C. 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) dated January 8, 2009 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for gabapentin enacarbil, extended release tablet 600 mg for moderate to severe Restless Leg Syndrome.

Please refer to the September 2, 2009, teleconference between you and Beverly Conner in which you were informed that a Risk Evaluation and Mitigation Strategy (REMS) will be required for this application. This letter is the formal communication of the REMS requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for gabapentin enacarbil to ensure that the benefits of the drug outweigh the risks of suicidality and potential adverse effects on patients' ability to drive.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that gabapentin enacarbil poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of gabapentin enacarbil. FDA has determined that gabapentin enacarbil is a product for which patient labeling could help prevent serious adverse effects and has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use gabapentin enacarbil.

In addition to the risks of suicidality and potential adverse effects on patients' ability to drive, your Medication Guide should also address other risks of gabapentin enacarbil including somnolence, potential adverse effects on the developing fetus, and the potential for seizures if gabapentin enacarbil is stopped suddenly.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed gabapentin enacarbil.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include:

- a. An evaluation of patients' understanding of the serious risks of gabapentin enacarbil.
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Before we can continue our evaluation of NDA 22-399, you will need to submit the proposed REMS. The proposed risk minimization plan that you have submitted does not contain the REMS elements that we are requiring and is not sufficient.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide.

We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA #22, 399
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA #22, 399
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, please contact Beverly Conner at 301-796-1171.

Sincerely,

{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-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

RUSSELL G KATZ
09/21/2009



NDA 22-399

INFORMATION REQUEST

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.,
Manager, Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil extended release tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Submit the method development report for the proposed dissolution method or indicate the location in the original NDA submission.

The following requests pertain to your proposed (b) (4)

[Redacted content]

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

RAMESH K SOOD
09/14/2009



NDA-22-399

MEETING MINUTES

Glaxo Group Limited d/b/a GlaxoSmith Kline
Attention: Debra Lake, M.S.,
Manager Regulatory Affairs
Five Moore Drive P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil tablets.

We also refer to the teleconference between representatives of your firm and the FDA on August 31, 2009. The purpose of the meeting was to discuss the pediatric plan, Written Request, and PPSR as it pertains to the development of restless leg syndrome in pediatric patients.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beverly Conner, Regulatory Project Manager at (301) 796- 1171.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

NDA 22-399
August 28, 2009
Type Meeting B

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, NDA
Meeting Category: Development of Pediatric use in RLS
Meeting Date and Time: August 28, 2009
Meeting Location: Teleconference, CDER WO 4266 conference room
Application Number: NDA 22-399
Product Name: gabapentin enacarbil
Indication: Treatment of moderate to severe Restless Legs Syndrome
Sponsor/Applicant Name: Glaxo Group Limited d/b/a GlaxoSmith Kline

Meeting Chair: Dr. Russell Katz, MD, Director
Division of Neurology Products,
Division of Neurology Products

Meeting Recorder: Beverly Conner, Pharm.D.

FDA Attendees:

Susanne Goldstein, M.D., Medical Review
Gerald David Podskalny, D.O., Clinical Team Leader
Russell Katz, M.D., Division Director
Angela Men, M.D., Ph.D., OTS/OCP/DCP1 Clinical Pharmacology Team Leader
Terry Peters, Ph.D., Pharmacologist
George Greeley, Regulatory Health Project Manager
Hari Sachs, M.D., OND/PMHS Lead Medical Officer
Yaning Wang, Ph.D., OTS/OCP/DPM Pharmacometrics Team Leader
Alyson Karesh, M.D., Medical Officer OND/PMHS
Allen Rudman, Ph.D., Clinical Pharmacology, OTS/OCP Associate Director

Glaxo/Smith/Kline Attendees

Jeffrey Ambroso, MPH, Ph.D., DABT, Manager Research Toxicologist, Nonclinical Safety Assessment

- Eric Benson, M.S., Senior Director, Regulatory Affairs
- Ros Cheetham, M.S., Vice President, Neurosciences Medicine Development Center
- Chao Chen, Ph.D., Director, Clinical Pharmacology/Modelling & Simulation
- Maria Davy, Ph.D., Director, Clinical Pharmacology, Neurosciences Medicine Development Center

- Sarah DeRossett, M.D., Ph.D., Medical Director, Neurosciences Medicine Development Center
- Debra Lake, M.S., Manager, Regulatory Affairs

Background Information

GSK Purpose for this meeting:

- Obtain agency with GSK's request for a partial waiver of assessment of gabapentin encarbil in subjects with RLS < 13 years of age;
- Obtain agency with GSK's concurrence with GSK's request for deferral for the assessment of gabapentin encarbil in with RLS ≥ 13 years of age until approval of the for Indication in adults is received;
- Discuss and seek agreement on the Proposed Pediatric Study Request (PPSR) for gabapentin encarbil for RLS in subjects $\frac{9}{4}$ -17 years of age.

GSK believes studies of RLS in the pediatric population ≥ 18 years of age will be extremely difficult to conduct in a reasonable timeframe as stated in the original request for a waiver on January 9, 2009.

The following difficulties and challenges of conducting a Clinical study in RLS include the following:

Low prevalence of clinical symptoms in RLS pediatric population.

Lack of information about the clinical course in the RLS population and whether RLS has asymptomatic periods.

In the clinical setting there is lack of validation and consensus for diagnostic criteria that pertain to the RLS pediatric population.

There are separate RLS criteria for children (ages 2-12 years) and adults and adolescents (≥ 13 years).

There is not a validated diagnostic instrument for RLS pediatric subjects.

High co-morbidity of RLS with other conditions adds to the difficulties of diagnosis of definite primary RLS.

Published literature indicates that non-pharmacological treatments are used for the treatment of pediatric patients with RLS.

What kind of Impact will result with the recent recommendations for inclusion of class labeling for RLS with suicidality on the label.

As noted in the recent feasibility assessment there are challenges to clinical trial design a RLS occurs in 5 to 10% of adults in the US and Western Europe, 2 to 3% reporting clinically significant symptoms that requires treatment.

Outcome Measures: There is the need for a reliable diagnostic instrument for accurately identifying pediatric RLS subjects, a reliable method for assessing symptom severity is essential. Currently, there is no disease-specific scale for accurately assessing the severity of RLS symptoms in the pediatric population, making the accurate assessment of therapeutic outcomes extremely difficult. In the absence of a validated disease-specific severity rating scale for pediatric RLS, consideration is being given to the use of the International Restless Legs Scale (IRLS) in adolescents (≥ 13 years of age) for whom the adult diagnostic criteria can be used per expert consensus.

Questions

Pediatric Assessment

All requests for waivers and deferrals require review by the internal pediatric committee and are not finalized until the time of approval.

General

1. Because of the difficulties accurately diagnosing RLS in children (2-12 years of age) acknowledged in the literature and the fact that the diagnostic criteria utilized in adults are recommended only for adolescents aged ≥ 13 years [Allen 2003], as well as the lack of an IRLS severity assessment scale appropriate for use in children for use in children < 13 years of age of age, GSK requests a partial waiver for studying moderate-to-severe primary RLS in children aged < 13 years. Does FDA agree?

FDA Preliminary Response: A partial waiver can be granted if at least one of the following criteria is met:

- a. Studies are impossible or highly impractical.
- b. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested.
- c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- d. Reasonable attempts to produce a pediatric formulation for one or more of pediatric age group(s) for which the waiver is being requested have failed. Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the sponsor will be publicly posted.

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	GI-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA
NDA-22399	GI-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA
NDA-22399	GI-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

RUSSELL G KATZ
10/02/2009



NDA 22-399

INFORMATION REQUEST

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.,
Manager, Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil extended release tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Include tailing factor as a system suitability criterion in the method used for the determination of the assay, identification, and impurities determination of gabapentin enacarbil by HPLC in accordance with the USP <621>.
- A shelf-life of 36 months is proposed for the drug product. However, the post-approval stability protocol for the stability commitment denotes a 36 months time point as optional in long term storage testing. To cover the proposed shelf-life of 36 months for the drug product, 36 months time point testing is necessary. Change post-approval stability protocol for the stability commitment to include 36 months time point from optional testing to the required testing.
- Provide justification for not having friability test in stability testing of the drug product.
- The chemical name provided for the gabapentin enacarbil is (b) (4). In the current USP dictionary, the chemical name for gabapentin enacarbil is (1-[[[(1RS)-1-[(2-Methylpropanoyl)oxy]ethoxy]carbonyl]amino] methyl]cyclohexyl) acetic acid. Change the chemical name of the gabapentin enacarbil accordingly in the labeling.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
08/12/2009

REQUEST FOR CONSULTATION

TO (Office/Division): Raanan Bloom, OPS/PARS, (301)796-2185

FROM (Name, Office/Division, and Phone Number of Requestor): Don Henry
Project Manager, ONDQA, 301-796-4227 on behalf of
Chhagan Tele/Martha Heimann

DATE
August 3, 2009

IND NO.

NDA NO.
22-399

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
January 9, 2009

NAME OF DRUG
Gabapentin enacarbil

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
Neurology

DESIRED COMPLETION DATE
September 9, 2009

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This original NDA was received on January 9, 2009. A review of the environmental assessment is requested. This is an electronic submission.

SIGNATURE OF REQUESTOR
{ See appended electronic signature page }

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22399	----- ORIG 1	-----	----- SOLZIRA

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/s/

DON L HENRY
08/03/2009

RAMESH K SOOD
08/03/2009

From: [Conner, Beverly](#)
To: ["debra.h.lake@gsk.com"](mailto:debra.h.lake@gsk.com);
Subject: Supplementary Reporting Analysis Plan for Protocol Deviations in XP13512 (GSK 1838262)
Date: Wednesday, July 15, 2009 4:45:11 PM

Memo to GSK re: **Supplementary Reporting Analysis Plan for Protocol Deviations in XP13512 (GSK 1838262) Restless Leg Syndrome Studies**

XP052, XP053 and XP060

Dear Ms. Lake:

Amendment # 15, submitted 05/27/09 contained two tables (**Table 2 and Table 3**) of protocol deviations based on inclusion and exclusion criteria for Studies XP052, XP053 and XP060. The column containing number of deviations for each study is the total number of subjects; i.e. it does not differentiate who was on drug and who was on placebo. The division is requesting that the sponsor submit datasets (XPT files) that contain unique subject identifier, targeted dose of study drug/placebo, criteria, deviation subcategory, clinical background and deviation type. Each protocol deviation should be listed separately, i.e., if a subject has more than one deviation, each deviation should be listed independently. The sponsor may include the deviation type (major, minor), but all deviations should be included regardless of how GSK/Xenoport classified the violation.

The Division is requesting 'raw data' on protocol deviations. We are particularly interested in the Clinical Background column. The clinical background column should contain sufficient detail to allow the reviewer to determine the nature, severity and duration of the deviation and allow an independent assessment regarding the impact on the data collected for the patient. We would need to know if they were non-compliant, in what way they were non-compliant (resulting in under or over dosing), the number of study days the subject was noncompliant with blinded study medication. In this way, we will be able to best assess the type of deviation that occurred, if it impacted exposure response data. Please include the protocol violations for patients taking all dose levels not limiting the data to just subjects taking 600mg and 1200mg.

