CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203284 SUPPL # HFD # 180

Trade Name RAVICTI

Generic Name glycerol phenylbutyrate

Applicant Name Hyperion Therapeutics

Approval Date, If Known January 31, 2013

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)

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?

7 years – orphan designation

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# 20572 and 20573 Buphenyl

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:

Investigation #1: Study HPN-100-006, Randomized, Double-Blind, Cross-Over, Active-Controlled Study of the Efficacy and Safety of HPN-100 for the treatment of adults with Urea Cycle Disorders

Investigation #2: UP1204-003 Open-Label, Switch-Over, Dose-Escalation Study of the safety and tolerability of HPN-100 compared to Buphenyl in patients with Urea Cycle Disorders

Investigation #3: Study HPN-100-007, Long term (12 months) open-label study to assess ammonia control and safety in adult and pediatric patients' ≥6 years with Urea Cycle Disorders.

Investigation #4: Study HPN-100-005, Open-label switch over study in pediatric patients 6 to 17 years old with Urea Cycle Disorders to evaluate safety, tolerability and pharmacokinetics of Ravicti compared to Buphenyl. The switch over part of this study was 7 days on each drug.

Investigation#5: Study HPN-100-005SE, Long term (12 months) safety extension study that evaluated ammonia control and safety in pediatric patients ages 6 to 17 years old with Urea Cycle Disorders.

Investigation #6: Study HPN-100-012, Open-label switch over study in pediatric patients 29 days to <6 years with Urea Cycle disorders currently being treated with Buphenyl to assess PK, safety and ammonia control. No patients younger than 2 months were enrolled.

Investigation #7: Study HPN-100-012SE, Long term (12 months) safety extension study. The study is ongoing, (data cutoff date 01 March 2012.

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 ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒
Investigation #5	YES ☐	NO ☒
Investigation #6	YES ☐	NO ☒
Investigation #7	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 ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒
Investigation #5	YES ☐	NO ☒
Investigation #6	YES ☐	NO ☒
Investigation #7	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

All investigations listed in #2(c) were necessary for approval.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigations #1 thru #7

IND # 73,480 YES ☐ NO ☒

Explain:

There was a change in the sponsor in the middle of the NDA review cycle. Applicant has right of reference and notes in their updated exclusivity request, dated 1/8/13, that they are now the sponsor named on the 1571 for IND 43780. Please see additional comments at end of document for more information.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigations #1 thru #7

YES ☐

Explain:

NO ☒

Explain:

No certification was found in the NDA. Please see additional comments below.

(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:

Additional information:
In 2007, Hyperion entered into a Research and Collaboration Agreement with Ucyclyd Pharma (Medicis), original sponsor of IND 73480 and NDA 203284, regarding its products Buphenyl, Ammonul and glycerol phenylbutryate. In 2007, the agreement granted Hyperion the sole right and responsibility to developed glycerol phenylbutyrate for urea cycle disorders and hepatic encephalopathy (INDs 73,480 (b) (4), respectively), this included all regulatory responsibilities for the INDs. The ownership of the INDs remained with Ucyclyd/Medicis and Hyperion was designated as the regulatory agent with all responsibilities for the INDs transferred to Hyperion (see IND 73,480 serial number 011). Under the 2007 agreement, Hyperion's responsibilities also included the sole responsibility to write and manage the future NDA submission and FDA review for UCD on behalf of Ucyclyd/Medicis. The agreement also included a pre-negotiated option to purchase the full license rights to glycerol phenybutyrate (and potentially Buphenyl and Ammonul), which was to be triggered based on the PDUFA date for the glycerol phenylbutyrate NDA for UCD, with ownership of all corresponding applications for glycerol phenylbutryate (INDs and NDAs) being transferred to Hyperion upon execution of the purchase rights.

Per the Research and Collaboration Agreement, Hyperion submitted NDA 203284 in December 2011 on behalf of Uclyclyd/Medicis as the regulatory agent, and at that time, since the NDA was a Ucyclyd/Medicis application, a full right of reference to sodium phenylubyrate was made on the 356h form because Ucyclyd/Medicis owned both the glycerol phenylbutyrate and the Buphenyl (sodium phenylbutyrate) applications.

In the late 2011/early 2012, the agreement between Ucylcyd/Medicis and Hyperion was re-negotiated to an Asset Purchasing Agreement, which allowed Hyperion to purchase the full rights of glycerol phenylbutryate immediately, before the PDUFA date, with the option to purchase Buphenyl and Ammonul set for a later date. Hyperion executed the purchase right in March 2012 and at that time the ownership of the glycerol phenylbutyrate NDA 20-3284 and INDs 73,480 (b) (4) were transferred to Hyperion (see NDA 20-3284 amendment, dated March 23, 2012; IND 73,480 dated April 17, 2012).

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Name of person(s) completing form: Melanie Blank, M.D.
Title: Acting Cross Discipline Team Leader, DGIEP
Date: January 28, 2013

Nancy Snow, D.O. Medical Reviewer Feb. 1, 2013

Name of Office/Division Director signing form: Donna Griebel, M.D.
Title: Division Director, DGIEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JESSICA M BENJAMIN
02/07/2013

DONNA J GRIEBEL
02/07/2013

1.3. ADMINISTRATIVE INFORMATION

3. DEBARMENT CERTIFICATION

Ucyclyd Pharma Inc., a wholly owned subsidiary of Medicis Pharmaceutical Inc., certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

12-8-11

Ira Lawrence, MD
Chief Medical Office and Sr. Vice Research and Development

Date

Ucyclyd Pharma Inc.
7720 North Dobson Road
Scottsdale, AZ 85256
Phone: (480) 291-5629
Email: ilawrence@medicis.com

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

12/12/11

Klara A. Dickinson
Sr. Vice President Regulatory Affairs and Compliance

Date

Hyperion Therapeutics, Inc.
601 Gateway Boulevard, Suite 200
South San Francisco, CA 94080
Phone: (650) 745-7820
Email: klara.dickinson@hyperiontx.com

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203284 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: RAVICTI Established/Proper Name: glycerol phenylbutyrate Dosage Form: oral liquid		Applicant: Hyperion Therapeutics Agent for Applicant (if applicable):
RPM: Jessica M. Benjamin		Division: DGIEP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☒ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is 1/23/213	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[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.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• 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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☒ No paragraph III certification Date patent will expire
• [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*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): Approval 2/1/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2/1/13
• Original applicant-proposed labeling	12/23/2011
• Example of class labeling, if applicable	Buphenyl April 2008

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	1/30/2013
• Original applicant-proposed labeling	12/23/2011
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	12/31/12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptable 5/4/2012 12/2/2012; 5/4/2012
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 3/7/2012 ☒ DMEPA 10/18/2012 ☒ DMPP/PLT (DRISK) 1/28/2013 ☒ ODPD (DDMAC) 1/29/2012; 1/28/2012 ☒ SEALD 1/28/2012 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	3/7/2012 ☐ Not a (b)(2) 1/23/2012 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan drug designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	12/21/2012; 12/3/2012; 11/19/2012; 9/4/12; 8/13/2012; 6/27/2012; 6/15/2012; 3/23/2012; 3/5/2012; 1/3/2012;
❖ Internal memoranda, telecons, etc.	3/22/2012
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12/8/2010; 12/7/2010
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 1/14/2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Type A 5/7/2009; Type C 3/17/2008
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 2/1/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 1/31/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None 5
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review
• Clinical review(s) *(indicate date for each review)*	12/6/2012; 2/8/2012
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Pg 17 of clinical review dated 12/6/2012
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Ethics 1/11/2013; DPV1 8/15/2012; QT-IRT 5/31/2012
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None DRISK 12/31/2012
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 9/20/2012; 8/27/2012
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 1/18/2013; 3/29/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 1/23/2013; 1/2/2013; 2/14/2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 12/10/2012
• Supervisory Review(s) *(indicate date for each review)*	☐ None 12/10/2012
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/28/2012; 2/2/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 11/23/2012
❖ ECAC/CAC report/memo of meeting	☐ None 7/23/2012 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 1/16/2013; 11/13/2012; 2/28/2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Pg 92 of CMC review dated 11/13/2012
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 1/14/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

JESSICA M BENJAMIN
02/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

LABELING PMR/PMC DISCUSSION COMMENTS

Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs

Dear Ms. Dickinson:

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

We also refer to our September 4, 2012, letter in which we notified you of our target date of December 7, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On March 3, 2012, we received your March 3, 2012 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

If you have any questions, call me, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Package insert

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA M BENJAMIN
12/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284 **INFORMATION REQUEST**

Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs

Dear Ms. Dickinson:

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

We also refer to your NDA dated December 23, 2011.

We are reviewing the carton and container labels 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.

Container Labels (All Sizes)

1. Relocate the storage information and "Keep out of reach of children" to the back panel.

2. Relocate the dosage form, "Liquid" so that it appears beneath the established name.

3. Relocate the strength statement so that it appears below the dosage form and increase the prominence of the statement by using larger font.

4. Relocate the Medication Guide statement so that it appears below the strength statement and utilize a larger font so that the statement is more prominent.

5. Increase the prominence of the statement "For oral use only" and relocate the statement to the principal display panel.

6. Relocate the "each mL" statement on the principal display panel so that it appears on the side panel.

7. Include a "Usual dose statement" on the container label.

Container Label (Only 25 mL size)

1. Include the dosage form, 'Liquid' on the principal display panel, beneath the established name.

2. Include the statement, 'For oral use only' on the principal display panel.

3. Relocate the manufacturer information to the side panel to allow more space for the dosage form and route of administration, as mentioned above.

Carton Labeling

1. Relocate the strength statement so that it appears below the dosage form and increase the prominence of the statement by using larger font.

2. Relocate the Medication Guide statement so that it appears below the strength statement and utilize a larger font so that the statement is more prominent.

3. Increase the prominence of the "For oral use only" statement.

4. The carton labeling do not communicate the need for an oral dosing device, however due to the wide range of volumes that can be calculated to achieve the prescribed dose, we recommend a statement on the carton labeling that communicates to healthcare practitioners the need to dispense a dosing device that best accommodates the dose prescribed.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
12/03/2012

From:	Benjamin, Jessica
To:	Klara Dickinson
Cc:	Benjamin, Jessica
Subject:	NDA 203284 Information request
Date:	Monday, November 19, 2012 5:44:03 PM
Attachments:	NDA 203284 information request.msg

Hi Klara,

Please refer to NDA 203284 for Ravicti. As a result of our on-going review of this application, we have a follow-up information request to our request sent June 27, 2012 (attached):

For study #HPN-100-006 in adult patients, you stated that the mean HPN-100 dose was 12.5 +/- 5.5 mL. For study #
HPN-100-012 in children age 29 days - 6 years, you stated that the mean HPN-100 dose was 5.16 +/- 2.32 mL.
Provide an estimate of the mean HPN-100 doses expressed as mL/m2/day in each of these studies.

We request a response by COB November 27, 2012. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
11/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

REVIEW EXTENSION – MAJOR AMENDMENT

Hyperion Therapeutics, Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs
Hyperion Therapeutics Inc.

Dear Ms. Dickinson:

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

On August 23, 2012, we received your August 23, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 23, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 7, 2012.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
09/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284 **INFORMATION REQUEST**

Ucyclyd Pharma Inc.
c/o Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs
Hyperion Therapeutics Inc.

Dear Ms. Dickinson:

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

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

1. Provide specific genetic mutation for each patient for all studies.

2. For each neurological Adverse Event (AE), or adverse event of nausea, vomiting or headache, provide ammonia level and pharmacokinetics (PK) of phenylbutyrate (PBA) and phenylacetate (PAA) at time of AE. These data should be provided for all patients included in the safety analysis.

3. As a sensitivity analysis, for Study HPN-100-006, reproduce tables 14.2.1.1 – 14.2.4.3 along with table 14.2.7.1 (i.e., 25 total tables) from Section 14 of the clinical study report (CSR) utilizing the raw/non-normalized patient ammonia values. These non-normalized ammonia values should still be expressed in SI units (i.e. µmol/L). In addition, utilizing these non-normalized patient ammonia values, reproduce CSR Section 14 figures 14.2.3.1 – 14.2.3.3 along with figure 14.2.3.5 (4 total figures).

4. For the forty patients from Study HPN-100-106 who enrolled in study HPN-100-107, provide two figures which plot the mean (± standard deviation) concentration of blood ammonia (µmol/L) over time while these patients are being administered HPN-100 (NaPBA blood ammonia levels are not necessary for this figure). Time should range from the day of first dose of HPN-100 in Study HPN-100-106 through the point of last data cutoff in Study HPN-100-107. The first of these two figures should utilize the

normalized patient ammonia values (expressed in SI units), while the second figure should utilize the raw/non-normalized patient ammonia values (expressed in SI units).

5. Provide a subgroup analysis on gender for the primary efficacy analysis utilizing the normalized patient ammonia values (expressed in SI units). As a sensitivity analysis, reproduce this subgroup analysis utilizing the raw/non-normalized patient ammonia values (expressed in SI units).

6. Provide analyses of the relationship between the dose and important factors that investigators have taken into considerations for dose selection including but not limited to, individual age, protein intake, subtype of urea cycle disorders (UCD), and onset of UCD across all clinical trials in patients with UCD.

7. It is stated that there are no intermediate metabolites (i.e. mono- or di-glycerol phenylbutyrate). It is unclear whether these metabolites were measured in human plasma and/or in vitro studies. Guide the reviewer to the location of the supporting evidence.

8. We note that the bioanalytical assay validation, including stability testing, was done in the presence of acetonitrile. Clarify how the plasma PK samples were treated prior to storage/shipping at the clinical site for the analysis of GT4P for each study where GT4P was measured.

9. Clarify the timing of the dosing in Study HPN-100-006. It was stated on page 67 of the CSR that the third dose of HPN-100 was given 8 hours after the first dose and that this dose corresponded to dinner time. On the other hand, in Table 4 on page 22, it was stated that dinner was provided at 10 hours after the first dose of treatment.

10. Clarify the dosing frequency and the timing of HPN-100 administration for patients in Study HPN-100-012. In table 11.35 of PK report, only three doses were listed for each patient while listing 16.2.5.1. indicates that some patients received four doses.

11. We note that a summary letter report was submitted for HPN-100 (GT4P) assay in Study UP 1204-002, but it is unclear if a full bioanalytical assay report for GT4P in Study UP 1204-002 was submitted. Guide the reviewer to the location of the report.

12. We note that the positive control induced QT prolongation as early as 0.5 hours post-dose in the thorough QT study and that there was no return to a placebo/baseline-range reading. This QT-time profile after administration of moxifloxacin was rather unexpected given PK profile of moxifloxacin with a Tmax ranging 1-4 hour. Provide an explanation for these observations.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/13/2012

Executive CAC
Date of Meeting: July 17, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Alternate Member
David Joseph, Ph.D., DGIEP, Team Leader
Ke Zhang, Ph.D., DGIEP, Presenting Reviewer

Author of Draft: Ke Zhang

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

NDA# 203,284 (IND 73,480)
Drug Name: Ravicti / glycerol phenylbutyrate (GPB) / Glyceryl Tri (4-phenylbutyrate) (GT4P) / HPN-100
Sponsor: Hyperion Therapeutics

Background: HPN-100, a clear colorless to pale yellow liquid for oral administration, is a triglyceride containing three molecules of 4-phenylbutyric acid (PBA) linked to a triglyceride backbone. HPN-100 is hydrolyzed to glycerol and PBA following oral administration. PBA is then metabolized to phenylacetate/phenylacetic acid (PAA). Conjugation of PAA with glutamine followed by excretion in urine is utilized as an alternate means of metabolic disposal of nitrogen waste in patients with genetic defects in their urea cycle. The sponsor is seeking market approval of Ravicti (HPN-100) under NDA 203,284, as adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders. HPN-100 was developed for the proposed indication under IND 73,480. The same sponsor also (b) (4)

As part of the non-clinical program, two carcinogenicity studies were conducted including a 26-week oral carcinogenicity study in Tg.rasH2 mice and a 2-year oral carcinogenicity study in rats.

HPN-100 was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in human peripheral blood lymphocytes, or the rat micronucleus test. The metabolite, PBA, was not genotoxic in the Ames test, but was positive for the induction of structural chromosome aberrations in the presence of metabolic activation in the *in vitro* chromosomal aberration test in Chinese hamster ovary (CHO) cells. In the same study, PBA was negative in the absence of metabolic activation. However, PBA was negative in the presence and absence of metabolic activation in a repetition of the *in vitro* chromosomal aberration test in CHO cells. The metabolites PAA, phenylacetylglutamine (PAGN), and phenylacetylglycine (PAG) were not genotoxic in the Ames test or in the *in vitro* chromosomal aberration test in CHO cells.

Mouse 26-week Carcinogenicity Study:

Mice (Tg.rasH2) were treated by oral gavage with HPN-100 (neat) at 0 (water), 0 (water), 600, and 1000 mg/kg/day for 26 weeks. The dose levels were recommended by the Executive Carcinogenicity Assessment Committee (February 18, 2010 for IND 73,480), based on the MTD and the minimum feasible dose. Treatment with HPN-100 did not increase the incidence of any neoplasm.

Rat 2-year Carcinogenicity Study:

Rats (Crl:CD(SD)) were treated with HPN-100 (neat) at dose levels of 70, 210, and 650 mg/kg/day in males, and 100, 300, and 900 mg/kg/day in females via oral gavage for 24 months. These doses were recommended by the Executive Carcinogenicity Assessment Committee on August 12, 2008. Two control groups were used (water and corn oil). Treatment did not significantly change the survival rates. The terminal body weight was
7% and 11% lower in the high dose males and females, respectively, as compared to the water control group. The terminal body weight gain was 13% and 21% lower in the high dose males and females, respectively, as compared to the water control group.
Treatment-related non-neoplastic changes include focal hypertrophy in the adrenal cortex, pancreatic acinar cell hyperplasia, follicular cell hyperplasia in the thyroid gland, cystic endometrial hyperplasia of the uterus, Zymbal gland hyperplasia, basophilic foci in the liver (females only), and retinal atrophy in the eye (females only). Treatment with HPN-100 increased the incidence of the following neoplasms, as indicated by statistical significance in both the dose-response and pair-wise tests using the water control group, with exception of Zymbal's gland carcinoma in males: pancreatic acinar cell adenoma, carcinoma and adenoma or carcinoma, combined, in both sexes at the high dose, thyroid follicular-cell adenoma, carcinoma and adenoma or carcinoma, combined in high-dose females, adrenal cortical adenoma or carcinoma (combined) in high-dose females, uterine endometrial stromal polyp and endometrial stromal polyp or sarcoma (combined) at the high dose, and Zymbal's gland carcinoma in mid- and high-dose males and high-dose females. The increased incidence of Zymbal's gland carcinoma in males was considered to be drug- related based on the very low incidence of this neoplasm in historical control data. The tumor incidences with FDA statistical analysis are presented in the following tables.

	Organ Name	Tumor Name	0 mg Water Cont N=65	70 mg Low N=65	210 mg Med N=65	650 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Males	PANCREAS	#B ADENOMA, ACINAR C	1	0	3	8	0.000	1.000	0.243	0.008
		#M CARCINOMA, ACINAR	0	0	0	6	0.000	.	.	0.008
		ACINAR_CELL_ADENOMA or CARCINOMA	1	0	3	14	0.000	1.000	0.243	0.000

The incidence of Zymbal's gland carcinoma in males was 1/62 (water control), 2/62 (LD), 5/59 (MD) and 5/58 (HD).

	Organ Name	Tumor Name	0 mg Water Cont N=65	100 mg Low N=65	300 mg Med N=65	900 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Females	ADRENAL CORTEX	#B ADENOMA	1	2	1	7	0.004	0.509	0.735	0.027
		#M CARCINOMA	0	1	2	3	0.048	0.506	0.235	0.112
		ADENOMA or CARCINOMA	1	3	3	10	0.001	0.317	0.282	0.003
	PANCREAS	#B ADENOMA, ACINAR C	0	0	0	6	0.000	.	.	0.013
		#M CARCINOMA, ACINAR	0	0	2	6	0.001	.	0.235	0.012
		ACINAR_CELL_ADENOMA or CARCINOMA	0	0	2	12	0.000	.	0.235	0.000
	THYROID GLANDS	#B ADENOMA, FOLLICUL	0	1	2	9	0.000	0.506	0.235	0.001
		#M CARCINOMA, FOLLIC	0	2	2	5	0.012	0.253	0.235	0.024
		FOLLICULAR_CELL ADENOMA or CARCINOMA	0	3	4	14	0.000	0.129	0.053	0.000
	UTERUS	#B POLYP, ENDOMETRIA	2	5	4	12	0.001	0.217	0.305	0.004
		POLYP or SARCOMA	2	5	4	13	0.001	0.217	0.305	0.002
	ZYMBAL'S GLANDS	#M CARCINOMA	0	1	2	5	0.006	0.506	0.235	0.026

The number of Zymbal's glands examined in females was 63 (water control), 64 (LD), 65 (MD), and 62 (HD).

Executive CAC Recommendations and Conclusions: Mouse

study:

- The Committee concurred that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms. Rat study:
- The Committee concurred that the study was adequate.
- The Committee concurred that following were drug related.

  In males:

  - Pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose
  - Zymbal's gland carcinoma at the middle and high dose

In females:

- Pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose
- Thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose
- Adrenal cortical combined adenoma or carcinoma at the high dose
- Uterine endometrial stromal polyp and combined polyp or sarcoma at the high dose
- Zymbal's gland carcinoma at the high dose

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

cc:
DGIEP
DGIEP/J. Benjamin/PM
DGEIP/Dr. Zhang
DGIEP/Dr. Joseph
OND IO/A. Seifried

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/s/

ADELE S SEIFRIED
07/23/2012

DAVID JACOBSON KRAM
07/23/2012

From:	Benjamin, Jessica
To:	"Klara Dickinson"
Cc:	Benjamin, Jessica
Subject:	NDA 203284 information request
Date:	Wednesday, June 27, 2012 2:22:12 PM
Importance:	High

Hi Klara,

Please refer to NDA 203284 for Ravicti. As a result of our on-going review of this application, we have the following urgent information request:

1. Provide historical control tumor data in Crl:CD(SD) rats from the testing laboratory for the 2-year carcinogenicity study

in rats.

2. Provide a calculation of the rat to human ratio of AUC for PAA (total) in the high-dose males and females in the 2-year

carcinogenicity study, using an AUC from pediatric patients. Identify the clinical study from which the AUC value was obtained.

3. Provide a calculation of the rat to human ratio of AUC for PBA (total) in the high-dose males and females in the 2-year carcinogenicity

study. Perform separate calculations using AUC values from adult and pediatric patients, and identify the clinical studies

from which the AUC values were obtained.

We request a response by COB July 9. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

Appears this way on the original

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/s/

JESSICA M BENJAMIN
06/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284 **INFORMATION REQUEST**

Ucyclyd Pharma Inc.
c/o Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs
Hyperion Therapeutics Inc.

Dear Ms. Dickinson:

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

We also refer to your NDA dated December 23, 2011.

We are reviewing the clinical pharmacology section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In order to fully review your pharmacokinetic (PK) modeling and simulations, submit the following information:
    - Nonlinear mixed effects modeling software (NONMEM) model codes or control streams and output listings for model m31 as described in the HYPE-PCS-100 report.
    - Additional model codes or control streams for:
        i. Predicting exposure for the highest labeled sodium phenylbutyrate (NaPBA) dose and 50% of the lower labeled NaPBA dose as described in Section 4.3.1 of the HYPE-PCS-100 report.
        ii. Comparison of dosing regimens (mg/kg vs. g/m^2) as described in Section 4.3.1 of the HYPE-PCS-100 report.

    NONMEM input datasets for simulations should be submitted as SAS transport files (*.xpt). NONMEM output datasets do not need to be submitted. Model codes should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

2. Provide mean and individual PK parameters for glyceryl tri-4-phenylbutyrate (GT4P) in Study **UP-1204-001** (UCY0007) based on tables in APPENDIX 2: GT4P plasma

concentrations following administration of GT4P-F; and APPENDIX 3: GT4P plasma concentrations following administration of GT4P-API.

3. We note that intact HPN-100 (GT4P) was detected in plasma in Study UP-1204-001. In the report of Study UP-1204-001, unresolved issues such as pre-dose concentrations were noted without further explanation. However, in other studies where GT4P was measured, GT4P plasma concentrations were below detection limit at all time points. Provide an explanation for the differences in absorption of GT4P between **Study UP-1204-001** and other studies where GT4P was measured but not detectable.

4. The accumulation factor after multiple dosing was reported based on Cmax in study UP 1204-002 in hepatic impaired patients. Provide the accumulation factor based on AUC **(UP 1204-002**).

5. For Study UP 1204-003, only time-normalized AUC (TNAUC) was reported for blood ammonia. Provide individual AUC for blood ammonia without time-normalization and the sampling time period for the AUC for **Study UP 1204-003**. If such information is already submitted, provide the location of this information in the submission.

6. Provide a detailed explanation for the determination of the dose of HPN-100 for treatment naïve patients in **Study HPN-100-007**. The principal investigator may provide his/her rationale with relevant patient specific information such as protein intake at the time of dose determination.

7. We note that different assay kits for plasma ammonia were used at different study sites in **Study HPN-100-006.** For the quantitative comparison of plasma ammonia level between patients whose ammonia levels were determined using different assay methods, comparison of performance between assay kits is important. Provide information about performance comparison between different assay methods for plasma ammonia in **Study HPN-100-006**.

8. Provide the following information for each plasma ammonia assay method used in **Study HPN-100-006**:

Assay method	Site(s)	Number of subjects	Principle reaction	Linear assay range	Reference normal range specified for the assay	Specimen rejection criteria

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
06/15/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

METHODS VALIDATION MATERIALS RECEIVED

Ucyclyd Pharma, Inc.
Attention: Klara Dickinson
Sr. VP Regulatory Affairs
7720 N. Dobson Road
Scottsdale, AZ 85256

Dear Klara Dickinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ravicti (glycerol phenylbutyrate), and to our May 1, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on May 16, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
05/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

ATTENTION: Klara A. Dickinson
Senior Vice President, Regulatory Affairs and Compliance

Dear Ms. Dickinson:

Please refer to your New Drug Application (NDA) dated and received, December 23, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Glycerol Phenylbutyrate Liquid, 1.1 g/mL.

We also refer to your correspondence, dated and received February 22, 2012, requesting review of your proposed proprietary name, Ravicti. We have completed our review of the proposed proprietary name, Ravicti and have concluded that it is acceptable.

The proposed proprietary name, Ravicti 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 February 22, 2012, 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, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jessica Benjamin at (301) 796-3924

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
05/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

REQUEST FOR METHODS VALIDATION MATERIALS

Ucyclyd Pharma, Inc.
Attention: Klara Dickinson
Sr. VP Regulatory Affairs
7720 N. Dobson Road, Scottsdale, AZ 85256

Dear Ms. Dickinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ravicti (glycerol phenylbutyrate), liquid drug substance.

We will be performing methods validation studies on Ravicti (glycerol phenylbutyrate), liquid drug substance, as described in NDA 203284.

In order to perform the necessary testing, we request the following sample materials and equipments:

Current Methods

LA6-0174 revision 3 – impurities
LA6-0179 revision 2 - assay

Samples and Reference Standards

500 mg	(b) (4) secondary reference standard
10	Oral liquid finished product 25 mL containers P3326-25 mL
100 mg	(b) (4)
100 mg	
100 mg	
100 mg	
100 mg	
100 mg	
100 mg	
100 mg	
100 mg	
100 mg	
100 mg	

Equipment (These will be returned)

1	Symmetry C18, 100 mm x 4.6 mm, 3.5 µm column

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
05/01/2012

From:	Benjamin, Jessica
To:	"Klara Dickinson"
Cc:	Benjamin, Jessica
Subject:	NDA 203284 - request for information
Date:	Friday, March 23, 2012 1:36:09 PM
Attachments:	HighlightsofClinicalPharmacology.doc

Hi Klara,

Please refer to NDA 203284 for glycerol phenylbutyrate. As a result of our on-going review of this application, specifically the final results of QT Study Report HPN-100-010, we request the following information:

1. **Complete (update) the attached Clinical Pharmacology table**
2. **Update eg.xpt dataset with QTcI calculated for arm 2**
3. **Provide QTcI individual correction factor beta for each subject in arm 2 (a separate small dataset is fine)**

We appreciate a prompt response to our requests. Please let me know if you have any questions.
Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
03/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

FILING COMMUNICATION

Ucyclyd Pharma Inc.
c/o Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs
Hyperion Therapeutics Inc.

Dear Ms. Dickinson:

Please refer to your New Drug Application (NDA) dated December 23, 2011, received December 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ravicti (glycerol phenylbutyrate).

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 October 23, 2012.

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, midcycle, 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 4, 2012.

We request that you submit the following information:

1. Please submit the following information for reviewers to recreate pharmacokinetic modeling and simulations:

    - NONMEM model codes or control streams and output listings should be provided for all major model building steps. These should include the following models listed in Table 5.3:1 in the HYPE-CS-004 report: m0, m6a, m8a, m15 and m18. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

    - Model codes or control streams should be provided for the following simulations:
        i. Exposure predictions for the highest labeled NaPBA dose and 50% of the lower labeled NaPBA dose, as described in Section 5.4.2 of the HYPE-CS-004 report and summarized in Table 5.4:3 and Table 5.4:4.
        ii. Exposure comparison across different age groups, as described in Section 5.4.5 of the HYPE-CS-004 report.
        iii. Expousre prediction in patients < 6 years of age, as described in Section 5.4.6 of the HYPE-CS-004 report.

        NONMEM input datasets for simulations should be submitted as SAS transport files (*.xpt). NONMEM output datasets do not need to be submitted. Model codes should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

2. Submit a rationale for assuming the applicability of foreign data collected in clinical trials to the U.S. population.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The Highlights Overview section is limited in length to one-half page. Submit a waiver to the application since this section is longer than one-half page

2. The Highlights Limitation section is duplicated in your label. Only one Highlights Limitation statement must be placed at the beginning of the Highlights section, **bolded**, and it should read as follows: **"These highlights do not include all the information needed to use RAVICTI safely and effectively. See full prescribing information for RAVICTI."**

3. For drug products other than vaccines, the verbatim **bolded** statement "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or**

www.fda.gov/medwatch" must be included under Adverse Reactions, and must be present only once. You have included this statement twice in your label. Please delete one of the statements.

4. A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

5. Remove the periods after the numbers for the section and subsequent headings in the Table of Contents.

6. Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

7. For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

   "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

We request that you resubmit labeling that addresses these issues by March 26, 2012. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
03/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

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

DATE: March 21, 2012

SUBJECT: Memo of 90-day conference

APPLICATION/DRUG: NDA 203284

FDA Participants:
Dr. Victoria Kusiak, Deputy Director, ODE 3
Dr. Donna Griebel, Division Director, DGIEP
Dr. Andrew Mulberg, Deputy Director, DGIEP
Dr. Lynne Yao, Medical Team Leader
Dr. Nancy Snow, Medical Reviewer
Dr. Insook Kim, Clinical Pharmacology Reviewer
Dr. Sue Chih Lee, Clinical Pharmacology Team Leader
Dr. Kevin Krudys, Pharmacometrics Reviewer
Dr. Christine Garnett, Pharmacometrics Team Leader
Dr. Ke Zhang, Nonclinical Reviewer
Dr. David Joseph, Nonclinical Team Leader
Dr. Mike Welch, Biostatistical Team Leader
Kendra Worthy, DRISK, OSE
Anne Tobenkin, OSE
Jessica Benjamin, MPH, SeniorRegulatory Project Manager

Sponsor Participants:
Klara Dickinson, Senior VP of Regulatory Affairs and Compliance, Hyperion
Dr. Bruce Scharschmidt, Chief Medical Officer, Hyperion

(b) (4)

Discussion:
This was a 90-day conference for the new NDA 203284, glycerol phenylbutyrate for the chronic management of urea cycle disorders. The intent of this meeting was for the sponsor to present their new NDA to the FDA and field any questions we may have regarding the application. The sponsor's presentation is attached.

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/s/

JESSICA M BENJAMIN
03/22/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

NDA ACKNOWLEDGMENT

Ucyclyd Pharma Inc.
c/o Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs
Hyperion Therapeutics Inc.

Dear Ms. Dickinson:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Ravicti (glycerol phenylbutyrate)

Date of Application: December 23, 2011

Date of Receipt: December 23, 2011

Our Reference Number: NDA 203284

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JESSICA M BENJAMIN
01/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73,480 **MEETING MINUTES**

Ucyclyd Pharma Inc.,
Wholly owned subsidiary of Medicis Pharmaceuticals Inc.
Attention: Klara A. Dickinson
Senior Vice President Regulatory Affairs and Compliance
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Dickinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Glycerol Phenylbutyrate (HPN-100).