This should be done for Inclusion and Exclusion Criteria protocol deviations.

USUBID	Study #	Targeted Tx Arm	Inclusion/Exclusion Criteria	Deviation Subcategory
				Clinical Background
				Deviation Type
		600mg		
		1200mg		
		1800mg		
		2400mg		

Placebo

Please feel free to contact Beverly Conner with further questions.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
7/15/2009 05:01:13 PM
CSO

From: Conner, Beverly
Sent: Tuesday, June 30, 2009 8:39 AM
To: 'debra.h.lake@gsk.com'
Subject: Subject taking prohibited medications and non-compliance
 Dear Debra:

Please provide the data we requested listing subjects with protocol deviations for their pivotal RLS trials for XP13512 in the manner indicated in the sample tables attached. You do not need to include an analysis of the data by types of protocol deviations (i.e. major versus minor). Please do not apply any additional criteria to the data we requested, we are interested in the raw data as requested in the sample tables.

Subjects Taking Prohibited Medications

USBjid	Study ID	ARM	Prohibited medication class	Prohibited medication Established name and total daily dose taken	Date during DB study period prohibited medication 1 st taken	Date when prohibited medication stopped	Total Number of days during DB period prohibited medication taken
		Placebo					
		600 mg					
		1200 mg					
		1800 mg					
		2400 mg					

This should include all subjects who took a prohibited medication regardless of whether or not they met the sponsor's criteria of a major or minor protocol deviation. If a subject took more than 1 prohibited medication the sponsor should create a separate line for each prohibited medication taken by the subject. Please report all subjects receiving placebo or any strength of XP13512.

Subjects Non-Compliance

USBjid	Study ID	ARM	% compliance with Study Med	Total Number of days in DB period subject was noncompliant with blinded		

				study medication		
		Placebo				
		600 mg				
		1200 mg				
		1800 mg				
		2400 mg				

Please send the data as XPT files as soon as possible. Thank you.

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/s/

Beverly A. Conner
6/30/2009 10:08:38 AM
CSO



NDA 22-399

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Glaxo Group Limited d/b/a GlaxoSmithKline
P.O. Box 13398
Five Moore Drive,
Research Triangle Park, North Carolina 27709

ATTENTION: Debra H. Lake, M.S.
Manager, US Regulatory Affairs

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) dated September 15, 2008, received September 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil extended-release tablets 600 mg.

We also refer to your May 8, 2009 correspondence, received May 8, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

We object to the proposed trade name (b) (4)

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated May 8, 2009. In order to initiate the review of the alternate proprietary name, (b) (4), submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Daniel Brounstein, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0674. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist
6/25/2009 04:42:47 PM

From: [Conner, Beverly](#)
To: ["debra.h.lake@gsk.com"](mailto:debra.h.lake@gsk.com);
Subject: Information Request
Date: Friday, May 29, 2009 12:55:52 PM

Dear Ms. Lake,

The primary clinical reviewer in the Division of Neurology Products is requesting additional information regarding the clinical trials data supporting NDA application 22-399 Gabapentin Encarbil .

We request you amend the 120 safety update, adverse event table (ae.XPT) to include a column that list the actual dose of XP 13512 the patient received when the AE was reported. The actual dose column must only indicate the mg dose (i.e. 600 mg, or 1200 mg or 1800mg), please do not include the drug name or number. Please include a second column indicating the study week the AE was initially reported to the site investigator (i.e. Week 1, 2,3 etc.)

The next data request involves the Columbia Suicidality Scale (CSS); we request a data table (XPT) listing the total scores by visit for each subject for all studies in which it was used (see model table below for format). We are particularly interested in study XP052, XP053, XP055, XP060 and XP081. In addition please direct us to the place in the submission where GSK/Xenoport analyzed the CSS scores for change from Baseline reported by dose and study duration. We are also interested in the CSS scores during the taper and withdrawal phases of the protocols listed above. If this type of analysis of the CSS has not been submitted in the NDA package please provide us the analysis. The analysis and requested data table should include all visits where the CSS was administered included a final safety visit. Information we are seeking includes an analysis change in CSS from Baseline to end of study, change in CSS score by study visit (where the CSS was administered). The analysis should also include the actual dose patients were taking when the CSS was administered. If the trial was flexible dose design and only Baseline and completion/termination visit CSS data are available for comparison, please conduct the analysis by modal dose patients received during the trial.

USUBID	STUDYID	TREATMENT in mg for actual or modal dose	Visit number	Baseline CSS score	CSS score for visit	Change from baseline in CSS score	Met criteria for CSS related AE
--------	---------	--	--------------	--------------------	---------------------	-----------------------------------	---------------------------------

Y

N

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/25/2009 02:06:35 PM
CSO



NDA 22-399

**PROPRIETARY NAME REQUEST
- UNACCEPTABLE**

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Debra H. Lake, M.S.
Manager, US Regulatory Affairs
Five Moore Drive,
P.O. Box 13398
Research Triangle Park, North Carolina 27709

Dear Ms. Lake:

Please refer to your New Drug Application (NDA) dated September 15, 2008, received September 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gabapentin enacarbil 600 mg extended-release tablets.

We also refer to your January 14, 2009 correspondence, received January 14, 2009, requesting review of your proposed proprietary name, Solzira. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Daniel Brounstein, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0674. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

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

4/9/2009 10:16:15 AM

From: [Conner, Beverly](#)
To: ["debra.h.lake@gsk.com"](mailto:debra.h.lake@gsk.com);
Subject: Solzira 22-399
Date: Tuesday, April 07, 2009 1:46:17 PM

Dear Ms. Lake:

Please address and the following issues as soon as possible.

1. A complete listing of Protocol Deviations for each pivotal efficacy trial was not included in the NDA application. The current listing only included protocol deviations judged by the sponsor to be inclusion/exclusion errors. The sponsor is requested to submit a data set in XPT format, listing protocol deviations by study number, unique subject ID, study site number, and short description of the deviation. The sponsor should include a text table listing all Protocol deviations by site/investigator (not pooled). This table should list the number and percent of the total of protocol deviations for each site by study and include a brief description of the nature of the protocol deviation,
2. The sponsor (b) (4)
Study of the symptoms of RLS has been demonstrated in the medical literature. The NIH scale for RLS symptoms is validated in subjects as young as age 8. The division recommends granting a deferral for studying children ages 8-18 until Solzira is approved for use in adults and a waiver for below age 8. The sponsor must develop and submit with a plan to study Solzira in the pediatric population from ages <18 to 8 years old. The sponsor is directed to Division of Pediatric Drug Development (DPDD) for guidance in submitting the pediatric plan and application for the waiver. The sponsor is strongly advised to contact the DPDD early during this NDA review cycle.
3. Although the current XPT safety data sets include information for each study, the data should be reconfigured to match the pre-specified "safety groupings" (usually referred to as safety pools) for the clinical trials

included in this application. Each data set should include columns listing the unique subject identifier, study number/ID, the treatment arm and the dose of study medication the patient was receiving at time the AE was reported. The data should at the minimum include the MedDRA version used to code the AE data, Preferred term, (PT), HLT, HLTG and SOC , seriousness of the adverse event, if the event was resulted in death, outcome/disposition and action taken. The current data inter-mixed safety data (sorted by subject ID) from placebo controlled trials with data from the open-label trials (with no study ID number column) that followed making it difficult to identify in which study the patient reported the AE.

4. Exposure tables need to have unique subject exposures by study and by dose. The tables sent on 2/20/2009 are not acceptable. Subjects should only be counted in one time interval (row) per dose level reflecting their longest duration of exposure. If the subject's maximum exposure was 60 days they should be counted in that time interval and not in the shorter exposure intervals (i.e.0-30 day). The exposure tables must be reported in days not patient-days.

[Beverly Conner, Pharm.D.](#)
[Regulatory Health Project Manager](#)
[Division of Neurology](#)
[Office of Drug Evaluation I](#)
[Center for Drug Evaluation and Research](#)

Phone: 301-796-1171

Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/29/2009 09:31:25 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-399

Glaxo Group Limited
d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.
Manager, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your new drug application (NDA) dated January 8, 2009, received January 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Solzira (gabapentin enacarbil) extended release tablets, 600 mg.

We also refer to your submissions dated January 14, 2009, February 20, 2009, and February 25, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is November 9, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 24, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

However, we request that you submit, as soon as possible, the following information:

1. Provide representative Certificate of Analysis of the starting material, (b) (4) used in the manufacture of clinical drug substance batches.
2. Gabapentin enacarbil has been developed as a racemate; however, there is no systematic testing of the drug substance to ensure the consistency of the enantiomeric mixture. Include an appropriate test and acceptance criterion in the drug substance specification.
3. It does not appear that friability of the tablet was determined during the production as indicated in the one executed batch record provided in 3.2.R. The master batch record also includes the work-sheet for the determination of tablet friability (p. 31 to 35) with an acceptance criterion of not more than (b) (4). Provide a justification for the absence of this typical in-process testing.

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.

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of (b) (4)

If you have any questions, contact Beverly Conner, Pharm.D, Regulatory Project Manager, at (301) 796-1171.

Sincerely,

{See appended electronic signature}

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

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/s/

Russell Katz
3/13/2009 03:29:33 PM

REQUEST FOR CONSULTATION

TO (Office/Division): To Division of Biometrics, HFD 710
Attention: Dr. Karl Lin

FROM (Name, Office/Division, and Phone Number of Requestor):
FROM: Russell Katz, MD, Division Director, DNP
HFD-120/NEUROLOGY PRODUCTS

DATE
February 20, 2009

IND NO.

NDA NO.
22-399

TYPE OF DOCUMENT
Biometrics Consult

DATE OF DOCUMENT
January 8, 2009

NAME OF DRUG
,Solzira (gabapentin)

PRIORITY CONSIDERATION
High

CLASSIFICATION OF DRUG
Treatment Restless leg
syndrome

DESIRED COMPLETION DATE
March 30, 2009

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

COMMENTS / SPECIAL INSTRUCTIONS: DNP is requesting that Dr. Karl Lin do a statistical Carcinogenicity review. The nonclinical overview is under m 2.4. The Carcinogenicity information is found in 4.3. This is a consult for a NME, NDA 022-399, Solzira (gabapentin). Please review and comment on the acceptability of the carcinogenicity statistical information.

The nonclinical overview is under m 2.4.
The Carcinogenicity information is found in 4.3
\\CDSESUB1\EVSPROD\NDA022399\0000

Dr. Lin Please take a look at the data and look and see if it is functional. This is a resubmission.

Beverly Conner, Pharm.D.

Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Room 4209
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

SIGNATURE OF REQUESTOR

Beverly Conner

METHOD OF DELIVERY (Check one)

DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Beverly A. Conner
2/20/2009 03:14:28 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **OND Div Cardio Renal IRT Review,
Attention Devi Kozeli**

FROM (Name, Office/Division, and Phone Number of Requestor): **HFD-120
(Division of Neurology Products); Russell Katz, MD**

DATE
2/13/09

IND NO.
71,352

NDA NO.
22-399

TYPE OF DOCUMENT
**Clinical study XP078.
Study report**

DATE OF DOCUMENT
8/31/2006

NAME OF DRUG
SOZIRA (gapapentin)

PRIORITY CONSIDERATION
HIGH

CLASSIFICATION OF DRUG
restless legs syndrome

DESIRED COMPLETION DATE
April 29, 2009

NAME OF FIRM: **Glaxo Group Limited d/b/a GlaxoSmithKline**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

XP078 is a QT study (in GSReview 5.3.4.1). There was a consult for IND 71,352 Review dated 8/31/2006. Please review the QT study in module 1 of NDA 22-399. Below is the link for the NDA:

\\CDSESUB1\EVSPROD\NDA022399

Here is the History:

Date Activity

August 21, 2006 (Serial No. 049) Type C Meeting Briefing Document containing draft XP078 protocol

September 21, 2006 Type C Meeting to discuss design of XP078 study

November 22, 2006 FDA provides minutes to Type C Meeting and guidance on XP078 study design

April 27, 2007 (Serial No. 093) Submission of New Protocol, XP078

June 20, 2007 (Serial No. 100) Submission of Statistical Analysis Plan (SAP) for XP078

July 25, 2007 FDA provides comments for protocol and SAP for XP078

September 10, 2007 (Serial No. 109) Submission of Protocol Amendment 01 and revised SAP for XP078

October 4, 2007 FDA provides comments for the revised SAP for XP078

October 19, 2007 (Serial No. 118) Submission of FINAL SAP for XP078

SIGNATURE OF REQUESTOR

Beverly Conner, Pharm.D.

Regulatory Project Manager

301-796-1171

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Beverly A. Conner
2/20/2009 02:57:31 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 71,352

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Debra H. Lake, M.S.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1838262 (XP13512).

We also refer to the teleconference between representatives of your firm and the FDA on April 16, 2008. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Control (CMC) topics regarding the development of XP13512, in anticipation of NDA filing in the second half of 2008.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	GlaxoSmithKline
Application Number:	IND 71,352
Product Name:	GSK1838262 (XP13512)
Meeting Requestor:	Dr. Greg Bates, Vice President, Regulatory Affairs, XenoPort, Inc.
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, preNDA Meeting
Meeting Date and Time:	Wednesday, April 16, 2008 1430 – 1500 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	March 20, 2008
Meeting Chair:	Ramesh Sood, PhD
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of Pre-Marketing Assessment:

Ramesh Sood, Ph.D.; Branch Chief

Martha Heimann, Ph.D.; Pharmaceutical Assessment Lead

Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

EXTERNAL ATTENDEES:

Chris Beels, PhD, Director, Chemical Development, GSK
William Clark, PhD, Manager, Synthetic Chemistry, GSK
Fran Muller, PhD, Director, Pharmaceutical Development, GSK
John Roush, PhD, Investigator, Biopharmaceutics, GSK
Susan Holmes, MS, Associate Director, Global CMC Regulatory Affairs, GSK
Bob Reed, PhD, Vice President Pharmaceutical Operations, XenoPort
Stephen Raillard, PhD, Executive Director, Chemical Development, XenoPort
Sally Smikahl, Director, Regulatory Affairs, XenoPort
Jeffrey Brum, PhD, Manager, Physical Properties and Developability, GSK
Matthew Hemberger, PhD, Principal Scientist, Pharmaceutical Development, GSK
Alireza Kord, PhD, Director, Chemical Development Analytical Sciences, GSK
Brian Rhodes, Investigator, Pharmaceutical Development, GSK
Tom Roper, PhD, Director, Synthetic Chemistry, GSK
Gerald Terfloth, PhD, Manager, Chemical Development Analytical Sciences, GSK

1.0 BACKGROUND

XenoPort submitted IND 71,352 for XP13512, an oral to the Division of Neurology Products on December 9, 2004, supporting development of XP 13512, an oral prodrug of gabapentin being developed by XenoPort, Inc. for the treatment of patients with Restless Legs Syndrome (RLS). Further reference is made to XenoPort's submission of February 11, 2008 in which XenoPort requested the scheduling of a Pre-NDA (CMC) (Type B) Meeting to discuss and reach consensus on the acceptability of the chemistry, manufacturing and controls (CMC) information supporting the planned NDA for XP 13512 (GSK1838262) in the treatment of patients with primary Restless Legs Syndrome (RLS). FDA correspondence dated March 12, 2008 whereby FDA notified XenoPort that a teleconference had been granted, and had been scheduled for April 16, 2008, (14:30 - 15:00 ET). XenoPort provided the Pre-Teleconference Briefing Package on March 18, 2008, received March 20, 2008, which provides background information to CMC topics that XenoPort would like to discuss during the April 16, 2008, teleconference.

On April 7, 2008, XenoPort sent General Correspondence: Transfer of Sponsorship to IND 71,352 in which it was stated that the sponsorship of the IND would be transferred to GlaxoSmithKline (GSK) effective April 8, 2008.

On April 8, 2008, GSK sent General Correspondence: Transfer of Ownership of IND 71,352 in which it was stated that the sponsorship of the IND would be accepted by GSK effective April 8, 2008.

The preliminary responses to the questions contained in the briefing package were archived and sent to GSK to promote a collaborative and successful discussion at the teleconference. The teleconference occurred as scheduled on April 16, 2008. The minutes of the teleconference are recorded below.

2.0 DISCUSSION

- 2.1 Question a) Does the Agency agree that the proposed comparability protocol would support a drug substance manufacturing site change post-approval via the annual report?

FDA Response: At this time we do not have the resources to perform a detailed review of the proposed comparability protocol, or supporting data, prior to submission of the NDA. We note the following points with respect to the current proposal:

- The comparability protocol should define the scope of any manufacturing process or control changes that might be implemented during a site change and the specific testing that will be performed to evaluate the impact of each change.
- Batch analysis data for a minimum of three batches of XP13512 manufactured at the alternate site should be provided.
- A minimum of 3 months long-term and accelerated stability data should be provided.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. FDA clarified that as the drug substance is potentially a New Molecular Entity, a minimum of three months of long-term and accelerated stability data should be provided data for three batches of XP13512 should be provided.

- 2.2 Question b) Does the Agency agree that data consistent with the outlined comparability protocol could be submitted during the review to obtain approval of an alternate drug substance site of manufacture in the original NDA?

FDA Response: No. We will review the facilities and supporting data that are submitted in the original NDA; and we will review your proposed comparability protocol. We will not be able to review any additional manufacturing facilities (or data to support additional facilities) that are submitted after the initial NDA submission during the same review cycle.

Per our agreement at the end of phase 2 CMC meeting, we will also review additional stability data submitted within the first 5 months after NDA submission.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

- 2.3 Question c) Does the Agency agree that the batch release data from the pilot scale runs are sufficient to support the proposed API process changes to be implemented at validation?

FDA Preliminary Response: The pilot scale batch release data provided appear adequate to support the proposed process changes pending formal review of the NDA submission.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

- 2.4 Question d) Does the Agency agree that (b) (4) are acceptable as starting materials, given the detailed specifications and control of suppliers?

FDA Response: Based on the information provided in the briefing package, and pending formal review of the supporting data, we will agree to designation of (b) (4) as a starting material. Note, however, that we have concerns regarding the adequacy of the specification for this material. Please refer to our response to Item g (2.7).

As discussed during the end of phase 2 meeting, our primary concern with regard to designation of (b) (4) as a starting material is the requirement for relatively (b) (4) controls for a potential process impurity, i.e., (b) (4). The revised USP monograph, which incorporates a limit of not more than (NMT) (b) (4) for (b) (4), will become official on May 1, 2008.

We will agree to designation of (b) (4) as a starting material provided you adopt the USP limits for related substances. Alternatively, you may either obtain and submit certification from your suppliers that (b) (4) is not a potential impurity or demonstrate that significant levels of (b) (4) (or structurally related impurities) would not be carried over to the drug substance.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

- 2.5 Question e) Does the Agency agree that the tests contained in the proposed specification for (b) (4) are appropriate to control the quality of this material?

FDA Response: We are generally in agreement pending formal review; however, please refer to our response under Item g (2.7).

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

- 2.6 Question f) Does the Agency agree that DMFs for the suppliers of the starting materials are not required, given the detailed specifications and control of suppliers?

FDA Response: We agree with respect (b) (4). With respect to (b) (4) DMFs will not be required for a starting material provided you address the concerns outline in our response to Item d (2.4).

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

- 2.7 Question g) Does the Agency agree with the genotoxin control plan for (b) (4)?

FDA Preliminary Response: Based on the information provided in the briefing package, the control plan for (b) (4) appears reasonable pending formal review.

Note that, with respect to (b) (4), the adequacy of your control plan will be a matter of review based on our pharmacology review of the toxicology data provided in the NDA. Unless you are able to demonstrate that there are no special toxicological concerns for (b) (4), or provide robust data to demonstrate that the manufacturing process is capable of purging this impurity, you will need to control the impurity in the finished drug substance.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. GSK clarified that the studies FDA suggested were underway and that the data from these and other studies would be included in the NDA for review.

2.8 Question h) Does the Agency agree that the data provided justify that a particle size test is not required in the drug substance specification?

FDA Response: This will be a matter for review.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

2.9 Question i) Does the Agency agree that the content and format of the stability data files related to XP13512 drug substance are suitable?

FDA Response: The summary data format is generally acceptable; however, we note the following:

- Summary batch information (e.g., lot number, manufacturing site, date manufactured, batch scale, manufacturing process, date placed on stability, packaging, etc.) should be provided for each stability batch.
- The actual appearance of the drug substance should be reported at each time point rather than (b) (4)

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

2.10



- 2.11 Question k) Does the Agency agree that the protocol for the commercial image tablets can be discontinued, provided comparability through the (b) (4) month timepoint?

FDA Response: It is not clear what is meant by comparability. Based on the information provided in the briefing package it appears that the purpose for placing the debossed lots on stability was to provide bridging information to support the change in the dissolution method from (b) (4) to 24-hours. It appears that you included both dissolution tests in the protocol for non-debossed tablets at selected timepoints (0, 6 12, 24 etc.). If so, data from the 0, 6 and 12 month timepoints should be enough.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. FDA clarified that the long term data with the non-debossed product could support the commercial image data as long as the data through 12 months is acceptable. As these supporting data are outside the original stability bracket it is recommended that they remain on stability. The participants agreed that the non-debossed product would have 12 months of stability data at the time of NDA submission and be updated to 18 months during the course of the review cycle, and the debossed product would have six months of six months of stability data at the time of NDA submission and be updated to 12 months during the course of the review cycle. These data would then be used to determine the shelf life of the drug product.

- 2.12 Question l) Does the Agency agree that the data shown is in a suitable format, and that no additional types of tables are necessary for the presentation of stability data?

FDA Response: The summary data format is generally acceptable; however, we note the following:

- Any relevant changes to analytical procedures or acceptance criteria (e.g., the change from a (b) (4) dissolution test to a 24 hour test) should be identified.
- The actual appearance of the product should be reported at each time point rather than "(b) (4)".
- Stability data for dissolution testing should include individual tablet results at each sampling point in addition to mean values. For clarity, we recommend that individual tablet results be tabulated separately.

Meeting Discussion: GSK acknowledged receipt of FDA's preliminary responses. No further discussion occurred during the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time

4.0 ACTION ITEMS

There are no other action items other than those specified in the meeting discussion section above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

6.0 ATTACHMENTS AND HANDOUTS

There were no handouts or slides distributed at the meeting.