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2010. The purpose of the meeting was to address any major unresolved problems, identify those data that Hyperion is relying on to demonstrate the quality, purity and potency of the GPB, acquaint FDA reviewers with the general information to be submitted in the marketing application; discuss appropriate data required to support (b) (4) as a glycerol phenylbutyrate (GPB) drug substance supplier, and discuss the best approach to the presentation and formatting of data in the marketing application.

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

If you have any questions, call Cathy Tran-Zwanetz at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 8, 2010 at 10:00 AM
Meeting Location: FDA, White Oak, Building 22, Room 1313

Application Number: IND 73,480
Product Name: Glycerol Phenylbutyrate
Indication: Urea Cycle Disorder
Sponsor/Applicant Name: Hyperion Therapeutics

Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Cathy Tran-Zwanetz

FDA ATTENDEES

Marie Kowblansky, Ph.D., CMC Lead
Zhengfang Ge, Ph.D., CMC Reviewer
Cathy Tran-Zwanetz, Regulatory Project Manager

SPONSOR ATTENDEES

Hyperion Representative:
Klara A. Dickinson, Senior Vice President Regulatory Affairs and Compliance
Kamal Sigel, MS., Director, Quality Assurance

Chemical Development Consultant:
(b) (4)

1.0 BACKGROUND

Sponsor summarized the face-to-face meetings that have transpired between the Food and Drug Administration (FDA) and the Sponsor (either Ucyclyd Pharma or Hyperion) regarding the development of HPN-100 for the treatment of UCD. The FDA granted orphan drug designation to HPN-100 as a maintenance treatment of patients with deficiencies in enzymes of the urea cycle (Designation Request number 05-2035 on May 5, 2009) and Fast Track Designation on October 4, 2010. Hyperion believes the arguments presented in its August 2, 2010 Fast Track Request (IND SN.088) are fully supported by the new data from the Phase 3 and long-term safety studies and that the Fast Track designation awarded by FDA remains warranted.

List of Regulatory Meetings and Meeting Minutes
Meeting Date/Meeting Type/Purpose/Date of Meeting Minutes
12/12/2005 Type B Pre-IND Meeting 01/09/2006
03/17/2008 Type C Clinical and Preclinical Development Plan 04/10/2008
01/14/2009 Type B End of Phase 2 (EOP2) Meeting 04/14/2009
05/07/2009 Type A Special Protocol Assessment (SPA) Request 06/07/2009
a Refer to Appendix F for copies of meeting minutes

List of CMC Related FDA Correspondence
Letter Date Letter Type
01/24/2007 CMC comments and recommendations based on completed IND review
05/26/2010 Office of New Drug Quality Assessment Response to Hyperion Request for Advice Regarding CMC
09/30/2010 Office of Compliance Response to Hyperion Request for Advice Regarding Validation

The following summarizes the key recommendations and/or agreements made during meetings listed above, in some instances Hyperion has provided comment in italicized text.

The primary objectives of this pre-NDA meeting are to address any major unresolved problems, identify those data that Hyperion is relying on to demonstrate the quality, purity and potency of the GPB, acquaint FDA reviewers with the general information to be submitted in the marketing application; discuss appropriate data required to support (b) (4) as a GPB drug substance supplier, and discuss the best approach to the presentation and formatting of data in the marketing application.

2. DISCUSSION

Drug Substance

1. As discussed in Sections 6.2.1.1 and 10.4.2.6.2, Hyperion approached (b) (4)) to become a second supplier of GPB drug substance. (b) (4) was requested to develop a GPB manufacturing process having the following characteristics: (b) (4)

(b) (4) In addition to the (b) (4) information, Hyperion intends to present the chemistry manufacturing and controls (CMC) information on (b) (4) GPB drug substance process in the NDA.

a. Hyperion will present all CMC information from the (b) (4) registration campaign, including 6 months of real-time and accelerated stability data from the three registration lots. Will the Agency find this information acceptable for the review and consideration of (b) (4) as a commercial supplier of GPB Drug Substance?

FDA Response:
Your proposal for submission of CMC data for the (b) (4) drug substance is acceptable. However, in your NDA submission, you will need to commit to provide stability data (in the commercial container closure) for the first three batches of product manufactured with (b) (4) drug substance.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

b. Hyperion intends to include a Module 2.3.S and 3.2.S for the (b) (4) Process and a Module 2.3.S and 3.2.S for the (b) (4) process. Does the Agency find this acceptable?

FDA Response:
Yes, this is acceptable.
Discussion:
The sponsor accepted the responses, and no further discussion was needed.

c. Hyperion intends to generate a comparability report that compares the GPB drug substance made from the (b) (4) and (b) (4) processes. Hyperion intends to place this report in Module 3.2.R because it applies to both GPB drug substance processes. Does the Agency find this acceptable?

FDA Response:
Putting this information directly under 3.2S is preferred.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

2. A detailed description of the GPB impurities and the studies performed to identify unknown impurities occurring at a level of = (b) (4)% is presented in Section 10.4.3.2.1 and 10.4.3.2.3, respectively. Two lots of drug substance had one or more unknown impurities at levels of (b) (4)% at release. Levels of (b) (4)% of unknown impurities were observed in various lots of drug substance at intermittent time points during stability studies. These impurities did not increase

with time at various storage conditions. Hyperion has involved four different laboratory groups in attempts to identify four unknowns. Several structures were proposed for these unknown impurities based on LC MS data, and the synthesis of several compounds resulted in confirming the structure of one of the four unknown impurities as being present in GPB. Additional efforts at impurity identification are predicted to offer little chance of success. Does the Agency agree that further attempts to identify these low level unknown impurities are no longer required (note: Hyperion will continue to identify new unknown impurities, should they arise)?

FDA Response:
In view of our response to question 3, only impurities present at 0.1% or higher will need to be identified in the drug substance or drug product.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

3. Hyperion sought guidance from the Agency as part of its request for Advice submitted to IND 73,480 in March 2010 (SN.075). However, Hyperion would like to discuss and obtain the Agency feedback on the specification requirements specifically for impurities. As summarized throughout the Briefing Document the GPB drug substance is (b) (4) Due to the fact that the drug substance (b) (4), Hyperion believes it is warranted to apply the ICH guidance standards for Impurities in New Drug Products (Q3B(R2) to GPB drug substance. The maximum total daily dose of the drug product (b) (4) will be (b) (4) g/day. Therefore, Hyperion is proposing the following specification: Reporting Threshold (b) (4)%; Identification Threshold (b) (4)%; and Qualification Threshold 0.15%. Does the Agency agree with this approach?

FDA Response:
Since your drug product contains (b) (4) it will be acceptable for (b) (4) impurity limits to conform to the ICH recommendations for new drug products, as you have proposed. However, for five identified impurities you have proposed impurity limits that range between (b) (4)% (Table 48 of the briefing package), significantly exceeding the 0.15% ICH qualification threshold for (b) (4) g/day administration of the drug. Consequently, when you submit your NDA, for each of your identified impurities in the specification, you will need to limit the amount to 0.15%, or toxicologically qualify them if a higher limit is proposed.

Discussion:
For three of the identified impurities mentioned above, FDA agreed that the impurity limits proposed by Hyperion would be acceptable, specifically: (b) (4) *. This decision is based on the fact that GPB is a prodrug of PBA and the* (b) (4) *For the other two identified impurities,* (b) (4)*, the proposed* (b) (4)*% limits will need to be justified by the sponsor. Although it is reasonable from the CMC perspective to*

expect that (b) (4) *will be* (b) (4)*, leaving only a small amount of the* (b) (4)*", the toxicology reviewer (not present at this meeting) would like to see data to support this. In vitro data may be sufficient for this purpose. The following possible approaches for justification were discussed: 1) the sponsor may have data available from animal studies that were already completed, showing that the* (b) (4) *were absent from plasma, 2) demonstrate similar rates of hydrolysis for the* (b) (4) *in simulated intestinal fluid. Hyperion will submit an amendment to the IND, with a justification for the* (b) (4)*% limit.*

4. Glycerol phenylbutyrate is a triglyceride. However, it does not meet the definition of an oil as defined by FDA (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm). An oil is defined as "An unctuous, combustible substance which is liquid, or easily liquefiable, on warming, and is soluble in ether but insoluble in water. Such substances, depending on their origin, are classified as animal, mineral, or vegetable oils." A liquid is defined as a pure chemical in its liquid state (A liquid is pourable; it flows and conforms to its container at room temperature. It displays Newtonian or pseudoplastic flow behavior). Therefore, Hyperion has determined that the dosage form of GPB is a liquid and not an oil. Does the Agency agree?

FDA Response:
Our current thinking is that this dosage form may be defined as a liquid, but it is possible that our opinion may change as we review the information in your NDA.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

5. Proposed Expiry Period of 36-month: The following table summarizes the stability data that will be included in the NDA to support a proposed expiry period of 36 months all three configurations. The NDA will include real time stability data at 25°C / 60% RH storage (recommended storage condition) and accelerated stability data at 40°C / 60% RH storage. In addition, formal statistical regression analyses of all ICH recommended storage conditions will be presented.

Lot Number	Drug Substance Lot Number	Container Closure	Stability Initiation Date	Current Data Available	Data at Time of NDA Filing
(b) (4) Glass					
XA171	25003750	450-mL (b) (4)	September 2006	36 months	36 months
XA179	25006835	450-mL	September 2006	36 months	36 months
XA210B	27000906	25-mL	February 2009	18 months	24 months
XA223A	270007264	25-mL	September 2009	12 months	12 months
(b) (4) Glass					
XA210A	27000906	25-mL (b) (4)	February 2009	18 months	24 months
XA223B	270007264	120-m	September 2009	12 months	12 months

Hyperion intends to make available all three fill presentation ((b) (4) bottles), and estimates that the (b) (4) bottle will be the most widely distributed configuration with the (b) (4) being the second, and the (b) (4) being the most infrequently distributed configuration. Hyperion believes that the data generated from the studies listed above should support the approval of these three presentations, either in a glass or (b) (4) bottle. As discussed in detail in Section 10.5.7.1 and Section 10.5.7.4 the stability data in the (b) (4) glass presentation are extremely comparable. In addition, based on photostability studies, GPB is photo-stable. Does the Agency agree that the data presented would support its consideration of the three presentations in either (b) (4) or glass bottle?

FDA Response:
Based on the data you have presented, we believe that for the (b) (4) presentations either (b) (4) glass will be acceptable. However, for the (b) (4) container, only (b) (4) glass will be permitted until stability data in (b) (4) glass are provided.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

Additional Comment

Per ICH Q6A, please include testing for Uniformity of Dosage Units in the drug product specification when you submit your NDA.

Discussion:
FDA agreed with Hyperion that in-process testing could be conducted to fulfill this requirement.

Additional Question (received via email)

We have run into some issues with our current fill/finisher, Lyne Laboratories. They have recently communicated a lack of interest to be the manufacturer (packager) of the drug product unless the company (b) (4) . I am trying to ascertain if Lyne will take on our product if we come to agreement or if they have no interest in the business. Should they inform Hyperion that they refuse to package the commercial product, Hyperion is does not have the time to obtain extensive stability data from a new facility. Would it be possible to add this to the discussions on Wednesday? I realize this question is not in the briefing document, so the Agency may not be prepared for the discussion and there fore not able to discuss. If that is the case, we still wish to have our meeting. However, since the drug product is a (b) (4) Hyperion feels using previously FDA inspected and approved manufacturer, that fills the product using the exact container closure system, would warrant a minimal data package to support the approval of the facility. We would like to determine if submitted the NDA with data from the new manufacturer, would the Agency the NDA and data for review in the NDA application?

Discussion:

Since the drug product manufacturing operation (b) (4) *FDA agreed with Hyperion's proposal to submit the NDA with only minimal stability data (three months, at most) for product manufactured at the new manufacturing site, and the stability data for product manufactured at Lyn Laboratories would serve as primary stability data to support expiration dating.*

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

Sponsor will submit an amendment to the IND, justifying limits of (b) (4)% for the (b) (4) impurities.

5.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

CATHERINE A TRAN-ZWANETZ
01/05/2011

MARIE KOWBLANSKY
01/05/2011

MOO JHONG RHEE
01/05/2011
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073480 **MEETING MINUTES**

Hyperion Therapeutics, Inc.
601 Gateway Boulevard, Suite 200
South San Francisco, CA 94080

Attention: Klara A. Dickinson
Sr. Vice President Regulatory Affairs and Compliance

Dear Ms. Dickinson:

Please refer to your Investigational New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Glycerol Phenylbutyrate (HPN-100).

We also refer to the meeting between representatives of your firm and the FDA on December 7, 2010. The purpose of the meeting was to discuss the planned NDA submission of HPN-100.

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 me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes and slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: December 7, 2010 from 2-3 PM EST
Meeting Location: FDA White Oak Campus

Application Number: IND 073480
Product Name: HPN-100
Indication: Maintenance treatment of patients with deficiencies in enzymes of the urea cycle
Sponsor/Applicant Name: Hyperion Therapeutics, Inc.

Meeting Chair: Donna Griebel, M.D.
Meeting Recorder: Jessica M. Benjamin

Division of Gastroenterology Products
Donna Griebel, M.D., Director
Andrew E. Mulberg, M.D., FAAP, CPI, Deputy Director
Lynne Yao, M.D., Medical Team Leader
Tamara Johnson, M.D., Medical Reviewer
David Joseph, Ph.D., Pharmacology Team Lead
Ke Zhang, Ph.D., Pharmacology Reviewer
Jessica M. Benjamin, Regulatory Project Manager

Division of Biometrics III
Behrang Vali, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology
Insook Kim, Ph.D., Reviewer
Li Li, Ph.D., Reviewer

Office of Orphan Products Development
Jeff Fritsch, R.Ph., Regulatory Review Officer

SPONSOR ATTENDEES

Dion Coakly, Pharm.D.	Global VP, Clinical Operations
Klara Dickinson	Sr. VP, Regulatory Affairs and Compliance
Masoud Mokhtarani, M.D.	VP, Clinical Development
Bruce Scharschmidt, M.D.	Sr. VP and Chief Medical Officer
Darlina Sola	Regulatory Affairs
(b) (4)	
Wendy Swenson, Ph.D.	Project Management
(b) (4)	

BACKGROUND:

On November 1, 2010, Hyperion Therapeutics submitted a Pre-NDA meeting package to the Agency for their investigational product, HPN-100, for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle. Each of Hyperion's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the sponsor on December 6, 2010.

MEETING OBJECTIVES:

The main meeting objective was to discuss the clinical and nonclinical aspects of the planned NDA submission for HPN-100.

DISCUSSION POINTS:

Clinical Efficacy Questions

Question 1. *The phase 3 efficacy trial was conducted in accordance with the Special Protocol Agreement reached with the FDA (refer to FDA letter dated June 30, 2009, Appendix F). Data from this study indicate that HPN-100, when given at a PBA molar equivalent dose, is non-inferior to NaPBA in controlling plasma ammonia concentrations (see Section 10.4.2.3). The upper boundary (1.034; original scale) of the 95% confidence intervals for the difference between ammonia levels on HPN-100 and NaPBA was less than the predefined non-inferiority margin of 1.25. Analyses of the intent to treat (ITT), modified ITT (MITT), and per-protocol (PP) populations all yielded very similar results. Venous ammonia values assessed as 24 hour AUC ($NH3_{24\text{-}hour\ AUC}$) were non-significantly lower on HPN-100 vs. NaPBA (865.8 ± 660.5 µmol/L vs. 976.6 ± 865.4 µmol/L, respectively), as were average daily mean ammonia values (34.71 ± 25.166 µmol/L vs. 38.41 ± 31.778 µmol/L, respectively) and mean maximum ammonia values (60.4 ± 46.213 µ µmol/L vs. 70.83 ± 66.705 µmol/L, respectively). Does the Agency find* (b) (4)

FDA Response:

No, we do not agree. As we have previously advised you, pediatric patients constitute an important population of UCD patients who would potentially benefit from the availability of HPN-100, and who will be prescribed this product if approved. Furthermore, based on PK data from your Phase 2 study in pediatric patients (HPN-100-005), treatment with HPN-100 powder formulation resulted in a 90% higher PAA exposure than treatment with NaPBA. Increased exposure to PAA is a safety concern because exposure to PAA has been associated with neurotoxicity in human and animal studies. Therefore, the lack of sufficient safety and efficacy in the pediatric population is a serious concern. As stated during the EOP2 meeting on

January 14, 2009, a pediatric clinical trial evaluating dosing and safety in pediatric patients is necessary because HPN-100 will be used in pediatric patients. UCDs are commonly diagnosed in infancy and childhood, and your formulation (liquid and improved palatability) would lead to off label use in children (a significant proportion of the UCD population).

Hyperion has submitted PK data from Phase 2 studies in pediatric patients that demonstrated that PK in children and adults is not comparable, and that PAA exposure (both Cmax and AUC) in children is roughly doubled. This further increases our safety concerns about not having adequate pediatric data prior to product approval. Therefore, a clinical trial evaluating appropriate dosing and safety in pediatric patients is needed. We recommend that the results from a study evaluating dosing and safety of HPN-100 in pediatric UCD patients be included at the time of the submission of the NDA.

We recommend that you consider studying the doses in pediatric patients, which would provide comparable systemic exposure to PBA and PAA to those in adults. With potential CNS safety concerns associated with high systemic exposure to PAA and the possibility of elevated systemic exposure in subjects with hepatic impairment, it is important to identify the lowest effective dose as an initial dose.

Discussion:
The Division continues to express their concern regarding the potential for off-label use with the pediatric population. The Sponsor (b) (4) Specific review issues are likely include dosing in patients under 6 years of age and better understanding of the PAA levels in patients 6-17 years of age.

Question 2. *As listed in Table 4 (Section 6.2.1), and Table 42 (Section 10.9), the proposed NDA will include four UCD clinical studies: two phase 2 studies in adult and pediatric subjects (UP 1204-003 and HPN-100-005), a single phase 3 pivotal efficacy study (HPN-100-006), and 12-month open-label safety study, (HPN-100-007). Note that the phase 2 pediatric study HPN-100-005 also includes a 12-month safety extension. The proposed NDA will also include three phase 1 studies: single dose study in healthy volunteers (UP 1204-001), multiple dose study in hepatic impaired (cirrhotic) subjects and healthy volunteers (UP 1204-002), a thorough QTc study in healthy volunteers (HPN-100-010); and Part A of an on-going phase 2 study in cirrhotic subjects with episodic hepatic encephalopathy (HE) (HPN-100-008).*

Does the Agency find (b) (4) *?*

FDA Response:

No, we do not agree (see response to question 1).

Discussion:
There was no further discussion of this point.

Question 3. *The long term safety studies, HPN-100-005 and HPN-100-007 will be* (b) (4) *Hyperion proposes to include* (b) (4) *. Does the Agency agree with this approach or prefer* (b) (4) *?*

FDA Response:

No we do not agree. As stated during the EOP2 meeting held on January 14, 2009, we continue to recommend a minimum of 35-40 subjects with 12 months of safety data at the time of the NDA submission. Therefore, we recommend that your application include safety data that meet this criterion at the time of your NDA submission.

Discussion:
There was no further discussion of this point.

Question 4. *A phase 2 study (HPN-100-008) in cirrhotic subjects with episodic HE is being conducted* (b) (4) *. This study consists of two parts. Part A was an open label safety run-in to Part B, a double-blind placebo controlled phase. The purpose of Part A of the study was to evaluate the tolerability of two BID dosing regimens (9 mL and 6 mL) prior to initiating the double-blind phase of the study. Part A is complete, and based on the outcome of this study, Part B was initiated with a 6 mL BID dosing regimen. In order to provide full disclosure and additional safety and dosing information on cirrhotic subjects, Hyperion is proposing to provide an interim CSR, which will summarize the results of Part A of study HPN-100-008. Does the Agency agree with this approach or prefer that the interim CSR not be provided?*

FDA Response:

An interim CSR is acceptable for study HPN-100-008; however, a 120-day safety update is also required to report any additional safety findings from any ongoing clinical studies.

Discussion:
There was no further discussion of this point.

Question 5. *The proposed pooled analyses include the following: 24-hour area under the curve for blood ammonia ($NH3_{24\text{-}hour\ AUC}$) on steady state HPN-100 vs. NaPBA;*

Maximum ammonia values observed on NaPBA versus HPN-100; Ammonia values over time; correlation between U-PAGN (24-hour Excretion) and $NH3_{24\text{-}hour\ AUC}$; correlation between U-$PAGN_{24\text{-}hour\ Excretion}$ and dose of HPN-100 and/or NaPBA; rate (percentage) of ammonia values above the upper limit of normal (ULN) on NaPBA vs. HPN-100; and glutamine levels at steady state on NaPBA vs. HPN-100. Does the Agency agree on the proposed methods for integrating the efficacy data?

FDA Response:

The proposed methods appear acceptable.

Discussion:
There was no further discussion of this point.

Question 6. *In brief, the ISE analyses will be performed using the ITT population and will be repeated for subgroups based on baseline demographic and UCD characteristics including the following: Age groups 6-11 years, 12-17, 18+ years; gender; UCD type: OTC deficiency, non-OTC deficiency; age at onset: neonatal or infant (birth to <2 years), child or adolescent (>2 to <18 years), and adult (≥18 years). Subgroups based on race will not be examined individually due to low numbers of non-white subjects. Does the Agency agree with the proposal?*

FDA Response:

We agree.

Discussion:
There was no further discussion of this point.

Question 7. *The FDA April 2009 Guidance for Industry "Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document" notes that there may be situations in which Sections 2.7.3, Summary of Clinical Efficacy (SCE) would be sufficiently detailed to serve as the narrative portion of the ISE while still concise enough to meet the suggested size limitations for Module 2. In such situations, the ISE can be split across Module 2 and Module 5, with the narrative portion located in Section 2.7.3 and the appendices of tables, figures and datasets located in Section 5.3.5.3. Section 2.7.3 SCE will fulfill all requirements of the ISE and ISS textual part as required in accordance with NDA regulations 21 CFR 314.50(d)(5)(v) and meet the prescribed size limitations for Module 2. Because of the small datasets, Hyperion does not intend to* (b) (4) *The results of the integrated analyses will be summarized in the Module 2.7.3, with the corresponding tables (approximately 50 tables), listings (approximately 8 listings), and figures (approximately 8 figures) being provided in Module 5.3.5.3. Does the Agency find this approach acceptable?*

FDA Response:

This approach is not acceptable. Section 2.7.3 Summary of Clinical Efficacy may serve only as the narrative portion for the ISE, not the ISS. The narrative portion of the ISS should be placed in Section 2.7.4 Summary of Clinical Safety. It is acceptable to locate the appendices of tables, figures, and datasets in Module 5. However, adequate links should be provided for tables, figures, or datasets referenced in the narrative SCE.

Discussion:
There was no further discussion of this point.

Clinical Safety Questions

Question 8. Does the Agency find the overall number of subjects exposed to HPN-100 (see Section 10.5.2 of the briefing document) adequate to accept the NDA filing?

FDA Response:

No, we do not agree (see response to question 3)

Discussion:
There was no further discussion of this point.

Question 9. Hyperion intends to submit the proposed NDA at the (b) (4). At this time safety data on all UCD subjects treated with HPN-100 for at least (b) (4) months will be presented (see Section 10.5.1 and Table 27). In addition, safety data from (b) (4) UCD subjects treated for 12 months will be summarized as well as for (b) (4) UCD subjects treated for (b) (4) months. Hyperion acknowledges that the EOP2 meeting minutes indicate that the FDA recommended 35-40 subjects with 12 months of safety data. Hyperion believes the proposed dataset is consistent with ICH E1 guidance recommendations for chronic, non-life threatening conditions. Will the Agency accept the NDA filing with (b) (4) UCD subjects exposed with HPN-100 for 12 months?

FDA Response:

We do not agree (see response to question 3). Additionally, we note that urea cycle disorders constitute a group of metabolic disorders that are considered to be life-threatening, and therefore, ICH E1 recommendations do not apply for this product.

Discussion:
There was no further discussion of this point.

Question 10. The summary of safety in Module 2.7.4 will focus on summarizing the safety data of HPN-100 based on the eight clinical studies that will be included in the proposed NDA (see Question 2, Table 4 and Table 42) and will grouped and

analyzed as follows: UCD Studies with control periods (HPN-100-005, HPN-100-006, and UP 1204-003); UCD Studies with long term open-label follow-up (HPN-100-007 and HPN-100-005); Studies including healthy volunteers (UP 1204-001, UP 1204-002, and HPN-100-010); and Studies including hepatic impaired subjects (UP 1204-002 and HPN-100-008). Does the Agency agree with the grouping of the studies?

FDA Response:

We agree.

Discussion:
There was no further discussion of this point.

Question 11. *Adverse events (AEs), hyperammonemic crises, safety labs, electrocardiogram (ECG) and vitals will be summarized separately for the following UCD subgroups: Age groups 6-11 years, 12-17, ≥18 years; gender; UCD type: OTC deficiency, non-OTC deficiency; age at onset (for UCD patients): neonatal or infant (birth to ≤2 years), child or adolescent (>2 to <18 years), and adult (≥18 years). Does the Agency agree with this approach to analyzing the safety data?*

FDA Response:

We agree.

Discussion:
There was no further discussion of this point.

Question 12. *Duration of HPN-100 exposure will be summarized in the following groupings: 0-3 months, >3-6 months, >6-9 months, >9-12 months. For those subjects who may have >12 months exposure from the Treatment protocol HPN-100-011, Hyperion will present a narrative discussion of deaths, other SAEs, and other significant AEs. A formal analysis of HPN-100-011 will not be provided. Does the Agency find this approach acceptable?*

FDA Response:

We agree with this approach.

Discussion:
There was no further discussion of this point.

Question 13. *Hyperion* (b) (4) *because these are provided for the individual studies. Does the Agency find this acceptable?*

FDA Response:

We do not agree. The ISS should include fully integrated tables of key safety findings reflecting the entire safety population. Key safety findings that should be reported in the ISS include serious adverse events, common adverse events, events leading to subject discontinuation, significant safety issues, clinical safety assessments, and safety laboratory assessments.

Discussion:
There was no further discussion of this point.

Question 14. Similar to the ISE, Hyperion proposes that Module 2.7.4, Summary of Clinical Safety (SCS) would be sufficiently detailed to serve as the narrative portion of the ISS while still concise enough to meet the suggested size limitations for Module 2. As such, Hyperion intends to split the ISS across Module 2 and Module 5, with the narrative portion located in Section 2.7.4 and the appendices of tables, figures and datasets located in Section 5.3.5.3. Section 2.7.4 SCS will fulfill all requirements of the ISS textual part as required in accordance with NDA regulations 21 CFR 314.50(d)(5)(vi) and meet the prescribed size limitations for Module 2. The narrative portion of the ISS will reside in Module 2.7.4 and the post-text tables, figures and datasets for the ISS databases will be placed in Section 5.3.5.3. A clear explanation will be included in Module 2 and Module 5 linking to the respective documents located in the two modules. Does the Agency concur with this approach?

FDA Response:

This approach is acceptable.

Discussion:
There was no further discussion of this point.

Question 15. Hyperion believes the identified risks can be adequately mitigated through its proposed (b) (4) *summarized in Section 10.2.4 acceptable for the initial NDA filing?*

FDA Response:

A final decision regarding the requirement for a REMS will be made during the review cycle. Additionally, your (b) (4) **will be reviewed at the time of the NDA submission and, therefore, it is premature to comment on the adequacy of your plan at this time.**

Discussion:
There was no further discussion of this point.

Question 16. *In the EOP2 meeting minutes dated April 14, 2009 the Agency made the following comment "Please be aware that because of the small numbers of subjects available for study and the proposed chronic use of this product, additional safety data will be requested as a post-marketing requirements (PMRs) at the time of NDA approval. A long-term safety study (7-10 years) to assess growth and neurocognitive outcome and an establishment of a registry should be anticipated." As the Agency is aware, the UCD Consortium-sponsored longitudinal study, which is fund by the NIH under the auspices of the Orphan Drug Act, has already been enrolling for nearly 5 years. Hyperion believes that establishing a second registry that would directly compete with the NIH-funded registry for patient enrollment in this orphan population would be difficult and potentially jeopardize the UCD Longitudinal Study. If time permits at the preNDA meeting, Hyperion would like to more fully understand the Agency's thinking in this regard and how this may or may not impact Hyperion's* (b) (4)

FDA Response:

We understand that establishment of a separate registry from the UCD Consortium-sponsored longitudinal study may not be productive or feasible. However, we recommend that you consider all available options for collection of long-term safety data, including the use of the UCD registry as part of a post-marketing plan to evaluate the long-term safety of your product.

Discussion:
There was no further discussion of this point.

<u>Clinical Pharmacology</u>

Question 17. *Hyperion intends to present adult and pediatric analysis that include PK/PD based on weight adjustments, ammonia analyses during the switch over periods, long-term ammonia control, and safety. Does Agency agree on the methods for analyzing the effects between adult and pediatric subjects summarized in Section 10.3.2.5 and 10.3.2.7, and Table 19? Are there any other specific analyses the Agency would recommend?*

FDA Response:

We do not agree that AUC and Cmax in pediatric patients were normalized by adult body weight and dose. The AUC and Cmax should be presented and compared as they are with those in adults. You may consider normalizing appropriate PK parameters by actual body weight and actual dose for further analysis and interpretation of the data. We can not comment on the exposure-response relationship because the meeting materials do not include sufficient information. However, we have the following recommendations:

1. **We request that you provide a table of individual PK parameters and PD parameters with relevant information such as actual body weight, actual dose per dosing and formulation if different from the TBM formulation.**

2. **Doses used in different trials should be presented in a standardized manner with relevant demographic information. If available, dietary protein intake information should be provided.**

3. **Datasets for raw data and PK parameters from all clinical trials should be submitted.**

4. **You may consider a population PK approach to characterize PK.**

Discussion:
There was no further discussion of this point.

Datasets and Case Report Form Questions

Question 18. Hyperion intends the raw data for studies listed in Table 42 to be provided in CDISC SDTM (Version 1.2, Implementation Guide Version 3.1.2) format for all studies. Analysis datasets will be presented CDISC ADaM format (Version 2.1, Implementation Guide Version 1.0) for the following studies: HPN-100-005, HPN-100-006, HPN-100-007, and the ISE and ISS. For study UP 1204-003, the analysis dataset will be provided in accordance with Study Data Specifications (version 1.5.1), withdrawn 1999 FDA guidance. Hyperion does not intend to provide analysis datasets for the Phase 1 studies UP 1204-001, UP 1204-002, or HPN-100-010. Hyperion will provide the program files for the Phase 3 efficacy study only (HPN-100-006). Does the Agency concur with this approach?

FDA Response:

We agree with this approach. In addition we request that you also include, within the case report tabulations for studies HPN-100-005, HPN-100-006, and HPN-100-007, an annotated case report form (aCRF) and appriopriate metadata separately for both the SDTM and ADaM datasets. We prefer that these metadata conform to the latest CDISC/Define.XML standard, however a legacy Define.PDF format is also acceptable.

Discussion:
There was no further discussion of this point.

Question 19. Hyperion intends to provide narratives and case report forms (CRFs) for patients who died during the clinical study (there have been no deaths to date), who experienced an SAE, and/or discontinued due to an AE, whether believed to be drug related or not. Does the Agency concur with this approach?

FDA Response:

We agree. However, during the course of review, it may be necessary for you to provide additional case report forms as required for adequate review of the application.

Discussion:
There was no further discussion of this point.

Nonclinical

Question 20. Does the Agency find the non-clinical data package acceptable for filing the NDA application?

FDA Response:

Yes.

Discussion:
There was no further discussion of this point.

Question 21. At the time of NDA submission, a final study report from 6-month transgenic mouse carcinogenicity will be provided. For the 2-year rat carcinogencity study Hyperion will provide an audited draft report that will include histopathology; however, the statistical analysis of the tumor dataset (and the tumor datasets) will not be available. Hyperion proposes to submit the full report, with the statistical analysis of the tumor dataset (b) (4) *Does the Agency agree with this approach?*

FDA Response:

No. The final report of the 2-year rat carcinogenicity study including statistical analysis of the tumor dataset should be provided at the time of your original NDA submission.

Discussion:
The Division stated that complete carcinogenicity study should be provided at the time of NDA submission. If a complete study is not submitted, it may be a filing issue.

Post-meeting note:
The Agency will perform a filing review of your original NDA submission (i.e. the audited draft report of the 2-year rat carcinogenicity study) to determine whether the delay in submission of the final carcinogenicity study report, statistical analysis, and tumor dataset can justify a refuse-to-file action.