Linked Applications

Sponsor Name

Drug Name

IND 71352

GLAXO GROUP LTD
DBA GLAXOSMITHKLINE

GSK1838262

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

/s/

SCOTT N GOLDIE
09/23/2008

RAMESH K SOOD
09/24/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 71,352

Xenoport, Inc.
Attention: Greg Bates, D.V.M.
Vice President, Regulatory Affairs
3410 Central Expressway
Santa Clara, CA 95051

Dear Dr. Bates:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for XP13512.

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2007. The purpose of the meeting was to discuss your NDA submission for XP13512 to treat Restless Legs Syndrome.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: December 14, 2007
Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Location: White Oak Bldg #22, Room 1315
Application Number: IND 71,352
Product Name: XP13512
Received Briefing Package October 12, 2007
Sponsor Name: Xenoport, Inc.
Meeting Requestor: Greg Bates, D.V.M.
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Susan Daugherty
Meeting Attendees:

FDA Attendees:

Division of Neurology Products (DNP)

Russell Katz, M.D., Director
Norman Hershkowitz, M.D., Ph.D., Acting Medical Team Leader
Devanand Jilapalli, M.D., Medical Reviewer
Edward Fisher, Ph.D., Pharmacology Reviewer
Susan Daugherty, Regulatory Project Manager

Division of Biometrics II

Sharon Yan, Ph.D. Biometrics Reviewer

Division of Clinical Pharmacology

Veneeta Tandon, Ph.D., Clinical Pharmacology Reviewer

External Attendees:

Xenoport, Inc.

Ron Barrett, Ph.D., CEO
Greg Bates, D.V.M., Vice President, Regulatory Affairs
Ken Cundy, Ph.D., Senior Vice President, Pre-Clinical Development
Marie Lassauzet, D.V.M., Ph.D., Senior Director, Integrated product Safety
Ritu Lal, Ph.D., Senior Director, Pharmacokinetics and Drug Metabolism
Samantha Iki, Director, Project Management

GlaxoSmithKline (GSK)

Maria Davy, Ph.D., Clinical Pharmacology and Discovery Medicine
Sarah DeRossett, M.D., Ph.D., Director, Neurodegeneration, Neurosciences Medicine
Development Center
Michael Gold, M.D., Vice President, Neurology, Neurosciences Medicine Development

Center
Debra Lake, M.S., Manager, US Regulatory Affairs
Craig Metz, Ph.D., Vice President, US Regulatory Affairs
Eileen Monaghan, Pharm.D, Director, Neurodegeneration, Neurosciences Medicine
Development Center
Geoff Quinn, M.Sc., Biostatistics and Programming Manager, Neurosciences Medicine
Development Center

1.0 BACKGROUND

On December 13, 2004, IND 71,352 was submitted for XP13512 to treat Restless Legs Syndrome (RLS). In a letter dated October 1, 2007, the Sponsor requested a meeting to discuss their NDA submission. Preliminary FDA responses to questions contained in the background package and a copy of the Clinical Review Template were electronically mailed to the sponsor on December 13, 2007.

Questions from the sponsor are not bolded or italicized. Preliminary responses from the FDA are in bold after each question. The meeting discussion is bolded and italicized after the FDA Response to each question.

2.0 DISCUSSION

CLINICAL PHARMACOLOGY

Question 1: Does the Agency agree that the clinical pharmacology and pharmacokinetic studies proposed by XenoPort in this Briefing Document are sufficient to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:
We agree.

There was no discussion of the response to this question at the meeting.

Question 2: Does the Agency agree that the information described in this Briefing Document, including the radiolabel recovery study XP065, will provide sufficient characterization of the metabolism of XP13512 to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:
We agree

There was no discussion of the response to this question at the meeting.

Question 3: For the Population PK-PD analysis for XP13512, is the proposed list of raw data, data files, scripts, control and output files described in this Briefing Document acceptable to

support the filing and review of an NDA for XP13512 for RLS?

FDA Response:

Your proposal is generally acceptable. Further detail on file type is provided, below:

Please submit the applicable data from the following to support the population PK analyses and concentration-response relationship analyses:

- **All datasets used for model development and validation should be submitted as SAS transport files (*.xpt), also called version 5 SAS transport format. (see CDER's *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations*, found via the *Electronic Regulatory Submissions and Review* web page, <http://www.fda.gov/cder/regulatory/ersr/default.htm>). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
- **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). CDER's Portable Document Format Specifications are found at http://www.fda.gov/cder/regulatory/ersr/PDF_specification_v11.pdf.**
- **A model development decision tree and/or table which gives an overview of modeling steps.**

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

There was no discussion of the response to this question at the meeting.

Question 4: Does the Agency agree that the proposed approach of a reduced renal impairment study design as described in this Briefing Document is sufficient to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:

We agree.

There was no discussion of the response to this question at the meeting.

Question 5: Does the Agency agree that the current plan for examining, where available, data on the effects of gender and race/ethnicity from population PK analysis of the Phase III studies as described in this Briefing Document, represents sufficient information for the NDA and that no additional specific studies of gender, age, or race/ethnicity effects on pharmacokinetics would be required?

FDA Response:

We agree, provided there are adequate representation of the elderly and both the genders in the Phase 3 studies.

Discussion:

The Sponsor indicated that they would follow ICH Guidelines.

Question 6: Based on the rationale provided in this Briefing Document, can the Agency confirm that a PK study in hepatically impaired subjects is not required to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:

We agree.

There was no discussion of the response to this question at the meeting.

Question 7: Based on the data presented in this Briefing Document, can the Agency confirm that no specific drug interaction studies with cytochrome P450 substrates or inhibitors are necessary to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:

We agree.

There was no discussion of the response to this question at the meeting.

Question 8: Based on the rationale presented in this Briefing Document, can the Agency confirm that the two completed studies will be considered sufficient information to address the potential for drug-drug interactions of XP13512 in support of the NDA?

FDA Response:

We agree. Please include the justification in the NDA submission that antacids are unlikely to have an effect on XP13512 pharmacokinetics.

There was no discussion of the response to this question at the meeting.

Question 10: Is it acceptable for the clinical pharmacology/Phase I safety data to be summarized in the Summary of Clinical Pharmacology and Biopharmaceutics Summaries (m2.7.1 and m2.7.2) following the structure of the Clinical Pharmacology and Biopharmaceutics Review Aid outline and include, as appropriate, hyperlinks to the relevant safety information in the ISS?

FDA Response:

Yes. Please note that all Electronic Common Technical Document (eCTD) submissions must meet FDA's specifications, as detailed at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>.

There was no discussion of the response to this question at the meeting.

CLINICAL STUDIES – EFFICACY

Question 11: Does the Agency agree with the proposal to include an ISE with full text, tables, and datasets in module 5 of the eCTD, with a cross reference for m2.7.3?

FDA Response:

Module 2 should be a summary of what is in the ISE, as opposed to being a duplication of the ISE. The ISE is an integrated analysis of multiple studies. Linking from Module 2 to Module 5 is acceptable.

Discussion:

The Sponsor indicated that they would include the ISE in Module 5 and the summary in Module 2.

Question 12: Does the Agency agree with the proposal to combine only the XP052 and XP053 studies in the Integrated Summary of Efficacy?

FDA Response:

Yes

There was no discussion of the response to this question at the meeting.

Question 13: Is the proposal for the efficacy analysis by age, gender, and race for the principal 12-week efficacy studies (XP052 and XP053) acceptable?

FDA Response:

Yes. In addition, please include efficacy analysis by age, gender and race for the individual pivotal efficacy studies.

Discussion:

The Sponsor agrees to include the requested analyses for the individual pivotal efficacy studies (including XP060) as well in the ISE. The sponsor then proposes to hyperlink these analyses from the ISE to the individual study reports. Use of hyperlinks is acceptable to the Division provided that the application is easily navigable.

CLINICAL STUDIES - SAFETY

Question 14: We intend to provide an ISS in the format of the clinical safety summary (m2.7.4). Is this acceptable to the Agency?

FDA Response:

Please see also response to question 30. We request that you provide a separate stand

alone document that specifies where information is contained in the NDA for all sections/subsections of the FDA's Clinical Reviewer's Template and as recommended in the guidance, "Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" [<http://www.fda.gov/CDER/guidance/3580fnl.htm>] (February 2/05) which reviews these specific sections of the ISS and reviewer's template for the ISS. The guidance document and the annotated review template provide insight into the information necessary for various sections/subsections, and may also serve as additional check list for you to make sure that necessary information for review is included in the NDA.

We agree that grouping the three 12-week controlled studies (XP052, XP053 and XP081) is appropriate. However, 'Other RLS studies' (XP021, XP045 and XP083) are all controlled trials with approximately 263 subjects enrolled compared to 764 subjects in the 12-week controlled trials. Instead of "Other RLS studies", we propose "All controlled phase 2/3 trails" to include the 12-week and 2-week controlled trials (perhaps with the exception of XP021 as it has a cross-over design). Please note that this 'All Controlled Phase 2/3 trials' grouping will be in addition to the pooled three '12-week controlled trials'.

As you are aware, we provided you comments on 8/1/07 in the context of safety analyses for the statistical analysis plan for study XP052. We ask that you apply these safety analyses recommendations, particularly those concerning the analyses of treatment-emergent adverse events, vital signs, clinical laboratory analytes and ECG parameters, to all clinical studies (phase 1, 2 and 3) in the NDA package. All adverse events must be analyzed and presented – not just those adverse events that are deemed "drug-related".

In the proposed format (Appendix 8), under various headings (exposures, adverse events, laboratory and vital signs), results from 'Other RLS studies – your proposal' or 'All controlled phase 2/3 trials – our proposal' are presented individually. It would be useful to present the results both individually and combined.

In table 6 (page 74), it is not apparent why Overall AE incidence by dose analysis is not being done for study XP083 (130 subjects randomized to 1200, 1800 mg, diphenhydramine, and placebo parallel groups). Further, in the Integrated analyses of XP052, XP053, XP081, XP083 and XP 055, and Integrated analyses of XP021, XP045, XP052, XP053, XP060, XP081, XP083 and XP 055, it is not clear why Treatment related AEs analysis, Blood Pressure and ECG assessments are not being done.

In Appendix 5, there is a 11-page table of treatment-emergent AEs from study XP052. It is not apparent if there will be more concise summary tables in one page to facilitate easy comparison (which we prefer, in addition to the more complete tables) in the NDA submission. For example, a summary table listing the top 20 treatment-emergent AEs in the descending order of frequency (by study drug) for the study drug and placebo would be a more concise form of the 11 page table in Appendix 5.

Provide a coding dictionary "both ways" showing how all verbatim terms (VTs) were

mapped to preferred terms (PTs) and how all PTs had been mapped by VTs. It would be preferable if the coding dictionary is submitted as a SAS transport file. The MEDRA coding should also use the same version of MEDRA for all the analyses in all clinical studies.

Discussion:

The sponsor proposed a revised plan of pooling studies for the ISS (see the attached table containing a revised plan for the ISS that was presented by the Sponsor at the meeting). This revised plan will contain the previously proposed individual study reports, integrated analyses of three 12-week controlled studies (XP052, XP053 and XP081) and integrated analyses of the Long term studies (XP052, XP053, XP081, XP083 and XP055), and the Division's recommendation for integrated All controlled phase 2/3 trials (without XP021). This revised plan for ISS pooling was acceptable to the Division. In addition, the sponsor clarified that the All RLS studies category is not integrated and therefore the analyses will be presented side by side.

The sponsor proposes to apply the Division-recommended safety analyses to the following studies: XP052, XP053, XP 60, XP81, XP081, XP055, XP078 and XP021, but not to study XP045 as this is a legacy study and did not capture orthostatic blood pressure monitoring. Since there were only approximately 95 subjects in this legacy study, the Division agreed with the proposal. The sponsor also indicated that treatment-related AE analyses, blood pressure and ECG analyses will be made for the integrated 12-week controlled and long-term trials in addition to the individual study reports. The sponsor clarified that they intend to provide overall AE incidence by dose analyses for study XP083. Integrated analyses of the treatment-related AEs and laboratory results will also be provided for the All controlled trials; however, integrated analyses for ECGs and Vitals for the All controlled trials will not be provided as this data (with the exception of legacy study XP045) will be available in the Long term clinical trial pooling. These proposals were acceptable to the Division.

The sponsor clarified that the ISS will be contained in module 5 and a summary of the ISS will be in module 2. The sponsor accepts all other preliminary proposals.

Question 15: We have developed a process to specifically identify and analyze certain topics of interest identified by the Agency, as listed above. Does the Agency agree with the proposal for evaluating these topics of interest as described in this Briefing Document?

FDA Response:

In addition to the proposed analyses using the more restrictive definition of 'sudden sleep attacks' in the Sudden Onset of Sleep (SOS) Questionnaire (used in XP052, XP053, XP055 and XP060 studies), we also would like to see data on 'sleep attacks' without the qualifier 'sudden'.

In addition, you propose a search of AEs in the RLS studies of at least 12 weeks in duration for events with possible association with sleep attacks. Please include studies XP021, XP045 and XXP083 in this search. In the list of MedDRA terms include

‘sedation’, ‘motor vehicle accident’? You propose to provide narratives if the verbatim term suggests ‘sudden onset’ or occurred while driving. Please provide narratives even if the verbatim term does not suggest ‘sudden onset’ but suggests ‘sleep attack’ or if occurred while driving, eating, watching TV, conversing, operating potentially dangerous machinery or other active behaviors.

Brief assessment of cognition is used in studies XP053, XP081 and XP083; however, table 6 (page 75) does not appear to have an integrated analyses of BAC.

In your analyses of Augmentation, it is not clear if you propose to use the updated criteria (4-hour earlier onset of symptoms compared to symptom onset prior to treatment) for augmentation. In your analyses of RLS symptom-onset time data, please also present the symptoms-onset data as cumulative frequency function change from baseline to the end of the study for XP13512 and placebo, utilizing continuous data. This would be in addition to your other planned analyses of augmentation data.

Since, it is not entirely clear if Pathological Compulsive Behaviors (such as gambling, hypersexuality, eating) are specific to dopaminergic agents or to the disease (RLS, PD), it may be useful to search for AE terms (preferred and or verbatim terms) that may suggest cases of such behaviors.

Discussion:

The sponsor agreed to provide analyses on both “sudden sleep attacks” and “sleep attacks”, and include additional studies as suggested by the Division (see above) in the search of AEs with possible association with sleep attacks. It was clarified that a broad search using AE terms (including “sedation”) to identify potential cases of sleep attacks will be first done. Then the sponsor stated that clinical judgment would be used to filter these potential cases to identify subjects with sleep attacks. The Division suggested applying at this point, an a priori case definition of “sudden sleep attacks” and “sleep attacks” for the treatment and placebo groups, and provides narratives for those subjects that meet these criteria. In addition, the Division requested the sponsor to provide summary tables on the number of potential cases identified, number of cases meeting the criteria for “sudden sleep attacks” and “sleep attacks”, along with hyperlinks to these narratives.

In regard to augmentation, the Sponsor clarified that 24-hour patient diary of RLS symptoms-onset data was collected at baseline and at the end of the study, and that Augmentation was not diagnosed with or without the use of external Adjudication board. The Sponsor proposes to present the symptom-onset data as measures of central tendency at baseline, at end of the study and change from baseline. The Division suggested that in addition, the Sponsor look at the distribution of symptoms-onset times at baseline, at end of the study and change from baseline as a cumulative frequency function to compare the treatment groups to see if there is a shift from baseline. While the above data would be most meaningful in the 12-week controlled trials, however, given the relatively short duration (i.e., 12 weeks), the division asked the Sponsor to provide data on long term open label trials for change from baseline

shifts, and in particular to compare the symptoms-onset data in Study XP060 for subjects with 9 month exposure versus 6 month exposure to the study drug..

The Sponsor agrees to analyze AE terms that may be suggestive of compulsive behaviors in the 12-week controlled studies. With regard to labeling, if there was a significant difference in the incidence of these behaviors between the treatment groups, like any other adverse event with a similar difference, it may be included in the label. However, if no such significant difference in the incidence between treatment groups is found, then it may not be included in labeling.

Question 16: We intend to include summaries and analyses of laboratory data, including “markedly abnormal” values, as proposed by the Agency. Is this acceptable?

FDA Response:

Yes. In addition, please present information on clinical laboratory analytes which had been collected at an unscheduled visit and not as part of regularly scheduled study visit.

There was no discussion of the response to this question at the meeting.

Question 17: Does the Agency agree that the proposed ECG assessments in clinical studies in conjunction with the thorough QT/QTc Study XP078 constitutes adequate assessment of QT prolongation potential of XP13512?

FDA Response:

This may be possible with adequate incorporation of the ICH E14 Guideline titled, “The Clinical Evaluation of Qt/QtC Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” into your pivotal trials (e.g., multiple EKGs, single readers).

Discussion:

The Division notes that the response to this answer was in error. The correct answer is yes. As a formal thorough QT study has been conducted, the Division informed the Sponsor that pharmacodynamic (dose-QT response) analyses of the pivotal studies are optional but not required.

Question 18: We intend to include only those displays and criteria for QT interval classification that were proposed by the Agency. Is this acceptable?

FDA Response:

Yes.

There was no discussion of the response to this question at the meeting.

CLINICAL STUDIES - GENERAL

Question 19: Is the proposal for the provision of listings as described in this Briefing Document acceptable to the Division?

FDA Response:

Yes.

There was no discussion of the response to this question at the meeting.

Question 20: Is the proposal for the provision of narratives as described in this Briefing Document acceptable to the Division?

FDA Response:

In addition to your proposal to provide narratives for deaths, SAEs, AEs leading to withdrawal for all completed phase 2 and 3 studies, please provide narratives for these categories for all completed phase 1 studies as well.

In general, narratives should provide enough detail to permit an adequate understanding of the AE and have sufficient information to arrive at an independent conclusion. However, you should also provide a complete synthesis of all available clinical data and an informed discussion of the case (i.e., goes beyond what is in the CRF). At a minimum, narratives should include patient age and gender, signs and symptoms related to the adverse event being discussed, pertinent physical exam and laboratory findings, an assessment of the relationship of exposure duration to the development of the adverse event, concomitant medications with start dates relative to the adverse event, and other confounding factors if present. It should include the diagnosis or differential diagnoses, treatment provided, de-challenge and re-challenge (if available) results, outcomes and follow-up information. The timeline for events and their relation to the drug use should be clear. Pertinent negatives, as well as positive labs, should be included in the narration: e.g. bilirubin should be noted in patients with elevated LFTs even if the value is normal.

Discussion:

The Division noted that the narratives should be brief.

Question 21: Does the Division agree with the proposal for submission of SAS transport datasets?

FDA Response:

Yes. Data files are to be submitted in SAS XPORT transport format, also called version 5 SAS transport format.

There was no discussion of the response to this question at the meeting.

Question 22: Is the proposal to provide case report forms as described in this Briefing

Document acceptable?

FDA Response:

Please submit case report forms for all deaths, serious adverse events and adverse events leading to withdrawal for all completed phase 1, 2 and 3 clinical studies, and ongoing study (XP055) as of the general cut-off date (12/6/07). In addition, please include CRFs for deaths and SAEs for the ongoing study XP055 as of the cut-off date within 6 months prior to NDA submission, and also for the GSK-sponsored ongoing studies for other indications as of the cut-off date within 6 months prior to the NDA.

There was no discussion of the response to this question at the meeting.

REGULATORY

Question 9: Does the Agency agree with the proposal for submission of the NDA and 120-Day Safety Update as described above for completed and ongoing studies?

FDA Response:
Yes.

There was no discussion of the response to this question at the meeting.

Question 23: Does the Agency agree with the proposal to request a deferral to conduct studies in children and adolescents?

FDA Response:
We agree that you may request of deferral to conduct pediatric studies.

There was no discussion of the response to this question at the meeting.

NONCLINICAL

Question 24: Can the Agency confirm that no further studies are required to characterize the mechanism of action of XP13512 in RLS for the filing and review of an NDA for XP13512 for RLS?

FDA Response:
Yes.

There was no discussion of the response to this question at the meeting.

Question 25: Based on the new data presented in this Briefing Document, which includes new data requested by the Agency, does the Agency agree that the nonclinical pharmacokinetics/ADME studies completed to date are sufficient to support the filing and

review of an NDA for XP13512 for RLS?

FDA Response:

Yes.

There was no discussion of the response to this question at the meeting.

Question 26: Based on the information presented in this Briefing Document, does the Agency agree that the proposed list of nonclinical toxicology studies and general protocol design is sufficient to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:

Yes.

There was no discussion of the response to this question at the meeting.

Question 27: Does the Agency agree that the package of nonclinical safety pharmacology studies presented in this Briefing Document will be sufficient to support the filing and review of an NDA for XP13512 for RLS?

FDA Response:

Yes.

There was no discussion of the response to this question at the meeting.

Question 28: Is the nonclinical safety, toxicology, and genotoxicity package as described in the above section adequate to support the proposed NDA?

FDA Response:

On its face, yes.

There was no discussion of the response to this question at the meeting.

LABELING

Question 29: Does the clinical development plan have the potential to support the proposed labeling?

FDA Response:

This is a review issue. However, there are several comments.

The wording for the key diagnostic criteria for RLS in the currently approved labels does not include reference to (b) (4)

In section 10.1.3.1 of the label under the (b) (4),

In the Augmentation and Rebound in RLS section, it will need to be clarified that the controlled trials of XP13512 were not more than 12 weeks duration, and that the duration of these controlled trials may not be sufficient to adequately capture these events.

There was no discussion of the response to this question at the meeting.

CTD

Question 30: Does the Agency agree with the level of hyperlinking proposed for the NDA?

FDA Response:

Please provide link from the ISS to the specific CRF and to the specific narrative under discussion (rather than just to the general location of the narratives or CRFs). Please provide link from the summary tables in ISS/ISE to the specific data source(s) that are being referenced to in the summary tables.