Procedural

Question 22. HPN-100 was granted orphan drug status for maintenance treatment of patients with deficiencies in enzymes of the urea cycle on April 27, 2009 (Designation

Request number 05-2035), and (b) (4) *Does the Agency agree this is acceptable for NDA filing?*

FDA Response:

(b) (4) **, we consider the evaluation of safety and dosing of HPN-100 in pediatric UCD patients necessary based on the number of pediatric UCD patients that will be prescribed this drug (see response to question 1).**

Discussion:
There was no further discussion of this point.

Question 23. Hyperion intends to file the NDA in the electronic common technical document format (eCTD) and has contracted with (b) (4) *to perform the publishing.* (b) (4) *filed an acceptable eCTD pilot with the Center on* (b) (4) *(Pilot No.* (b) (4)*). Thus, Hyperion is requesting a waiver for the eCTD pilot. Does the Agency concur?*

FDA Response:

Yes, the eCTD pilot program is optional.

Discussion:
There was no further discussion of this point.

Question 24. Although likely preliminary, does the Agency think that the NDA for HPN-100 will be presented before an Advisory Committee?

FDA Response:

The decision to convene an Advisory Committee to discuss questions regarding an application will depend on the issues that the review raises. Therefore, it is premature to answer this question.

Discussion:
There was no further discussion of this point.

Additional Comments:

1. **We recommend that you reference the most recently approved labeling for other UCD drug products to guide the labeling for your product.**

2. **We recommend that you conduct a dose proportionality study to guide a dosage adjustment in patients with hepatic impairment and pediatric patients.**

3. **The bioanalytical assay validation report for ammonia must be submitted.**

4. **It is unclear if adequate bioequivalence/relative bioavailability information is available. We note that the study UP 1204-001 was not conducted with the approved NaPBA products i.e. Buphenyl tablet and powder. As you plan to rely on safety finding of Buphenyl, an adequate bridge between the reference product and the proposed product should be established. Because patients should be switched either from Buphenyl tablet or powder to the proposed product, we recommend that you provide relative BA information between Buphenyl powder and your product as well.**

5. **We remind that the in-study assay validation for each analyte must be provided.**

6. **We noted that you conducted in vitro drug metabolism study and protein binding study. Please, include the summary of these studies in the summary of Clinical Pharmacology and individual study reports in module 5.**

7. **It was noted that 24 patients were diagnosed with genotyping. We request that you provide the genotype information as available.**

8. **In Table 7 on page 44, we noted that PK parameters from healthy subjects and subjects with cirrhosis were combined for evaluation of food effect. We recommend that food effect should be assessed by comparing PK parameters obtained in healthy subjects.**

9. **It was noted that you propose in the label that the dose may be given** (b) (4) **or via nasogastric tube. While it is premature to discuss the labeling at this point, you should justify the adequacy of each administration method.**

   - **The stability of HPN-100 in** (b) (4) **should be studied to support the labeling.**

   - **The administration method via nasogastric tube should be justified and adequate relevant information should be provided in the labeling e.g. rinse with adequate amount of liquid should be recommended in the label.**

10. **It was noted that you propose in the label that the dose may be adjusted based on protein intake by** (b) (4)**, you should provide adequate justification for the proposal.**

11. **Your NDA will be considered a 505(b)(1) application if you intend to rely for approval upon data you own or to which you have obtained a right of reference (e.g., right of reference to NDA 20573 for Buphenyl). However, if you intend to rely, in part, upon data that you do not own or to which you have not obtained a right of reference, your NDA will be a considered a 505(b)(2) application.**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf) .

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Discussion:
There was no further discussion of this point.

20 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JESSICA M BENJAMIN
01/05/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 73,480

Hyperion Therapeutics
Attention: Klara Dickinson
Senior Vice President, Regulatory Affairs and Compliance
601 Gateway Blvd, Suite 200
South San Francisco, CA 94080

Dear Ms. Dickinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Glycerol Tri (4-Phenylbutyrate)(HPN-100).

We also refer to the meeting between representatives of your firm and the FDA on May 7, 2009. The purpose of the meeting was to discuss remaining issues and uncertainties regarding Hyperion's Phase 3 protocol for HPN-100-006.

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 me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
LCDR/USPHS
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 7, 2009
TIME: 11:00 a.m. – 12:00 p.m. EDT
LOCATION: White Oak Bldg 22 Room 1415
APPLICATION: IND 73,480
DRUG NAME: Glycerol Tri (4-Phenylbutyrate)(HPN-100)
TYPE OF MEETING: Type A

MEETING CHAIR: Ethan Hausman, M.D., Clinical Officer, Clinical Reviewer

MEETING RECORDER: Stacy Barley, R.N., M.S.N., M.H.A., Regulatory Project Manager

FDA ATTENDEES: (Title and Office/Division)
Donna Griebel, M.D., Director, Division of Gastroenterology Products (DGP)
Ethan Hausman, M.D., Clinical Reviewer, DGP
Lynne Yao, M.D., Clinical Reviewer, DGP
Mike Welch, Ph.D., Statistical Team Leader, Division of Biometrics III
Behrang Vali, M.S., Statistical Reviewer, Division of Biometrics III
Peter Vacarri, B.S., Pharmacology Reviewer, Orphan Drug
Sue Chi Lee, Pharm. D., Ph.D., Pharmacology Team Leader, Office of Clinical Pharmacology
Lydia Velazquez, Pharm. D., Special Assistant Director, Office of Clinical Pharmacology
Stacy Barley, R.N., M.S.N., M.H.A., Regulatory Project Manger, DGP
Richard Ishihara, Regulatory Project Manager, DGP

EXTERNAL CONSTITUENT ATTENDEES:

Klara Dickinson, Senior Vice President, Regulatory Affairs
Bruce F. Scharschmidt, M.D., Senior Vice President & Chief Medical Officer
Toni Martinez, Vice President, Clinical Operations
Masoud Mokhtarani, M.D, Vice President, Clinical Development
Joe Mauney, Director Biostatistical and Statistical Programming

(b) (4)

BACKGROUND:

A Type B End-of-Phase 2 meeting was held between Hyperion and the FDA on January 14, 2009, to discuss the Phase 3 protocol HPN-100-006. Hyperion submitted a Special Protocol Assessment (SPA) to the FDA on February 18, 2009. Upon completion of the FDA review, a "No Agreement" letter was issued on April 3, 2009. Hyperion formally requested a type A meeting to discuss remaining issues and uncertainties regarding the Phase 3 protocol HPN-100-006.

MEETING OBJECTIVES:

The main meeting objectives are to resolve remaining issues of Hyperion's Phase 3 protocol HPN-100-006.

DISCUSSION POINTS:
Questions from Hyperion Therapeutics are in plain text. The preliminary FDA responses sent to Hyperion on May 6, 2009, are in **bold text**. The meeting discussion from May 7, 2009, is in ***bold italics***.

Questions and Answers

1. The Agency proposes the 24 hour area under the curve (AUC) for blood ammonia (NH3) as the primary efficacy measure. The Agency further stated that "The pharmacodynamic non-inferiority limit for $NH3_{24\ hour\ AUC}$ should be within pre-determined and clinically acceptable limits. In order to demonstrate non-inferiority of HPN-100 as compared to the effect of Buphenyl, the lower bound of the two-sided 95% confidence interval of $NH3_{24\ hour\ AUC}$ means ratio between HPN-100 and Buphenyl should be at least 80%." Hyperion interprets this suggestion to mean that the lower boundary of the two-sided 95% confidence interval of $NH3_{24\ hour\ AUC}$ mean observed on BUPHENYL should equal or exceed 80% of the $NH3_{24\ hour\ AUC}$ mean observed on HPN-100.

   Background: Hyperion concurs with $NH3_{24\ hour\ AUC}$ as the primary efficacy measure but wishes to clarify how this would be calculated and the terminology used in this submission. As outlined in more detail in the accompanying HPN-100-006 protocol (see Appendix A) and Statistical Analysis Plan (SAP, see Appendix B), $NH3_{24\ hour\ AUC}$ on Study Days 14 and 28 would be calculated based on NH3 values determined at 8 time points between 0 and 24 hours, including two time points between 12 and 24 hours (as suggested by the Agency) with all ammonia values equally weighted (i.e., no differential weighting of time points). This is referred to as AUCtau, which equals AUC from dose time (time of initial dosing) to Tau (sampling interval). For the purpose of the primary efficacy analysis, (b) (4) [redacted] described in more detail in references included with this Briefing Document in Section 6 (Gabrielsson and Wiener 2006, WinNonLin User's guide).

Hyperion understands the limitations of using a fixed value as a non-inferiority margin (as proposed for the EOP2 meeting) and concurs with the Agency's proposal of using a ratio; however, the Company views the proposed ratio of means of (b) (4) as corresponding to limits that are (b) (4)

a. Does the Agency concur with $NH3_{24\ hour\ AUC}$, (b) (4), as the primary efficacy endpoint?

FDA RESPONSE:

At this time we cannot agree with your proposal of (b) (4) as the primary endpoint. You will need to provide a detailed description of how you plan to (b) (4) including definitions for all terms, and clarify how (b) (4) eliminates (b) (4) in order for us evaluate your proposal.

If you plan to include an analysis of (b) (4) in your protocol and statistical analysis plan, you should include a detailed description of how (b) (4), and include definitions of all terms. Your SAP must also present (b) (4) for BUPHENYL and HPN-100. Substantial differences in performance of the two products will raise review concerns.

Additional Discussion:

Hyperion agreed, based on internal discussions and previous FDA recommendation, that $NH3_{24\ hour\ AUC}$, (b) (4), will be used as the primary efficacy endpoint in this study.

The FDA recommended that Hyperion report efficacy results based on the Intent-to-Treat (ITT) and Per Protocol (PP) patient populations. All analyses using the Modified Intent-to-Treat (MITT) patient population were agreed by FDA and Hyperion to be supportive in nature. Missing values for patients from the ITT population would require a pre-specified imputation strategy, and this should be presented in the protocol or SAP with descriptions of various sensitivity analyses to test missing data assumptions. It was suggested by the Agency that Missing at Random (MAR) should be assumed for any imputation strategy (such as Multiple Imputation) adopted for the primary analysis, while Missing Completely at Random (MCAR) can be assumed for imputation strategies (such as a Complete Case

Analysis) corresponding to any sensitivity analysis. Hyperion stated they will consider using these approaches.

The Protocol and analysis plan should ideally be submitted together. If Hyperion decides to postpone the submission of the SAP, the protocol should at a minimum include detailed information regarding the planned (b) (4). Note that it was determined later in the meeting that there will be no planned (b) (4)

As stated in the FDA preliminary responses, the SAP must also present ammonia concentration time profiles for BUPHENYL and HPN-100. Substantial differences in performance of these two products may raise review concerns. The FDA reiterated that Cmax values should be reported, and Hyperion acknowledged that Cmax will be reported.

b. Does the Agency concur with a (b) (4) pharmacodynamic non-inferiority limit of (b) (4)?

FDA RESPONSE:

For ammonia, our primary concern is the upper confidence limit since elevated ammonia levels are harmful to patients. Please provide additional justification for the upper limit.

Additional Discussion:

Hyperion clarified that $NH3_{24\ hour\ AUC}$ values would be presented as a ratio (i.e., HPN-100/BUPHENYL). Hyperion believes that the upper confidence limit (the ratio of $NH3_{24\ hour\ AUC}$ values) of (b) (4) compared to 1.25 is not clinically significant, and therefore, asked if the upper limit of (b) (4) would be acceptable to the FDA. The FDA recommends Hyperion to use the 1.25 upper limit. However, the FDA emphasized that the final action taken will be based on the totality of the data presented in the submission.

2. The Agency stated that "given the variability in blood NH_3 in patients with UCDs we recommend increasing each treatment period to two weeks. Endpoint comparisons should be made on day 14 of each treatment period. Additional comparisons between the two treatments on $NH3_{24\ hour\ AUC}$ should be done on day seven of each treatment period."

   Hyperion agrees to extend the duration of the study as recommended with the endpoint comparisons being made on Day 14 on each treatment period (see Section 5.1) and agrees to obtain information on NH3 on study days 7 and 21. However, Hyperion is proposing an alternative approach to assessing NH3 on these days that would provide clinically meaningful information on NH3 control while minimizing the burden to study subjects as well as potential safety issues associated with both travel to the study site and two additional hospitalizations within the 4-week study period.

Background: In developing the clinical protocol HPN-100-006, Hyperion has built upon the experience gained during the conduct of the Phase 2 Study (Clinical Protocol UP1204-003) and worked closely with UCD experts, including those in the NIH-funded UCD Consortium. Based on this experience and detailed feasibility assessments at ~23 sites in North America, a 4-hospitalization requirement within a 4-week study period, including overnight blood sampling as planned on Days 14 and 28, would represent a major burden for study subjects and an impediment to enrollment. Moreover, disruption of the daily schedule associated with travel to a distant study site and overnight stay can pose safety issues. Therefore, as described in more detail in Section 5.1, Hyperion proposes an alternative approach involving study visits on Days 7 and 21 with three NH3 and PK samples drawn over the course of 12 hours. Safety labs, an electrocardiogram (ECG) and a timed urine collection for PAGN would also be obtained on Days 7 and 21. Specifically, a blood sample for NH3 and PK would be collected in the morning after an overnight fast (AM sample) and two samples for NH3 and PK would be drawn approximately 8 and12 hours later in the day (PM samples). The AM sample would be drawn fasting and prior to drug administration and would assess NH3 at a time corresponding to trough drug levels and, presumably, low NH3 production. The PM samples would be drawn approximately two hours before and two hours after dinner and drug administration. This would correspond to peak levels of both drug and NH3 production. In the case of patients for whom two additional extended clinic visits on Study Days 7 and 21 as well as the associated travel time would pose an unreasonable logistic burden or be judged by the investigator to pose a safety risk, Hyperion has evaluated and proposes that the same information (i.e. safety labs, ECG, PK and NH3 samples) be obtained in the context of (b) (4) (see Section 5.1 of this Briefing Document, under 'Clinical Protocol,' Comment 2).

a. Does the Agency agree with the proposed approach to obtaining information on NH3 on study days 7 and 21?

<u>FDA RESPONSE</u>:

No. We have the following comments regarding your study design:

1. **We do not agree that (b) (4) on Days 7 and 21 are adequate to assure patient safety. HPN-100 is an investigational agent that has been administered to a limited number of patients and clinical experience with HPN-100 is not well described. Adequate safety monitoring of all patients enrolled in the Phase 3 trial should be performed; which would include in-clinic assessments of all patients on Days 7 and 21. While we agree with your proposed plan for safety monitoring that would not require 24 hour hospitalization on study days 7 and 21, assessments at Days 7 and 21 should include core physical and neurological examination by an appropriately qualified investigator or co-investigator (e.g., vital signs, directed physical examination, and clinical laboratory assessments) and collection of 24-hour urine samples.**

<u>Additional Discussion:</u>

Hyperion will provide the patients with a 24-hour urine collection container(s) on Day 1, along with instructions for the proper collection of the urine. Hyperion stated that the urine will be (b) (4)

Hyperion agreed that patients will be seen at study/clinic sites on Days 7 and 21.

2. We can not comment on the adequacy of your cardiac monitoring plan because you have not yet performed a thorough QT study. Therefore, please submit your plan for a thorough QT study for HPN-100.

Additional Discussion:
Hyperion stated that a thorough QT study is currently being developed.

3. Your protocol states that patients who can not ingest Buphenyl tablets may ingest Buphenyl powder. A better approach would be that all patients receive the same formulation, for instance powder, in order to minimize confounders and variability in your study results. Also, keep in mind that you will have a limited number of patients enrolled in this study and it would be in your best interest that you capitalize on everyone being on the same formulation.

Additional Discussion:
Hyperion proposed the use of tablets rather than powder in the protocol. The FDA strongly urged the Sponsor to select one formulation that would be used for all patients. Hyperion stated that it would be unlikely that an adult would be unable to ingest tablets. FDA recommended that if Hyperion elects to provide tablets as the preferred form of Buphenyl, then enrollment should be limited to patients treated with Buphenyl tablets. If this is not possible, the Agency recommended, at a minimum, that patients be maintained on the same formulation of BUPHENYL throughout the entire study. Hyperion stated that they would make every effort to maintain all patients on tablets, however Buphenyl powder will be used if needed. If a patient must change dosage form after enrollment in the study, then these patients should be clearly identified in the study report and in the efficacy and safety assessments.

FDA stated that use of multiple Buphenyl formulations (powder and tablet) in the study might affect efficacy and safety assessments due to differences in bioavailability, and that analyses by dosage form would be necessary

4. In the event an NDA is submitted, a determination of efficacy will be based on your ITT and your Per Protocol (PP) populations. Analyses of your primary endpoint based on the modified ITT (MITT) will be considered supportive.

Additional Discussion:
Refer to Question 1a.

5. **Your individual and overall study stopping rules are not adequate. For example, stopping criteria should rely on objective criteria only and not [redacted] (b) (4), such as any patient experiencing a Grade 4 or higher adverse event should be discontinued regardless of [redacted] (b) (4). Overall study stopping rules should be modified to state that the study will be stopped if 2 patients experience the same Grade 4 or higher adverse event regardless of relatedness to HPN-100.**

   If study stopping criteria are met, you must notify FDA, and your study will be place on clinical hold.

Additional Discussion:
The Agency reiterated its position that if two patients experience the same NCI CTCAE Grade 4 then the FDA must be notified and the study will be placed on clinical hold.

Hyperion expressed concern about the integrity of the study if safety analyses require unblinding of clinical data. Hyperion asked how they should manage these AEs without introducing inherent bias due to unblinding. The Agency suggested that the sponsor should be blinded to all aspects of the study to minimize any incurred bias, and may consider using a Contract Research Organization (CRO) to conduct the study. This CRO would remain blinded throughout the study except for a small designated unblinded team within the organization whose purpose is to communicate safety issues to the DSMB. All parties will unblind post database lock. Hyperion will take into consideration FDA's recommendation, but did not agree to this plan.

Additional Discussion:
The maximum recommended dose of Buphenyl in current labeling is 600 mg/kg/day in patients weighing less than 20 kg, and 13 gram/m^2/day in heavier patients, with safety and efficacy in doses higher than 20 gram/day not described. Please include similar maximum daily doses of HPN-100 in mg/kg/day and gram/m^2/day in your protocol.

6. **Please provide draft electronic case report forms and an investigator brochure.**

No Additional Discussion.

3. The Agency recommends against [redacted] (b) (4).
   The Agency has also requested details regarding the specific method to be administered for the [redacted] (b) (4)

   Background: [redacted] (b) (4)

(b) (4)

a. Does the Agency concur with this approach?

FDA RESPONSE:

We are aware this is an orphan disease and the population available for study may be limited; (b) (4)

Additional Discussion:

Hyperion stated that they will not (b) (4) **.**

Additional Comments:
Clinical Pharmacology

1. **Keep in mind that for the assessment of relative bioavailability, blood concentrations and NOT urine concentrations will be the determining factor. The active metabolite PAA should be included in this assessment. In addition, bioavailability between two products is best assessed with a single dose approach.**

Therefore, we recommend that PK samples be collected on Day 1 and at steady state. Please refer to our BA Guidance for further information.

2. **Determination of steady-state is typically approached by sample collection for three consecutive days to demonstrate that blood concentrations are not continuing to increase.**

Additional Discussion:
Hyperion stated that (b) (4) ***; but indicated that PK studies of HPN-100 were performed in Phase 2 studies. The FDA stated that a full PK assessment to include demonstration of steady-state with HPN-100 in patients with UCD will be required as part of the NDA submission.***

Statistical

3. **We recommend you perform your primary analysis on both the Intent to Treat (ITT) and Per Protocol (PP) populations. The ITT population is defined as all subjects who receive the study drug. Your use of a modified ITT population (ITT patients with at least 12 hours of NH3 data on days 14 and 28) is not consistent with ICH E9 and would best serve as a secondary or supportive analysis.**

4. **For your ITT analysis, it is not clear how patient data are handled when the patient has no post-dose data for one of the treatments (i.e. completely missing** (b) (4) **for one of their treatments). Your protocol and SAP should detail a missing data handling plan that addresses all possible missing data conditions and proposes several sensitivity analyses for missing data assumptions.**

5. **You have not proposed any multiplicity adjustment procedures for the analysis of your secondary efficacy variables. If you anticipate labeling for these variables, you should propose appropriate multiplicity adjustments to control the overall type I error.**

Additional Discussion:
At the end of the meeting, the Agency requested that Hyperion include (in the protocol or SAP) the exact equation to be used in the calculation of the Confidence Interval for the ratio of HPN-100 and BUPHENYL $NH3_{24\ hour\ AUC}$ ***values.***

Linked Applications	Sponsor Name	Drug Name / Subject
IND 73480	HYPERION THERAPEUTICS	GLYCERYL TRI (4-PHENYLBUTYRATE) (GT4P)

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

/s/

STACY R BARLEY
06/07/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 73,480

Hyperion Therapeutics Inc.
Attention: Klara Dickinson
Sr. Vice President, Regulatory Affairs and Compliance
601 Gateway Blvd, Suite 200
South San Francisco, CA 94080

Dear Dr. Dickinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glycerol tri (4-phenylbutyrate)(HPN-100).

We also refer to the meeting between representatives of your firm and the FDA on January 14, 2009, and the corresponding meeting minutes dated February 13, 2009. The purpose of the meeting was to discuss appropriate regulatory strategy for HPN-100, which you proposed to be a 505(b)(2) application, and the Phase 3 clinical program that would be required to support a New Drug Application (NDA) submission for HPN-100.

We additionally refer to the electronic correspondence from you to Ms. Stacy Barley dated February 25, 2009, in which Hyperion expressed concerns regarding the meeting minutes. In response to your electronic correspondence, we have revised the meeting minutes to include an addendum to address your concerns. Please refer to the meeting minutes below, which include an addendum to the original minutes.

If you have any questions, contact Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Anne Pariser, M.D.
Acting Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 14, 2009
TIME: 11:00 a.m. - 12:00 p.m. EDT
LOCATION: White Oak Bldg 22 Rm 1315
APPLICATION: IND 73,480
DRUG NAME: Glycerol Tri (4-Phenylbutyrate) (HPN-100)
TYPE OF MEETING: Type B

MEETING CHAIR: Joanna W. Ku, M.D., Acting Medical Team Leader

MEETING RECORDER: Stacy Barley, RN, M.S.N., M.H.A.

FDA ATTENDEES: (Title and Office/Division)

Division of Gastroenterology
Donna Griebel, M.D., Director
Joanna Ku, M.D., Acting Medical Team Leader
Lynne Yao, M.D., Clinical Reviewer
David Joseph, Ph.D., Acting Pharmacology Team Leader
Wes Ishihara, Regulatory Project Manager
Ke Zhang, Ph.D., Pharmacology Reviewer
Todd Phillips, Pharm.D., Regulatory Project Manager
Stacy Barley, RN, M.S.N., M.H.A., Regulatory Project Manager

Pediatric and Maternal Health Staff
Hari Sachs, M.D., Medical Officer
Elizabeth Durmowicz, M.D., Medical Officer
Matthew Bacho, Regulatory Project Manager

Division of Biometrics III
Mike Welch, Ph.D., Statistical Team Leader
Behrang Vali, M.S., Statistical Reviewer,

Office of Clinical Pharmacology
Jane Bai, Pharm. D., Ph.D., Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Klara Dickinson, Senior Vice President, Regulatory Affairs
Crystal Browning, Senior Manager, Regulatory Affairs
Bruce F. Scharschmidt, MD, Senior Vice President & Chief Medical Officer
Toni Martinez, Vice President, Clinical Operations
Masoud Mokhtarani, Vice President, Clinical Development
Brendan Lee, M.D., Ph.D., Biogenetics and Pediatrician

(b) (4)

Joe Mauney, Director, Biostatistical and Statistical Programming

BACKGROUND:

The FDA issued a Clinical Hold letter dated November 1, 2006, to Hyperion for HPN-100. As stated in the hold letter, Hyperion was strongly encouraged to request an end of phase 2 (EOP-2) meeting to discuss the design of the Phase 3 clinical trial upon completion of Phase 2. Hyperion has completed the Phase 2 clinical study in adult UCD patients.

MEETING OBJECTIVES:

The purpose of the meeting was to seek agreement of the following:

1. The design of the Phase 3 clinical trials necessary to support the initial marketing approval for HPN-100,
2. The patient population to be studied including the specific UCD subtypes and distribution of age groups,
3. The number of patients exposed and duration of patient exposure necessary to support an assessment of the safety of HPN-100 in the treatment of UCDs, and
4. And the submission of the NDA as a 505(b)(2) application.

DISCUSSION POINTS:

Questions from Hyperion Therapeutics are in plain text. The preliminary FDA responses sent to Hyperion on January 13, 2009, are in **bold text**. The meeting discussion from January 14, 2009, is in ***bold italics***.

<u>Questions and Answers</u>
Clinical Questions:

1. BUPHENYL® (sodium phenylbutyrate) is currently approved for CPS, OTC and ASS deficiency states, which correspond to the UCDs in the original NaPBA treatment protocol developed by Dr. Saul Brusilow that generated the observational data supporting the approval of BUPHENYL®. Data from the NIH-funded UCD Consortium-Sponsored Longitudinal Study indicate that BUPHENYL® is also prescribed for patients with ASL, ARG, HHH and CITRIN deficiency states (Section 4.3.2.2). Hyperion is not aware of data to suggest that the metabolism or mechanism of action of HPN-100 should vary among UCDs and is seeking a label consistent with its anticipated use. Due to the rarity of the UCDs, it is likely not informative to stratify for UCD subtypes, and Hyperion proposes that all eligible patients be enrolled in the pivotal efficacy study and be included in the primary efficacy analysis.

    b. Consistent with Agency guidance provided during the preIND meeting in which the Agency indicated a 505(b)(2) application was acceptable, Hyperion intends to file a

505(b)(2) application, with BUPHENYL® being the referenced listed product to support safety. Does the Agency find the proposed UCD patient population acceptable under the 505(b)(2) scenario?

FDA Response:

We are not opposed to your plan to enroll patients with different urea cycle disorder (UCD) subtypes into your Phase 3 study. Because different UCD subtypes may have unexpected and different responses to HPN-100 treatment, HPN-100 can only be indicated for the population in whom safety and efficacy have been adequately studied. If you plan to seek an indication for the use of HPN-100 in the treatment of all UCD subtypes, it will be necessary to collect adequate efficacy and safety data in patients with all UCD subtypes.

Under a 505(b)(2) application, our previous safety findings for BUPHENYL® may be used as supportive evidence for HPN-100 in the subtypes of UCD that have been previously studied with BUPHENYL®.

Additional Discussion:

Hyperion agrees with FDA's comments.

2. At the preIND meeting, the Agency indicated it would accept blood ammonia value as the primary efficacy measure for the Phase 3 study. Hyperion is proposing blood ammonia as the primary efficacy measure, with (b) (4) [redacted]. The selection of ammonia is based on a large body of literature linking levels of blood ammonia to clinical outcome in UCD patients (Section 4.2).

   a. Does the Agency agree that ammonia as the primary efficacy measure would be acceptable to support the approval of HPN-100 for the treatment of UCD?

   FDA Response:

   We agree that ammonia as a primary efficacy measurement is acceptable. You propose that (b)(4) [redacted] **However, this method may not capture the variability of ammonia levels over a 24-hour period. Instead, ammonia AUC should be used as a clinical endpoint measurement of efficacy since measurement of ammonia AUC will provide a better estimate of the overall effect rather than the effect at a certain time point (please see pre-IND Meeting Minutes from December 15, 2005).**

<u>Additional Discussion:</u>

Hyperion agrees with FDA's comments. The Agency clarified that ammonia AUC would not be considered sufficient as a single primary efficacy endpoint. The Agency stated that both the measurement of ammonia AUC_{0-24} and plasma phenylacetylglutamine (PAGN) AUC_{0-24} should be included as co-primary efficacy measures (see Questions 4 and 5).

3. At the preIND meeting, the Sponsor proposed a cross-over design for the Phase 3 efficacy study. The Agency agreed, provided there is sufficient "washout" to minimize or eliminate drug carry-over effect. Hyperion is proposing a cross-over study design for the pivotal efficacy study (Protocol HPN-100-006, Appendix 11.2). As discussed in Section 6.1, subjects will be randomized to receive either BUPHENYL® or HPN-100 for (b) (4) weeks, and then will be crossed-over to the other treatment for (b) (4) weeks. For reasons of safety, subjects cannot undergo a drug-free washout period. However, based on the PK analyses conducted to date, BUPHENYL® and HPN-100 metabolites both reach steady state and exit the body (i.e. are washed out) within 1-4 days, and ammonia also appears to respond rapidly (e.g. hours to days) to changes in drug levels. The proposed crossover study design requires one week on either BUPHENYL® or HPN-100 prior to measurement of ammonia, an approach consistent with that used in the Phase 2 adult UCD study (UP 1204-003).

   a. Does the Agency find the cross-over design acceptable?

   <u>FDA Response:</u>

   Your current proposal has no blood ammonia sampling between 12 and 24 hours after each drug reaches steady state (at least 7 days after the start of BUPHENYL® or HPN-100). Based on the excretion patterns of phenylacetylglutamine (PAGN) resulting from administration of BUPHENYL® or HPN-100, we would like to recommend that at least 2 more blood ammonia samples be taken between 12 and 24 hours after administration during the proposed Phase 3 clinical trial. With at least 2 blood ammonia samples added between 12 and 24 hours after dosing, your proposed cross-over design would appear reasonable (see Question 4 response).

   <u>Additional Discussion:</u>

   Hyperion agrees with FDA's comments.

   b. Does the Agency find the "wash-out" period sufficient?

   <u>FDA Response:</u>

   Yes, a washout of 7 days is acceptable given that phenylacetate (PAA), the active drug, has a half life of approximately 8 hrs in patients with severe hepatic

impairment, and approximately 1-2 hours in subjects with mild to moderate hepatic impairment or healthy subjects.

<u>Additional Discussion:</u>

No additional discussion.

c. Does the Agency concur that a pivotal efficacy study of (b) (4) duration would be sufficient to support approval, assuming satisfactory results?

<u>FDA Response:</u>

We cannot answer this question at this time. The duration of the pivotal trial will depend on outcomes of the Pediatric PK/PD/Safety Study (the Pediatric Study), and the final study design of the pivotal trial (see answer to Question 4). Additionally, as you have proposed, a long-term (e.g., 52 week) extension study will be required to establish the safety of HPN-100 for chronic use in UCD patients.

<u>Additional Discussion:</u>

Hyperion agrees with FDA's comments.

4. The proposed pivotal efficacy study (HPN-100-006) involves a non-inferiority design, as suggested in the Agency's 1 November 2006 Clinical Hold letter, with ammonia as the primary efficacy measure and a non-inferiority margin of (b) (4) µmol/L of ammonia. As outlined in Section 6.1.6, the proposed non-inferiority margin of (b) (4) µmol/L is well below the level typically associated with symptoms, corresponds to approximately (b) (4) % of the estimated treatment benefit of BUPHENYL®, and is (b) (4) % of the maximum observed standard deviation of blood ammonia levels in the recently completed Phase 2 UP 1204-003 study in adult UCD patients (see Section 5.1.5 for a summary of ammonia results).

   a. Does the Agency find the non-inferiority margin acceptable to support the approval of HPN-100?

   <u>FDA Response:</u>
   Due to additional post-meeting discussion the response has been modified. Your new response is reflected below in the Meeting Addendum section of the minutes.

5. In the Agency's 1 November 2006 Clinical Hold letter, it requested that the efficacy study be double blind. Although formulating a placebo for BUPHENYL® (sodium phenylbutyrate) is technically feasible, matching the distinct taste and odor of BUPHENYL® to effectively blind BUPHENYL® -experienced patients to their treatment group assignment is likely not

feasible (Section 6.1.3). Since subjects are required to have been on BUPHENYL® before they enter the study, they will recognize the difference between placebo and BUPHENYL® and effectively become unblinded. In addition, subjects taking the maximum BUPHENYL® dose of 20 grams per day would be required to take (b) (4) tablets during the (b) (4) week study, (b) (4) of which would be placebo. To accommodate a double blind study, it would furthermore be necessary to utilize a double-dummy design due to the different product presentations (tablet or powder vs. liquid oil), which would increase the already burdensome drug volume and likely impact overall study compliance. Given the unblinding risk, treatment burden and difficulty of blinding BUPHENYL® -experienced patients, as well as the fact that the primary efficacy measure of blood ammonia concentration is not subject to bias, Hyperion is proposing a randomized, controlled, open-label design for the efficacy trial.

a. Does the Agency find the proposed randomized, controlled open-label design acceptable for the efficacy trial?

FDA Response:

Due to additional discussion post-meeting, the response has been modified. Your new response is reflected below in the Meeting Addendum section of the minutes.