Although it is not required, it would be more helpful if you provided a separate stand alone document of the FDA's Clinical Reviewer's template with hyperlinks from that document to the relevant section(s) of your NDA [the annotated Clinical Review template is included as an attachment to these preliminary comments to your questions]. This document can serve as an excellent tool to help the reviewer conduct a more efficient review and can serve to benefit both the reviewer and sponsor, and save time for the reviewer from contacting the sponsor to request assistance to find information in the NDA.

Please also consider providing tables using the formats shown in the example tables/listings at the end of this safety report guidance for tables for which specific guidance from the DNP has not already been provided.

If the Sponsor has run a sample eCTD through our system, they should provide the sample number. If not, we recommend that they do so. (Ref: CDER's *Electronic Common Technical Document (eCTD)* web page- <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>.)

Discussion:

The Sponsor noted that GSK will be filing the NDA and that they have experience filing eCTD applications.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

The table presented by the Sponsor at the meeting is attached.

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Revised Plan for the ISS

	Individual Study Reports	12 week Controlled	Long Term Integration	All Controlled Ph 2/3 Trials	All RLS
	Proposed in Briefing Document	Proposed in Briefing Document	Proposed in Briefing Document	Added based on FDA request	Proposed in Briefing Document
Integration Studies	Not applicable All studies	Integrated XP052, XP053, XP081	Integrated XP052, XP053, XP081, XP083, XP055	Integrated XP052, XP053, XP045, XP081, XP083 (w/o XP021)	Side by side XP021, XP045, XP052, XP053, XP055, XP060, XP081, XP083
AEs	Provided	Provided	Provided	Add at FDA request	Provided
Labs	Provided	Provided	Provided	Not provided	Not provided
ECGs	Provided	Provided	Add at FDA request	Not provided	Not provided
Vitals	Provided	Provided	Add at FDA request	Not provided	Not provided

Date: December 14, 2007

Linked Applications

Sponsor Name

Drug Name

IND 71352

XENOPORT INC

XP13512

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

01/09/2008

From: Wheelous, Teresa A
Sent: Wednesday, November 22, 2006 9:02 AM
To: 'Greg Bates'
Subject: IND 71352 Sept. 21, 2006 Meeting Minutes
Greg,

The following is a copy of the official meeting minutes of our Sept. 21, 2006 meeting for IND 71,352.

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 21, 2006

TIME: 10 AM – 11 AM

LOCATION: White Oak, Conference Room 1419

APPLICATION: 71,352 for XP13512 for Restless Legs Syndrome

TYPE OF MEETING: Type C Guidance Meeting

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Dr. Russell Katz – Division Director

Dr. Marc Walton – Deputy Division Director

Dr. John Feeney – Group Leader

Dr. Leonard Kapcala – Medical Reviewer

Dr. Devanand Jillapalli – Medical Reviewer

Dr. Sharon Yan – Biometrics Reviewer

Dr. Shari Targum – Medical Reviewer, IRT/QT Team

Dr. Stephan Ortiz – Clinical Pharmacologist, IRT/QT Team

Dr. Joanne Zhang – Statistician, IRT/QT Team

CDR Teresa Wheelous – Sr. Regulatory Management Officer

XENOPORT, Inc. ATTENDEES

Daniel Canafax, Pharm.D. - Vice President, Clinical Development

Kenneth Cundy, P.D -, Senior Vice President, Preclinical Development

(b) (4)

(b) (4)

David Savello, Ph.D. - Head of Regulatory Affairs

Pierre Trân, M.D. - Senior Vice President and Chief Medical Officer

(b) (4)

Gregory Bates, D.V.M. – V. P., Regulatory Affairs

BACKGROUND:

The July 7, 2006 meeting request was granted on July 27, 2006, and the meeting package was received August 22, 2006.

MEETING OBJECTIVES:

Purpose of this meeting is to obtain Agency concurrence on (1) the design of two human clinical studies which will investigate the effects of XP13512 on a patient's ability to drive a

motor vehicle (protocol SP083), (2) the effects of XP13512 on the QT/QTc interval (protocol XP078), and (3) to discuss and concur on the panel of neurocognitive tests to be used in XP083

and in various other studies of XP13512 in RLS patients.

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DISCUSSION QUESTIONS:

Thorough QT/QTc Study Design (XP078)

1.1a Xenoport believes that the XP078 study, utilizing a supra-therapeutic dose identified

through the conduct of the XP069 study, is appropriately designed to assess the effect of XP13512 on QT/QTc interval. We believe that this study, as designed, will provide adequate assessment of potential XP13512 effects on cardiac repolarization. Does the Agency concur that the XP078 study is acceptable as planned to provide an adequate assessment of XP13512 with regards to cardiac safety?

Pre-Meeting Comments:

No, the Agency does not concur that the XP078 study is acceptable as planned. We have concerns regarding the dosing of moxifloxacin and the suprathreshold dose for this trial.

The sponsor proposes open-label moxifloxacin administration to all subjects in the last period. We recommend that the sponsor should consider blinding (double dummy) moxifloxacin and administering moxifloxacin as one of 4 blinded treatments in a randomized, varying sequence. The sponsor may want to re-consider the design of the study. A Williams Square is one option.

With the information provided, the Agency cannot concur with the suprathreshold dose selection. If the sponsor wishes to gain concurrence regarding the suprathreshold dose, results from Study XP069 will need to be reviewed by the Agency.

Additional Comments

1. For purposes of controlling for the effect of study procedures on QT interval, in addition to drawing blood samples after XP13512 is dosed, we recommend that blood samples be drawn at baseline and after subjects receive moxifloxacin.

2. We recommend that you prespecify an algorithm for QT measurement (e.g., which leads used).

3. Please submit the data in CDISC format. If you are unable to submit the data in CDISC format, then the project manager should be contacted to discuss a suggested format and content of datasets.

4. Addition of an outlier analysis, as follows:

- Assess the occurrence of QTc > 450ms, > 480ms and > 500ms over all timepoints.

- Assess categorical QTc increment > 30 msec, and > 60 msec

- Conduct all outlier analyses for both time-averaged and time-matched data.

5. All ECGs should be centrally read and blinded to the reader.

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6. The following analyses and graphical presentations of the data are recommended:

- Mean baseline QTc and QTc vs. time stratified by dose group.
- Calculate the mean by time for the $\Delta QTcI$, $\Delta QTcF$ and $\Delta QTcB$ (baseline corrected QTc) for each treatment. The QTcI for each individual subject can be derived from all “baseline” ECGs obtained from each of the 4 periods.
- Calculate the mean by time for the $\Delta\Delta QTcI$, $\Delta\Delta QTcF$ and $\Delta\Delta QTcB$ (baseline and placebo corrected QTc) for each treatment.
- Report the maximum mean $\Delta\Delta QTc$ and upper 95% CI for each correction
- Mean and upper one-sided 95% confidence interval of $\Delta\Delta QTc$ vs. time stratified by dose group
- Overlaid mean $\Delta\Delta QTc$ and mean plasma concentrations for each analyte vs. time stratified by dose group
- Individual plots of $\Delta\Delta QTc$ and plasma concentrations for each analyte vs. time
- $\Delta\Delta QTc$ vs. concentration plot with slope calculated using a linear mixed effects model

7. We are interested in understanding the relationship between drug exposure and effect on QTc interval. In addition to the primary statistical analysis of the data as defined by ICH E14 guidance, the Clinical Pharmacology team plans to use a linear mixed effects modeling approach to estimate the population slope (β) and standard error of slope (SE_{β}) of the plasma concentration and $\Delta\Delta QTc$ (placebo and baseline-adjusted QTc) interval for each analyte (e.g. parent, any metabolite(s)). The mean maximum effect and upper one-sided 95% confidence limit will be computed from the mean maximum plasma concentration. The mean maximum effect and upper one-sided 95% confidence limit can be computed from the mean maximum plasma concentration (C_{max}) for each dose using the following equations:

Upper 95% CI : (1.65)

Mean Max Effect :

$$\frac{C_{max} SE C}{C}$$

• + • •

.

β β

β

8. Note that in addition to fitting a linear model to the data, the need for a model relating delays in maximum concentration and maximum response will be evaluated. Additionally, the need for an Emax model relating concentration to response will be considered.

If you choose to perform these analyses, we encourage you to submit the results, along with any analysis datasets.

9. Please submit all ECG waveforms collected to the FDA's ECG warehouse.

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10. The DNP is concerned with the QTc dosing proposal for XP13512. The “thorough” QTc study should be designed to characterize or exclude QTc prolongation and ordinarily should not be designed in a manner that might require additional QTc investigation. First, it is not clear if 6000 mg daily is an appropriate “supratherapeutic” dose. We do not know the maximal therapeutic dose which could be 1200, 1800, or even 2400 mg daily. The “supratherapeutic” dose should be potentially the highest, tolerable exposure that a patient could experience if he/she received the maximally recommended therapeutic dose and then experienced increased exposure because of other factors (e.g. drug-drug interaction, inhibition of metabolic pathway, renal or hepatic impairment). A drug-drug-interaction and/or effect of renal impairment are the most likely factors that could increase exposure to XP13512.

Second, even if 6000 mg/day was a reasonable “supratherapeutic” dose, you would not know the dose at which QTc prolongation begins if the 6000 mg dose produces QTc prolongation and the 1200 mg dose not. There is no intermediate dose being studied that would provide such important information.

Third, it is possible that 1800 (or even 2400 mg daily) could be a maximal therapeutic dose. We know that you plan to assess the safety and efficacy of XP13512 in a dose-response study comparing placebo, 600, 1200, and 1800 mg daily. If this study suggested that 1800 mg was more effective dose than 1200 and did not have a markedly worse safety profile, then your QTc study would not even be investigating this dose, which would be important.

11. We recommend additional “baseline” and on treatment ECG/Holter data collections at time “0”, +1, +21, +24 hrs) (in addition to your other proposed times of +2,4,6,7,8,9,10,12,15,18,22.5 hrs) and delete the 22.5 hrs for all 4 “blinded” treatment (including moxifloxacin). Ideally data should be collected throughout the whole dosing interval.

12. It is not clear if subjects whether subjects need to be supine during most of monitoring (e.g. protocol says remain supine form 6-12 hrs) post-dosing). If patients were allowed to ambulate feely at certain times throughout the data collection period and not at other times, this plan would seem to enhance the risk for introducing noise in the data. It may be advisable to maintain the same restriction throughout the total study period.

13. We recommend considering PK sampling at all ECG/Holter data collections.

14. We recommend considering excluding subjects with any history of ventricular arrhythmia from your QTc study as well as your study assessing tolerability of 4800 mg and 6000 mg daily.

15. The DNP notes that you will enroll additional subjects if the drop-outs exceed 6 subjects, a number we expect that will be exceeded.

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16. We recommend orthostatic vital signs (supine and standing blood pressure and pulse after a defined standing time such as 2 minutes) at all the DNP recommended timepoints for collecting QTc/Holter data with the exception that it would not be necessary to awake subjects from sleep after 15 hours. The final

orthostatic assessment could be completed at + 24 hours after dosing. These important data could be collected after QTc/Holter data collection and before PK sampling. We did not think that your protocol planned any systematic orthostatic data collection after dosing. The QTc study provides an excellent opportunity to collect important data not known.