6. The pivotal efficacy study (HPH-100-006) discussed in Section 6.1 (draft protocol provided in Appendix 11.2) will enroll at least (b) (4) UCD patients, including at least (b) (4) pediatric patients between the ages of 6 - 17, with at least (b) (4) years of age.

   a. Does the Agency agree with the proportion of adults and children ages 6-17?

   FDA Response:

   The total number of patients enrolled in your pivotal trial should include sufficient numbers of patients to assess clinically meaningful and statistically significant effects of HPN-100 in patients with UCDs. Also, sufficient numbers of patients should be exposed to the drug to allow adequate evaluation of the safety of the drug in patients that will likely be taking the drug. Corresponding effect sizes and assumptions regarding the specified subgroups should also be given in order to validate the number of patients to be enrolled into those subgroups. The results of the Pediatric Study could be used to inform the number of pediatric patients that will need to be studied in the pivotal study. We will be able to answer this question after reviewing data from the Pediatric Study. If the PK/PD profile in children differs substantially from adults, you may not be able to demonstrate bioequivalence in a study that includes the full age range of patients.

Additional Discussion:

Hyperion concurred with the FDA's pediatrics comments. Hyperion stated their intent to initiate the pivotal efficacy study in adults prior to completion of the Pediatric Study. The Agency noted that Hyperion's currently proposed pivotal study includes pediatric patients aged 6 to 17 years. The Agency advised that the Pediatric Study should be completed prior to the pivotal efficacy study so to properly inform the design of a pivotal trial that will include pediatric patients. If Hyperion proceeds with the pivotal study prior to the completion of the Pediatric Study, the pivotal study will need to be re-designed to exclude children. The Agency stated that extrapolation of efficacy from adult data may be possible for a pediatric clinical trial, but extrapolation of safety and dosing for pediatric patients would not likely be acceptable. Hyperion stated their understanding.
The Agency noted that Hyperion has applied for orphan designation for HPN-100, and stated that a deferral of pediatric studies could be requested if orphan status is not granted.

7. Prior to enrolling pediatric patients into the pivotal efficacy study, Hyperion will study 10 pediatric UCD subjects between the ages of 6 - 17, including at least four patients between the ages of 6 - 11 (refer to Section 6.2 for study summary or Appendix 11.1 for the draft Protocol HPN-100-005). The design of this safety and PK/PD study is based upon the design of protocol UP 1204-003 (summarized in Section 5.1.1) and involves a (b) (4)) conversion from BUPHENYL® to HPN-100 and a Data Safety Monitoring Board (DSMB) review of the safety and ammonia data from the first six subjects (three ages 6 - 11 and three ages 12 - 17). Assuming that the DSMB review of safety and ammonia data meets the safety criteria set forth in the protocol and satisfactory study completion, pediatric subjects ages 6 - 17 would subsequently be enrolled into the pivotal efficacy study.

   a. Does the Agency concur with the design of the pediatric PK/PD study?

FDA Response:

The proposed design of the Pediatric Study appears reasonable. If there are safety concerns due to a lack of sufficient ammonia control at the time of switch-over from a 100% BUPHENYL® dose to a 50% BUPHENYL®-equivalent dose of HPN-100, then your proposed (b) (4) design is acceptable. Otherwise, we recommend that you consider a switch-over study using a 1-step design (i.e., a switch-over from 100% BUPHENYL® to 100% BUPHENYL®-equivalent dose of HPN-100 in a single step).

Additional Discussion:

Hyperion requested clarification regarding blood draws, asked if additional blood draws were required as part of the Pediatric Study, and stated that increasing the number of blood draws in the Pediatric Study may be difficult for younger children.

The Agency acknowledged that blood draws in the pediatric population may be more difficult. However, in order to capture the full PK/PD in the Pediatric Study, adequate sampling must be performed to capture Cmax. The Agency would also consider population PK studies if they are performed appropriately.

b. Assuming a satisfactory DSMB review, does the Agency concur with allowing pediatric subjects ages 6 - 17 to enroll in the pivotal efficacy study?
FDA Response:

Yes. However, if the results of the PK/PD profile in children are different from adults, you may not be able to demonstrate bioequivalence in a study that includes the full age range of patients.

Additional Discussion:

No additional discussion (see answer to Question 6).

8. Consenting subjects who complete the pediatric safety and PK/PD study (Protocol HPN-100-005), and subjects who complete the pivotal efficacy study (Protocol HPN-100-006), will be eligible to enter an open-label 12-month safety extension study (Protocol HPN-100-007, Appendix 11.3), which is summarized in Section 6.3 of this briefing document. Enrollment of the pediatric subjects will only be allowed after all 10 pediatric subjects have safely and successfully completed the study. The average duration of exposure at the time of the NDA will be (b) (4) months, with an estimated 35 - 40 subjects exposed for at least (b) (4) months. Should some patients drop out before completion of the (b) (4) week efficacy study, or elect to not participate in the open-label safety extension, the safety extension protocol will allow for the enrollment of UCD patients taking BUPHENYL® (sodium phenylbutyrate) who have not participated in Protocols HPN-100-005 or HPN-100-006 in order to ensure that at least 40 patients are enrolled in the safety extension study.

a. As summarized in Section 6.4.2, the accessible United States (US) UCD patient population currently taking BUPHENYL® (sodium phenylbutyrate) is between (b) (4) patients (US sales estimates between (b) (4) patients, and the UCD Consortium-Sponsored Longitudinal Study has enrolled ~100 patients on BUPHENYL®). The total HPN-100 exposed UCD population is anticipated to range from ~40 to 50, which represents approximately (b) (4) % of the projected US BUPHENYL® UCD population, and 40% of the UCD Consortium Longitudinal Study population on BUPHENYL®. This will be in addition to (b) (4) healthy adults and 24 subjects with cirrhosis exposed in protocols UP 1204-001, UP 1204-002, and the planned QTc study. Does the Agency find this number of patient exposures acceptable to support an NDA filing?

FDA Response:

See answer to Question 8b.

b. The average duration of exposure at the time of the NDA will be (b) (4) months, with an estimated 35 - 40 subjects exposed for at leas (b) (4) months. Hyperion will provide a safety update after (b) (4) after the filing of the NDA at which time it is estimated that 25 - 30 will have (b) (4) months exposure with an average exposure of (b) (4) months. Does the Agency find the duration of exposure appropriate to support a 505(b)(2) NDA filing?

FDA Response:

Due to additional post-meeting discussion, the response has been modified. Your new response is reflected below in the Meeting Addendum section of the minutes.

9. (b) (4) is used by (b) (4)% of UCD patients in the UCD Consortium-Sponsored Longitudinal Study and most patients in certain other countries [e.g. the United Kingdom (UK); Section 6.1.5] are on (b) (4) NaPBA. The use of (b) (4) appears largely attributable to patient or physician preference and/or drug accessibility. Hyperion therefore proposes to allow co-administration of (b) (4) in the pivotal efficacy and safety studies as outlined below, both in order to (b) (4)

a. The pivotal efficacy study will, at the discretion of the investigator, allow for concomitant use of (b) (4) so long as it accounts for no more than (b) (4)% of the total ammonia scavenging activity. Does the Agency find this approach acceptable?

FDA Response:

No, the concomitant use of (b) (4) during this study is not acceptable.

Additional Discussion:

No additional discussion.

b. The safety extension protocol will allow reintroduction or co-administration of (b) (4) (b) (4) at the discretion of the investigator for those patients who were taking previously. Does the Agency find this approach acceptable?

FDA Response:

No, please see answer to Question 9a.

Additional Discussion:

No additional discussion.

10. As discussed in Section 7.1, a Phase 1b study in patients with hepatic impairment has been completed and suggests no difference between healthy adults and adults with cirrhosis with respect to their conversion of HPN-100 to PAGN and ammonia scavenging; nor was there any relationship observed between plasma levels of PAA and glomerular filtration rate. Further, an assessment of renal function in UCD subjects enrolled in the UCD Consortium-Sponsored Longitudinal Study indicates that the renal function of this patient population is similar to healthy individuals. The pharmacokinetics of a single dose of HPN-100 have also been studied in relation to meals and found not to differ between the fed and fasted states.

    a. Hyperion finds study UP 1204-002 adequate to meet the criteria for subjects with hepatic impairment and does not plan further studies in this specific patient population to support the NDA for UCD. Does the Agency agree?

    FDA Response:

    Due to additional discussion post-meeting, the response has been modified. Your new response is reflected below in the Meeting Addendum section of the minutes.

    b. Hyperion recognizes that PAGN is cleared by the kidneys and plans to examine the relationship between renal function and PK in the phase 3 trials. Since PK/PD modelling suggests that HPN-100 bioavailability may differ between healthy adults and UCD patients (Section 5.2.3), Hyperion views further examination of drug handling in the target population as most likely to be informative and does not plan further studies of HPN-100 in non UCD patients with renal impairment. Does the Agency agree?

    FDA Response:

    Due to additional discuss post-meeting, the response has been modified. Your new response is reflected below in the Meeting Addendum section of the minutes.

    c. Hyperion finds study UP 1204-002 adequate to address the effect of meals on HPN-100 absorption and does not plan additional fed-fasted studies. Does the Agency agree?

FDA Response:

The acceptability of Study UP 1204-002 is a review issue. If adequately designed, the outcome of such study would be acceptable without additional fed-fasted studies.

Additional Discussion:

No additional discussion

11. As discussed in Section 7.2, analysis of clinical studies compiled to date do not provide consistent evidence of gender-related differences in the metabolism of HPN-100, nor does PK/PD modeling suggest a gender difference. However, Hyperion will continue to examine the gender related handling of HPN-100 in clinical protocols HPN-100-005 and HPN-100-006, both of which are anticipated to enroll a disproportionally large number of females with OTC deficiency. Does the Agency concur with this approach?

FDA Response:

The proposed approach appears reasonable. We recommended that you conduct a statistical analysis of the combined results from all studies to determine whether gender influences the metabolism of HPN-100.

Additional Discussion:

No additional discussion.

Non-Clinical Questions:

12. Hyperion's analysis of the age of the cynomolgus monkeys that participated in the 13-week repeat-dose toxicity study ((b) (4) 510010) found that the animals qualified as juveniles (Section 9.3.1). In addition to this study, a juvenile toxicity study (QBU00007) in Crl:CD(SD) rats is in progress to detect adverse effects of HPN-100 treatment of neonatal rats from postnatal day 2 to at least postnatal day 90 and then thru cohabitation to the end of gestation. Included in study QBU00007 is a separate arm with at least 10 animals per sex per dose that will have been treated for 49 days which will include toxicokinetics and clinical, gross and microscopic pathology. To provide the Agency the 4-weeks of juvenile toxicity data requested in the 17 March 2008 meeting, Hyperion proposes to generate a QA audited interim report to summarize the findings in this group of animals (treated 49 days) to support the initiation of the proposed clinical study in pediatric UCD patients between the ages of 6 - 17.
    a. Will the previously filed 13-week juvenile primate study ((b) (4) 510010) and a 49-day QA-audited interim report from study QBU00007 provide sufficient data to support the initiation of the clinical study in pediatric patients 6 - 17 years of age (Protocol HPN-100-005)?

FDA Response:

Yes, your proposal is acceptable. However, the 49-day interim report of the toxicity study in neonatal/juvenile rats should contain information on all toxicity parameters including histopathology. A complete set of data tables should be provided. This study report should be provided for review and evaluation prior to initiation of the Pediatric Study.

Additional Discussion:

No additional discussion.

13. Hyperion submitted a Special Protocol Assessment (SPA) for its rat and mouse carcinogenicity study proposals. Dosing of the rat carcinogenicity study commenced on 8 October 2008 ([redacted] (b) (4) study no. [redacted] (b) (4) 671007); however, it was not possible for Hyperion to implement the Agency's recommendation on the mouse protocol and a revised proposal submitted to the Agency on 26 September 2008 (SN.040). Feedback from the Agency is still pending. Since submitting the revision of the mouse protocol, Hyperion has investigated the possibility of mouse carcinogenicity studies utilizing the Tg.rasH2 mouse. Hyperion intends to conduct its dose range study to determine whether that model is suitable for evaluation of HPN-100. If so, a new SPA for a definitive mouse carcinogenicity study using a Tg.rasH2 mouse model will be submitted for review.

FDA Response:

Please see answer to Question 14.

14. Since there are no preclinical data that raise a concern of potential carcinogenicity - including full batteries of genotoxicity, and pending successful completion of the dose range study, Hyperion will contend that the Tg.rasH2 mouse carcinogenicity study rather than a traditional mouse is acceptable. Does the Agency concur with this strategy?

FDA Response:

We recommend that you submit an amendment containing a rationale for conducting the Tg.rasH2 mouse carcinogenicity study instead of a 2-year study in mice. Your proposal will be presented to the Executive CAC for their concurrence.

Additional Discussion:

No additional discussion.

Pediatric Assessment Plans:

15. Based on the 17 March 2008 meeting minutes, Hyperion has updated its Pediatric Assessment Plan to continue discussions regarding the development of HPN-100 in the pediatric population. Hyperion is in the process of requesting orphan designation; however, a decision will not be rendered as of the time the End of Phase 2 meeting. As described in Sections 6 and 8, Hyperion intends to initiate studies in pediatric subjects ages 6 - 17. Should orphan designation not be granted to HPN-100 for the treatment of UCD, Hyperion will (b) (4) Will the Agency grant (b) (4)?

FDA Response:

As stated in the Type C Meeting Minutes from March 17, 2008, studies in younger children, including neonates and infants would be required under Pediatric Research Equity Act (PREA) since this group of pediatric patients is impacted by UCDs. A (b) (4)

If HPN-100 receives orphan designation, PREA would not apply, but studies in children 0-6 years of age would still be strongly encouraged, in order to provide labeling for patients less than 6 years of age.

Additional Discussion:

Hyperion requested clarification on the timing of (b) (4) ***request, appreciating that a final decision is not made until the time of approval. The Agency clarified that the Sponsor's formal request for*** (b) (4) ***must be submitted at the time of NDA submission.***

Additional Comments:

We have general comments regarding your proposed study procedures:

A. Protocol 100-006 (Pivotal Study)

1. **Stopping rules should include known pregnancy.**
2. **Safety laboratory studies and electrocardiograms (ECGs) should be collected more frequently (e.g., weekly) to ensure adequate safety monitoring.**
3. **Safety laboratory studies should be collected when adverse events are reported.**
4. **Weekly study visits should be conducted at a clinical center to ensure proper specimen collection and accurate adverse events reporting.**
5. **Diet should be controlled, and protein intake should be accurately recorded during the study period.**
6. **On study visit days, all meals should be taken at pre-specified times to control for the effects of meals on ammonia levels.**
7. **The case report forms (CRFs) should incorporate questions that specifically address the adverse events that were observed in the Phase 2 trials, e.g., gastrointestinal events.**

B. Protocol 100-005 (Pediatric PK/PD/Safety Study)

1. **Since we do not know the PK values for children, we would recommend adequate frequent PK samplings to capture Cmax and half-life.**
2. **Safety laboratory studies and ECGs should be collected more frequently (e.g., weekly) to ensure adequate safety monitoring.**
3. **Diet should be controlled and protein intake should be accurately recorded during the study period.**
4. **On study visit days, all meals should be taken at pre-specified times, to control for the effects of meals on ammonia levels.**
5. **The risks of oral liquid oil preparations should be addressed, as the use of oil based products, such as mineral oil, can be associated with aspiration pneumonia and malabsorption of fat soluble vitamins (21 CFR 201.302). Lipoid pneumonia as a result of mineral oil aspiration is of concern in both adult and pediatric patients, especially in patients with neurocognitive impairment. Patients with predisposing factors represent 75% of adult cases of exogenous lipoid pneumonia.[1] Both adult and pediatric patients with UCDs are more likely than the general population to have neurodevelopmental disability, and hence may be at higher of aspiration of an oil based product.[2] Please provide information regarding the type of oil used in the product, and the risk of aspiration and/or malabsorption of fat soluble vitamins. If aspiration may be a risk in pediatric patients with UCDs, then efforts to reduce the risk of aspiration (e.g., administration with food) should be incorporated in the protocol. Monitoring patients for fat soluble vitamin levels to rule out malabsorption should also be considered.**

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[1] Bandla HP, Davis SH, Hopkins NE. Lipoid pneumonia: A Silent Complication of Mineral Oil Aspiration. Pediatr. 1999;103(2):E19.

[2] Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders: Twenty years later. J Pediatr., 2001;138:S46-S55.