We also recommend that you similarly collect orthostatic vital signs in Study 69 which is assessing tolerability of high doses of XP13512 up to 4800 and 6000 mg daily in a relatively small number of subjects. Prior to treatment, we recommend that a set of 3 orthostatic vital sign measurements be collected (~ 15-20 minutes apart) and be used as an average for comparing post-dosing changes.

Meeting Discussion Comments

- The sponsor thought that some DNP questions about the QTc protocol and analyses had already been addressed in the protocol and could be clarified in the protocol and/or Statistical Analysis Plan (SAP).
- Although the sponsor does not yet know the maximal therapeutic dose of XP13512 and the maximal exposure that a patient could experience with any potential drug-drug interaction (DDI) and/or renal impairment, the sponsor thinks the 6000 mg dose will adequately cover a potential maximal exposure to XP13512. The sponsor acknowledged that it could be problematic if the 6000 mg dose showed QTc prolongation and the 1200 mg did not because it would not be possible to know at which dose QTc prolongation begins. The sponsor noted that it would consider studying an intermediate dose (between 1200 and 6000 mg) of XP13512.
- QTc signal at any dose is a cause for potential concern which can possibly be addressed in labeling.
- The comprehensive set of clinical pharmacology studies, which ordinarily would have been completed at this point, would suggest data on the maximum exposure dose prior to conducting the QT study.

1.2 Design of Driving Study (XP083)

1.2a XenoPort believes that the XP083 study, as designed, will adequately assess the potential effects of XP13512 treatment on driving ability. Does the Agency concur that the design of the XP083 study is appropriate to assess the effect of XP13512 on driving ability?

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Pre-Meeting Comments:

No. Pharmacodynamic effects on driving and cognition should be assessed at or just after Tmax (8 – 9 hours) and a later time point.

Meeting Discussion Comments:

- If the sponsor wants to make a label claim that XP13512 does not show a deleterious effect in driving, the proposed study assessing effects of XP13512 on driving (i.e. simulation) and cognitive function should be designed for a noninferiority analysis to show not only that XP13512 is inferior to diphenhydramine (the positive sedating control), but also that it is similar/equivalent to placebo. The DNP emphasized that showing that XP13512 is not statistically different from placebo does not necessarily mean that it is equivalent to placebo. This issue

could also be considered in a non-inferiority analysis.

- The DNP noted that the gabapentin/Neurontin label is not necessarily relevant to what should or should not be considered in a label for XP13512. It is difficult to envision a label for XP13512 without reviewing the relevant data.
- The sponsor acknowledged that the present study design does not allow one to assess an effect on driving or cognition near T_{max} (~ 8 hrs with feeding), a time when patients might actually be driving. Discussion ensued about this issue. It was decided that this concern could be addressed by dosing XP13512 in the morning and conducting testing in the afternoon, a time when subjects are also at an increased risk of sleepiness (unrelated to any drug) and also by dosing at 5 pm with additional testing on the following morning. Using such a paradigm, the am dosing would need to be conducted on the day before 5 pm dosing with more than a 24 hour interval between dosing but not by dosing XP13512 on the morning after 5 pm dosing on the previous day.
- The results of this driving simulation/cognitive assessment study could potentially be described in labeling in combination with the totality of findings from other related data.

1.2b Xenoport believes that the partial interim analysis described for the XP083 study will

appropriately allow for an adjustment in sample size, if necessary, to ensure a definitive outcome. We feel that, since XP13512 data will not be assessed and since the assessment of data will be conducted by an independent DSMB and will be kept blinded from the sponsor and investigators, no statistical penalty should be assessed for the partial interim analysis. Does the Agency agree that the statistical approach to the partial interim analysis for study sample size adjustment is acceptable?

Pre-Meeting Comments:

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We have some questions and concerns regarding the analytic plan for your driving impairment study:

1. Please clarify what is your current estimate of the diphenhydramine-related driving impairment (i.e., the difference between diphenhydramine and placebo assessments)?
2. Your current analytic plan appears to be designed to ensure that a statistical difference between diphenhydramine and placebo is demonstrated, and then to test if a difference between XP13512 and placebo has been demonstrated. This is an inappropriate approach to assessing the effects of XP13512 on driving ability. Considering that this is a safety-related outcome, the objective of this study should be to describe a limit of how much driving impairment might be associated with XP13512. The appropriate analysis is to calculate a confidence interval on the XP13512 - placebo difference, and to consider the limit value of that C.I. as the potentially drug-associated impairment. Consequently you prospectively determine the magnitude of driving impairment (either as absolute impairment or as a fraction of the diphenhydramine-associated impairment) that you wish to be able to exclude. Your study sample size calculation must then also take this statistical goal into consideration. Please be aware that in reviewing the risks and

benefits of XP13512 FDA will consider the results of the driving impairment study as the potential amount of drug-associated impairment described by the confidence interval.

3. Your current plan for the interim analysis appears to provide decreasing enrollment from 120 total patients to 60 total if at the interim analysis with 15 patients per group there is a statistically demonstrated difference between diphenhydramine and placebo. We strongly advise you to not decrease the sample size of the study as doing so will increase the likelihood of the study failing to provide adequate information on the effects of XP13512. See also the preceding comment.

4. We suggest that the interim analysis is best used only for increasing the sample size to achieve the desired study goals or to terminate the study for futility. It should not be used to decrease the study size. Please also describe clearly the criteria for observed interim results that (e.g., of diphenhydramine treatment effect size, variance, recalculated sample size, or other factors) that would direct the DMC to conclude futility of the study and suggest termination.

Meeting Discussion Comments

- The DNP emphasized that the sponsor should not stop subject enrollment or the study early if the positive control showed a statistically significant effect on driving vs placebo at any interim analysis. Stopping the study early could result in inadequate collection of desired safety data.

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1.2c Xenoport believes that the incorporation of the BAC assessment battery as part of the XP083 study will provide appropriate information with regard to cognition in patients with RLS. Does the Agency concur that the BAC assessment battery is appropriate to assess the potential effects of XP13512 on cognition?

Pre-Meeting Comments:

The Division agrees that the BAC assessment battery is appropriate to assess the potential effects of XP13512 on cognition.

Additional Comments:

- The DNP recommends that you conduct a hERG study at high concentrations for gabapentin.
- The DNP is concerned that the dose escalation from 2400 mg (sustained release formulation) to 4800 mg in a single step in Study XP69 may be too great and could be associated with significant safety risk. Previously, subjects treated with highest doses (which were much lower) experienced an increased incidence of predominantly a variety of CNS and gastrointestinal adverse reactions. From what we know, the highest single dosing administration was 2800 mg (immediate release) and the highest administration of the same formulation with multidosing was 4200 mg/day (2100 mg BID) but these subjects were gradually titrated to this high daily dose. With the sustained release formulation, the highest exposure was 2400 mg/day in a multidosing experience and these patients had also undergone titration to this high dose over several days.
- The DNP thinks that adding another intermediate dose such as 3600 mg may be a

more reasonably, conservative approach.

- The DNP is concerned that the relatively small enrollment of patients in each treatment group (e.g. N = 25 /group) in study XP 81 (assessing dose response of XP13512 on efficacy and safety) is too small to expect useful/informative results. You recently submitted this protocol as a result of feedback/DNP recommendations made previously. We note that you did not use any sample size calculations to estimate a sample size. In the absence of reasonable data to use for sample size estimation, we would expect that enrollment of approximately 60-70 patients per treatment group would provide more useful and reliable information for characterizing the dose-response curve for efficacy and safety of XP13512.

- Previously, the DNP recommended that a preferred dose response study (of at least 3 months duration) would involve 5 treatment groups including placebo, 600, 1200, 1800 and 2400 mg daily. Such a study would more likely be able to inform of not only the least effective dose but also the maximally effective dose if 1800 mg and 2400 mg showed similar efficacy. In your proposed study, if 1800

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mg shows more efficacy than 1200 mg as we expect it might, you will not know if 1800 mg is the maximal therapeutic dose because a higher dose was not studied.

- Ordinarily, a good randomized, fixed, dose-response study is conducted assessing a wide range of doses to characterize the dose response for efficacy and safety and to suggest doses to be studied in pivotal trials. In contrast, your development plan does not seem to plan to use results from this study (XP81) to suggest doses for your pivotal studies because your 3 pivotal studies have already been designed and some started studying only a single dose (1200 mg) with the exception of one pivotal study assessing 2 doses 600 mg and 1200 mg (following our previous recommendations).

Meeting Discussion Comments

- Although the DNP recommends (and has recommended previously) that dose response be studied to characterize the shape of the dose-response curves for efficacy and safety, the sponsor has already planned 2 pivotal studies to assess the efficacy and safety; one study investigates the effect of XP 13512 at 1200 mg (vs placebo) and the other study evaluates efficacy of XP13612 at 600 and 1200 mg (vs placebo). Another pivotal study has been initiated to show that efficacy from 1200 mg of XP13512 is maintained over a prolonged period of many months.

The DNP noted that proposed pivotal study dose of 1200mg was selected prior to having adequate dose-response findings from an adequate single dose finding/characterization study and that all across-study comparisons from previous small, short-term studies are inadequate for characterizing dose-response of XP13512. Despite the fact that the sponsor thinks that 1200 mg is an ideal daily dose, the DNP does not necessarily concur with that view.

- Study 081 is a recently planned dose ranging/finding study using daily doses of 600 mg, 1200 mg and 1800 mg (vs placebo). This study, which plans only 25 patients per treatment group, is designed to collect some dose-response/exposure response information. The DNP was concerned that this study might not provide adequate dose-response information primarily because of its small size

(considering dropouts and individual patient variability) and lack of a 2400 mg dose group. An alternative, higher N for each treatment group in Study 81 could be beneficial. The sponsor noted that it does not expect that doseresponse/exposure response information will be determined from this study alone but that this information will be determined from this study in conjunction with other PK exposure-response information analyzed according to an exposureresponse model. The sponsor thinks that the exposure/concentrations for each dose of drug will vary approximately 2 fold and ultimately that analyses of exposure/concentration-response data will indicate appropriate dosing for XP13512.

- The sponsor is willing to accept the risk of focusing on studying 1200mg doses in the pivotal studies. Based upon its analyses of previously collected data, the sponsor expects study 081 to show that doses above 1200mg do not yield greater improvement than the 1200 mg dose. The sponsor did note that it would consider IND 71,352

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revising Study 81 to add another daily dose group of 2400 mg, a dose group the DNP considers highly desirable.

- If the 1200mg dose is shown to be effective, despite the fact that dose response has not been adequately characterized, it would still be possible to consider XP13512 for approval. It is good that at least 600 mg is being investigated vs 1200 mg and placebo in one pivotal study and this study could show if this low dose is effective or if 1200 mg is the lowest effective dose. Considering the possibility there could be limited dose-response efficacy data at the time of NDA submission, this limitation could be reflected in labeling (e.g., cautionary safety description) by restricted labeling recommending against using higher doses that may be more effective but that had not been adequately studied in the clinical development program for collecting supportive efficacy and safety data.

- The sponsor acknowledged the DNP recommendation and noted that it would add another dose 3600 mg to Study 69 so that the dose escalation step from 2400 mg to 4800 mg would not be so great.

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/s/

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 6, 2005
TIME: 11 AM – 12:30 PM
LOCATION: White Oak, Conference Room 1419
APPLICATION: 71,352 for XP13512 for Restless Legs Syndrome
TYPE OF MEETING: End of Phase 2

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Dr. Russell Katz – Division Director
Dr. John Feeney – Group Leader
Dr. Howard Chazin – Medical Reviewer
Dr. Edward Fisher – Pharmacology & Toxicology Reviewer
Dr. Lois Freed – Pharmacology & Toxicology Supervisor
Dr. Mehul Meta – Clinical Pharmacology & Biopharmaceutics Supervisor
Dr. Raman Uppoor – Clinical Pharmacology & Biopharmaceutics Team Leader
Dr. Veneeta Tandon – Clinical Pharmacology & Biopharmaceutics Reviewer
Dr. Kun Jin – Biometrics Team Leader
CDR Teresa Wheelous – Sr. Regulatory Management Officer

XENOPORT, Inc. ATTENDEES

Ron Barrett, Ph.D., Chief Executive Officer
Daniel Canafax, Pharm.D., Vice President, Clinical Development
Kenneth Cundy, Ph.D., Senior Vice President, Preclinical Development
Carol Francisco, Ph.D., Statistical Consultant, ICON Clinical Research
Samantha Iki, M.S., Project Manager
Ritu Lal, Ph.D., Senior Director, Pharmacokinetics and Drug Metabolism
Tim McCullough, Ph.D., Senior Director of Toxicology

(b) (4)

David Savello, Ph.D., Head of Regulatory Affairs
Luana Staiger, Regulatory Consultant
Pierre Trân, M.D., Senior Vice President and Chief Medical Officer

BACKGROUND:

The September 30, 2005, meeting request was granted on October 14, 2005. The meeting package was received on November 8, 2005. Additional clinical questions, responding to the special protocol assessment comment letter, were provided in a November 24, 2005 submission

MEETING OBJECTIVES:

The sponsor's goal is to obtain concurrence from the Division on the adequacy of the overall plans for the clinical and nonclinical studies intended to support the filing of a NDA in Restless Legs Syndrome.

DISCUSSION QUESTIONS:

NONCLINICAL PHARMACOLOGY AND PHARMACOKINETICS

1. **Does the Division of Neurology Products concur with the original agreement with the Division of Anesthetic, Critical Care, and Addiction Drug Products that the development of the racemate is acceptable?**
 - Yes, the Division agrees that the racemate can be developed.
2. **Does the Agency agree that the completed studies described in Section 5 represent sufficient characterization of the nonclinical pharmacokinetics and ADME of XP13512 to support filing of an NDA?**
 - The Agency agrees that the nonclinical PK and ADME completed studies are sufficient for characterization.

NONCLINICAL TOXICOLOGY

3. **Does the Agency agree that the nonclinical toxicology program is sufficient to support the filing of an NDA for RLS?**
 - The nonclinical toxicology program appears adequate in form.
4. **Assuming that there is a finding of pancreatic acinar cell tumors in rats from XP13512 exposure, does the Agency agree that, like gabapentin, this specific finding is not an issue for approval of XP13512?**
 - The significance placed on any animal tumor findings will depend on the strength of the signal compared to that seen with gabapentin taking into account the new indication and the efficacy demonstrated clinically.
5. **Does the Agency agree that the carcinogenicity study reports can be submitted during the NDA review, no later than the time of the 4-month safety update, if not available by the time of the NDA filing?**
 - No, the carcinogenicity data package should be complete at the time of NDA submission.

CLINICAL PHARMACOLOGY

- 6. Does the Agency agree that these clinical pharmacology studies are sufficient to support labeling and filing of an NDA for the treatment of primary RLS?**
 - Induction potential of XP 13512 or gabapentin are not known. The sponsor should evaluate the in vitro induction potential of XP 13512.
- 7. Does the Agency agree that no further studies are required to characterize the mechanism of action of XP13512 in RLS?**
 - The Agency agrees that no further studies are required to characterize the mechanism of action XP13512.
- 8. Does the Agency agree that the completed studies and the planned population PK analysis from the Phase 3 studies will be sufficient to characterize the pharmacokinetics of XP13512 in the target RLS population?**
 - The Agency agrees that the completed studies and the planned population PK analysis from the Phase 3 studies will be sufficient to characterize the PK of XP13512.
- 9. Does the Agency agree that the completed studies and the planned radiolabel recovery study are sufficient characterization of the metabolism of XP13512 to support the filing of an NDA?**
 - The Agency agrees.
- 10. Does the Agency agree that the proposed approach of using population PK data and a separate study of XP13512 in patients with severe renal impairment and patients on hemodialysis will be sufficient to characterize the dosing requirements in patients with renal impairment?**
 - The Agency agrees.
- 11. Does the Agency agree with the current plan for examining, where available, data on the effects of gender and race/ethnicity from population PK analysis of the Phase 3 studies, and that no additional specific studies of gender or race/ethnicity effects on pharmacokinetics will be required for filing of an NDA for RLS?**
 - The Agency agrees.
- 12. Does the Agency agree that a study of the pharmacokinetics of XP13512 in patients with hepatic impairment is not required for filing of an NDA for the treatment of RLS?**

- In general, the Agency agrees, since the fraction of the pro-drug hydrolysed in the liver tissues was small compared to the intestinal epithelium, that a PK study in hepatic impaired subjects will not be necessary.

13. Does the Agency agree that the data obtained from completed studies and the planned population PK analysis from the Phase 3 studies will be sufficient to characterize the pharmacokinetics of XP13512 in elderly patients with RLS?

- The Agency agrees.

14. Does the Agency agree that no specific drug interaction studies of XP13512 with substrates or inhibitors of cytochrome P450 enzymes are required for filing of an NDA?

- The Agency agrees.

15. Does the Agency agree that the proposed study design will be sufficient to address the potential for interaction between XP13512 and drugs that share a common transport pathway for absorption?

- The Agency agrees.

16. Does the Agency agree that the proposed study design will be sufficient to address the potential for interaction between XP13512 and drugs that share a common transport pathway for elimination?

- The Agency agrees.

Additional Comments:

- Since the sponsor plans to conduct the Phase 3 studies with food, the sponsor should evaluate the effect of various meal types (low fat and medium fat) on the exposure to gabapentin from the prodrug XP13512.
- Since the sponsor plans to rely on population analysis for evaluation of the effect of covariates, the population PK analysis plan should be submitted in advance for review.

PROPOSED INDICATION AND CLINICAL PLAN

17. Does the Agency agree that the proposal to study a single dose level of (b) (4) QD ((b) (4) XP13512 SR tablets) in the Phase 3 studies is sufficient to support filing for XP13512 SR tablets for the treatment of primary RLS?

Yes.

18. Does the Agency agree that a one-week taper upon treatment discontinuation with XP13512 SR tablets is adequate and that a separate study to evaluate tapering of the XP13512 dose is not required for filing?

Yes. No separate study to evaluate tapering is necessary.

19. Assuming a positive outcome, do the designs of studies XP052, XP053, and XP060 meet the current FDA scientific and regulatory standards (i.e., adequate and well-controlled) to establish the substantial evidence of effectiveness standard required for filing of XP13512 for the treatment of primary RLS?

Yes.

20. Does the placebo-controlled, treatment-withdrawal design of study XP060 meet the Division's requirement for the 6-month maintenance of efficacy standards required for filing of XP13512 for the treatment of primary RLS?

Yes. The Division reiterated its recommendations to change XP060 to a 24 week randomized withdrawal study and XenoPort agreed.

21. Does the Agency agree that it is acceptable to capture the primary endpoint data (i.e., IRLS rating scale) electronically utilizing the (b) (4) system developed by (b) (4)?

Yes. A contact in the Division of Scientific Investigations (DSI) will be provided to XenoPort.

- 22. Should the clinical plan be executed as described and XenoPort meets the ICH exposure guidelines, including 1500 subjects exposed to XP13512 at any dose and for any duration, 300 subjects exposed for 3 months, and 100 subjects exposed for 12 months, does the Agency agree that this will be sufficient to support the required safety exposure for an NDA filing for the treatment of primary RLS?**

Yes. (The sponsor noted that this question should be corrected to read “300 subjects exposed for 6 months”.)

- 23. Does the Agency agree that the 12-month exposure data not available at the time of the NDA filing can be submitted during the NDA review, with the 4-month safety update, and that the data will be considered as part of a complete submission package, if implemented as outlined?**

Yes, however, the Division requested that, if possible, more long term data be made available at the time of the initial NDA filing.

- 24. Does the Agency agree to consider a separate submission and proposal for cardiovascular assessment that does not include conducting a thorough QTc study with XP13512?**

The Division felt that a formal QTc study was necessary. However, the sponsor can utilize data from Phase I and Phase II trials in order to try to justify that a separate study is not necessary. However, all data collected would still need to meet the requirements of the ICH Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

- 25. Does the Agency agree that the current proposed overall safety evaluation plan is sufficient to support the filing of an NDA for XP13512 for the treatment of primary RLS?**

Yes, however two safety issues require further clarification. The SPA letter related the need for evaluation of augmentation and rebound. The Division agrees that the 24 hour RLS symptom record will help to assess these concerns. The other clinical concern is the need to assess cognitive effects of this product and specifically the effect the drug may have on ability to drive. The appropriate method(s) to evaluate this safety risk may require more discussion. Please refer to Question 28 below.

- 26. Does the Agency agree that clinical studies of XP13512 in children and adolescents should be waived under PREA?**

The Division prefers to defer a decision regarding granting a waiver as it is still evaluating the treatment of this disease entity in pediatric patients.

- 27. Should the clinical plan be executed as described, and assuming positive results, does the Agency agree that this plan is adequate to support approval and labeling of XP13512 SR tablets for the indication of treatment of primary RLS?**

Yes, however the sponsor will need to address further the way to assess time to onset of effect.

- 28. Does the Division agree that an evaluation of cognitive function does not need to be incorporated into study XP052, and that a separate discussion can be held to determine the most appropriate means to address this safety issue?**

The Division is concerned that cognitive impairment, somnolence or dizziness may occur at any point after dosing and this would require formal safety evaluation. A driving model for safety evaluation may be a good way to evaluate the potential for these common adverse events to affect driving. The Division and the sponsor did not come to an agreement as to whether this evaluation should be part of the current study or a separate study.

- 29. Does the Division agree that a special analysis of the conventional treatment-emergent adverse event data in the placebo-controlled studies will be sufficient to assess the potential for suicidality?**

Yes, however the Division has developed a detailed plan for analyzing data related to suicidality and will provide it to XenoPort.

- 30. Assuming we can come to agreement on the questions above, in addition to those that will be addressed at the End of Phase 2 meeting, does the Division agree that the Special Protocol Assessment for Study XP052 can be concluded and that a letter confirming the approval of the Special Protocol Assessment can be provided to XenoPort?**

No. A formal response to the SPA including the final statistical plan is still outstanding.

- 31. Does the Agency have a preference for a particular NDA format for an indication in RLS?**

The Agency prefers the electronic common technical document (eCTD) format. (Refer to <http://www.fda.gov/cder/regulatory/ersr/ectd.htm> for specific instructions.)

The Agency also prefers the CDISC Standard Data Tabulation Model (SDTM) as the preferred format for data submissions.

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/s/

Russell Katz
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