C. Protocol 100-007 (Extension Study)

1. **Patients should not be allowed to be maintained on (b) (4) (see answer to Question 9).**
2. **Safety monitoring should be conducted more frequently (e.g., ECG, safety laboratory studies, and study visits should be conducted at least monthly).**
3. **Additional stopping rules for individual patients and for the study should incorporated, as you have proposed for your pivotal study.**
4. **We would encourage you to enroll as many patients as possible to adequately establish the long term safety of HPN-100 (see Question 8b). In addition, the age distribution of patients in the long term study should reflect the epidemiology of patients with the disease and enroll a satisfactory number of pediatric patients.**
5. **Please consider evaluating inter-current illness episodes (e.g., number and type) as an additional secondary endpoint. These data may be useful when evaluating the number of hyperammonemic events.**
6. **Please note that all measurements of growth should be standardized and replicated.**
7. **Neuropsychological testing with a validated, standardized tool approved by the Agency should be performed at study entry and appropriate intervals as part of a longer term safety study (see below).**
8. **Please be aware that because of the small number of subjects available for study and the proposed chronic use of this product, additional safety data will be requested as Post Marketing Requirements (PMRs) at the time of NDA approval. A long term safety study (7-10 years) to assess growth and neurocognitive outcome and the establishment of a registry should be anticipated.**

MEETING ADDENDUM:

Note that this meeting addendum includes response changes due to discussion after the industry meeting.

FDA Response to 4.a. with Discussion from Meeting:

We acknowledge our prior recommendation to consider a non-inferiority design during your drug development program, and we agree that this type of study design may be used in Phase 3 trials. However, we have the following concerns regarding your proposed pivotal study design:

1. **An important criterion in designing a non-inferiority trial includes that the non-inferiority margin must be no larger than the effect the control can be reliably assumed to have had in the study and that also reflects the fraction of the control effect that is considered clinically essential (refer to ICH E10). You have not provided adequate justification to support your choice of the non-inferiority margin of (b) (4) µmol/L blood ammonia level. You state that a sample to sample difference of (b) (4) µmol/L would not result in a change in management in a clinically stable UCD patient, and that a difference of (b) (4) µmol/L is well below the level of 100 µmol/L, a level which requires**

medical intervention. However, a change of (b) (4) µmol/L may be clinically significant in a patient if the increase results in a blood ammonia level > 100 µmol/L. Furthermore, data provided from a retrospective review of patients receiving BUPHENYL® does not provide adequate information regarding the treatment effect since there are no data for baseline (non-treatment) ammonia levels in either medication compliant or non-compliant patients. Also, it is unclear from your background package how this (b) (4) µmol/L level would be would be calculated or derived (e.g., difference in average daily ammonia level, or difference in log transformation of daily ammonia level). Because you are proposing to study (b) (4) ammonia levels of HPN-100 in your current study design, you must provide data demonstrating the effect of BUPHENYL® on (b) (4) ammonia levels in order to justify your selection of (b) (4) µmol/L ammonia level non-inferiority margin.

2. **Given the small numbers of patients you plan to enroll in your pivotal trial, as well as the relatively small margin (M) of (b) (4) µmol/L of ammonia you have selected, we are concerned that there may be considerable difficulties with achieving the non-inferiority objective in your pivotal study. Also be aware that your study may not be appropriately powered to show (b) (4)**

3. **You have included (b) (4) in your protocol. Any decision criteria resulting from the (b) (4) should be clearly specified. We recommend that any (b) (4). Otherwise we recommend that you adopt an appropriate (b) (4).**

4. **Primary clinical endpoints should include both the measurement of ammonia AUC_{0-24} as well as plasma phenylacetylglutamine (PAGN) AUC_{0-24}. Note that this will change sample size considerations. Please note that the methods for the analysis of all primary and important secondary endpoints should be pre-specified in the protocol. In addition, the corresponding statistical analysis plan (SAP) should be submitted prior to the start of the study.**

Given these limitations and the insufficient details contained in your study design proposal, we cannot agree with your current Phase 3 study design. We encourage you to submit your final protocol for a special protocol assessment (SPA) during which time we could thoroughly review the design and statistical analysis plan for your pivotal trial. We also recommend that you consider alternate study designs for your Phase 3 clinical trial, including but not limited to, a bioequivalence trial of BUPHENYL® versus HPN-100. Data from your Phase 2 studies suggests that TN-ammonia AUC and PAGN AUC of HPN-100 may be equivalent or, in fact, superior to BUPHENYL®. We may accept a bioequivalence approach for the pharmacodynamic (PD) endpoints of TN-ammonia AUC_{0-24} and plasma PAGN AUC_{0-24} if the treatment difference did not result in a clinically unacceptable outcome (e.g., TN-ammonia AUC >100 µmol/L). If you choose to conduct a bioequivalence study, you should pre-specify the bioequivalence limits for the PD endpoints and provide justification for these limits.

<u>Additional Discussion:</u>

Based on data provided by Hyperion that suggest better correlation of plasma PAGN levels between BUPHENYL® and HPN-100, compared with urinary PAGN excretion (Table 9 and Table 10 pages 37-38), the Agency recommended that serum PAGN, rather than 24-hour urine PAGN, be used as the appropriate co-primary efficacy measure.

Hyperion stated they are receptive to the bioequivalence study but would like additional clarification regarding the study design. Hyperion believes that a reasonable bioequivalence limit is (b) (4) µmol/L; however, the Agency stated that Hyperion had not provided sufficient evidence in the background package to support a bioequivalence limit of (b) (4) µmol/L.

Although the Agency generally recognizes a bioequivalence range of 80-125%, in this case, there are two different pharmacodynamic endpoints (i.e., plasma ammonia AUC_{0-24} and PAGN AUC_{0-24}) and there is no clear mathematical relationship between these endpoints. Therefore, the Agency would recommend a bioequivalence range for PAGN toward 125%, and a bioequivalence range for ammonia toward 80%.

The Agency stated that diet should be controlled during the study.

Note that in response to Hyperion's questions post-meeting, FDA agrees that no specific recommendations regarding bioequivalence or non-inferiority limits were finalized during the meeting. Hyperion did agree, though, to a bioequivalence range for ammonia toward 80% if bioequivalence was chosen over non-inferiority. Upon further review during post meeting discussion, the Agency recommends that the bioequivalence range for PAGN should be toward 125%. We remind you that your choice of bioequivalence or non-inferiority limits should be justified. This information should be provided in the Special Protocol Assessment.

FDA Response to 5.a. with Discussion from Meeting:

We would not reject an open-label design for your pivotal trial as we agree that blinding may be difficult to achieve in this study. However, an open-label design may impact compliance, which may affect efficacy. Additionally, other factors such as reporting of adverse events or adherence to study procedures may be subject to bias with an open-label design. Therefore, we strongly recommend that the study be conducted as a double-blind trial.

<u>Additional Discussion:</u>

Hyperion stated a shorter study would minimize patient's medication burden over a longer period of time. Hyperion proposed a double-blind, cross over trial with a considerably shorter study (e.g., (b) (4) weeks), where each patient would serve as his/her own control. The FDA stated that it would consider such a study design when it is submitted under the SPA. However, the Agency stated that if it is not feasible to conduct a double-blind study, at a

minimum, the analysis of the primary efficacy measures (e.g., PAGN and ammonia levels) must be blinded. Additionally, Hyperion must be blinded to treatment assignment.
Note that in response to Hyperion's questions post-meeting, FDA recommends that if it is not feasible to conduct a double-blind study, at a minimum, the analysis of the primary efficacy measure (e.g., PAGN and ammonia levels) must be blinded. Additionally, Hyperion must be blinded to treatment assignment.

FDA Response to 8.b. with Discussion from Meeting:

You state that the total UCD population in the US is approximately 400 patients. Since HPN-100 may provide a benefit in the long term treatment of UCDs, there may be substantial interest in participation in this study. Therefore, you may be able to enroll more than 10% of the UCD population in your study. Additionally, although the total patient exposure being adequate to support approval is a review issue, we will likely require safety data collected in UCD patients with a minimum of 12 months of exposure to HPN-100. These data should be included at the time of the NDA filing.

<u>Additional Discussion:</u>

There was additional clarification regarding the total number of patients in the US with UCDs who are being treated with BUPHENYL®. Hyperion stated that in the US, there are approximately 300 UCD patients, but only (b) (4) of these patients are being treated with BUPHENYL®. Therefore, Hyperion estimates that if the HPN-100 study population were to include 50-60 patients, they would constitute a significant number ((b) (4)%) of the US population that is currently being treated with BUPHENYL®. After further internal discussion following the meeting, the Division concurs that this is a reasonable study population. However, a minimum of 35-40 patients with 12 months of safety data should be submitted at the time of the NDA filing.

The Agency agrees to review safety data as supportive evidence from other sources that include long-term (e.g., 6-12 months) studies in UCD patients treated with HPN-100.
Note that in response to Hyperion's questions post-meeting, FDA reminds Hyperion that during the EOP2 meeting, Hyperion stated that they would have 12-month safety data on 38 patients exposed to HPN-100 at the time of the filing of the NDA. Based on this information during post meeting discussion, we determined that a minimum of 35 to 40 patients with 12 months of safety data should be included at the time of the NDA submission.

FDA Response to 10.a. with Discussion at Meeting:

Based on the results from Study UP 1204-002, there was no relationship between the half-life of PBA or PAGN and the subject's liver function (Child-Pugh grade). Though the half-life of PAA seemed to increase with the severity of hepatic impairment, the final production of PAGN did not show any relationship with hepatic impairment. Therefore it is acceptable that no further studies be conducted in non-UCD patients with hepatic

impairment. However, we would require that a subset of UCD patients with known liver impairment (e.g., patients with AL deficiency) be studied and have further efficacy, safety, and PK/PD testing (e.g., PBA, PAA, PAGN) be performed as part of your Phase 3 trial.

<u>Additional Discussion:</u>
In response to Hyperion's questions post-meeting, please refer to the additional discussion under Question 10.b.

FDA Response to 10.b. with Discussion at Meeting:

We agree PK/PD studies in non-UCD patients with renal impairment are not required. However, there are patients with UCDs who have abnormal kidney function. In Study 1204-003, the maximum serum creatinine measured was 1.7 mg/dl, which is abnormal. Additionally, some UCD patients enrolled in the UCD Consortium-Sponsored Longitudinal Study also have abnormal kidney function since measured serum creatinine ranged from 0.1 mg/dl to 3.3 mg/dl. Therefore, we would require that a subset of UCD patients with known renal impairment (chronic kidney disease) be studied and have further efficacy, safety, and PK/PD testing (e.g., PBA, PAA, PAGN) be performed as part of your Phase 3 trial.

<u>Additional Discussion:</u>
In response to Hyperion's questions post-meeting, FDA acknowledges that Hyperion could not pre-specify a defined subset nor commit to enrolling a specific number of UCD patients with clinically significant renal or hepatic impairment, and that Hyperion would make an effort to enroll such patients.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 73480	HYPERION THERAPEUTICS	GLYCERYL TRI (4-PHENYLBUTYRATE) (GT4P)

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

/s/

ANNE R PARISER
04/14/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 73,480

Hyperion Therapeutics, Inc.
Attention: Klara A. Dickenson, Sr. Vice President
Regulatory Affairs and Compliance
601 Gateway, Suite 200
South San Francisco, CA 94080

Dear Ms. Dickenson:

Please refer to your Investigational New Drug Application IND 73,480 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HPN-100 (formerly known as GT4P) Solution.

We also refer to the Type C meeting between representatives of your firm and the FDA on March 17, 2008. The purpose of the meeting was to discuss specific questions regarding your clinical and nonclinical programs for HPN-100.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Hee (Sheila) K. Lianos, R.Ph., PharmD.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 17, 2008
TIME: 1:00 pm – 2:00 pm
APPLICATION: IND 73,480
DRUG NAME: HPN-100 (formerly GT4P)
TYPE OF MEETING: Type C
MEETING CHAIR: Anne Pariser, M.D.
MEETING RECORDER: Hee K. Lianos, R.Ph., PharmD.

FDA ATTENDEES: (Title and Office/Division)

Division of Gastroenterology Products (DGP)
Anne Pariser, M.D., Medical Team Leader
Lynne Yao, M.D., Medical Officer
Sushanta Chakder, Ph.D., Acting Pharmacology Team Leader
Ke Zhang, Ph.D., Pharmacology Reviewer
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
Julieann DuBeau, M.S.N., R.N., Chief, Project Management Staff
Hee K. Lianos, R.Ph., PharmD., Regulatory Project Manager

Pediatric and Maternal Health Staff (PMHS)
Lisa Mathis, M.D., Associate Director
Felicia Collins, M.D., Medical Officer
Rosemary Addy, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:
Hyperion Therapeutics
Crystal Browning, Senior Manager, Regulatory Affairs
Wayne Davis, Ph.D., Vice President, Clinical Operations
Klara Dickinson, Sr. Vice President, Regulatory Affairs and Compliance
Chris Rivera, President & CEO
Hoi Leung, Ph.D., Vice President, Biostatistics
Marvin Garovoy, M.D., Sr. Vice President, Clinical Development
Sharron Gargosky, Ph.D., Chief Scientific Officer

(b) (4)

BACKGROUND:

On March 9, 2006, Ucyclyd Pharma, Inc. submitted the original (initial) IND protocol to IND 73,480 for Glyceryl Tri (4-phenylbutyrate) (GT4P) Solution for the investigational use of GT4P for the proposed indication of maintenance treatment of patients with deficiencies in enzymes of the urea cycle. On December 12, 2007, Ucyclyd Pharma, Inc. designated Hyperion Therapeutics as an authorized representative of the sponsor who, within the same submission, requested a Type C Meeting to discuss: 1) proposed changes to the clinical protocol for the ongoing Phase 1/2 study UP 1204-003; 2) a pediatric assessment plan for the HPN-100 (formerly known as GT4P) clinical development program; and 3) the nonclinical toxicology plan to support the HPN-100 clinical development program.

On February 15, 2008, Hyperion submitted background information and questions for the meeting. Preliminary responses to the questions posed by the sponsor were sent to the sponsor contact (Hyperion Therapeutics) on March 13, 2008. On March 17, 2008, a Type C face-to-face Meeting was held between Hyperion Therapeutics, Inc. and the Agency.

MEETING OBJECTIVES:
The purpose of this meeting is to clarify and discuss FDA's March 13, 2008 responses to Hyperion's questions, as needed.

DISCUSSION POINTS: Following introductions, Hyperion's questions from the February 15, 2008, background information package were used as the basis for further discussion regarding their clinical studies, pediatric plan, and nonclinical toxicology plan.

The format of these minutes provides for Hyperion's questions in regular typeface, followed by the Agency's responses in **bolded** print, followed by the March 17, 2008 meeting discussion in ***italic and bolded*** print.

DISCUSSION:

Questions and Responses

(Amendment to Protocol UP 1204-003)

Hyperion proposes to amend Protocol UP 1204-003 to [redacted] (b) (4) (see Section 11.2 and Appendix 0).

Agency Comment: Highlighted references are not found.

1. The PK/PD modeling described in Section 11.1 indicates that HPN-100 is ~60% bioavailable compared to the mole equivalent dose of Buphenyl® (label dose 9.9 to 13 g/m^2/day or 245 to 321 mg/kg). To [redacted] (b) (4), Hyperion is proposing

to amend protocol UP 1204-003 to include [redacted] (b) (4) Does the Agency agree that [redacted] (b) (4) is a reasonable [redacted] (b) (4) HPN-100 bioavailability issues in UP 1204-003?

Agency Response:

No. The preliminary PK data from the three UCD patients treated in Study UP 1204-003 were very different from the results obtained in healthy subjects. Based on the preliminary data from the three UCD patients, HPN-100 behaved like Buphenyl in two out of three patients (per results on pages 54 to 56 in the meeting package). As such, we do not recommend the [redacted] (b) (4) at this time, and we do not agree with amending the protocol as proposed. Please collect PK data on the remaining seven patients under the existing protocol. You should also determine the cause of the disparity in findings between healthy subjects and UCD patients.

2. Hyperion would like to explore the possibility of including [redacted] (b) (4) of Buphenyl® to ensure a good understanding of metabolism and safety of HPN-100 [redacted] (b) (4) prior to designing a Phase 3 study. The current UP 1204-003 amendment proposes [redacted] (b) (4) that would be [redacted] (b) (4). In population simulations, the [redacted] (b) (4) Does the agency agree that [redacted] (b) (4) in protocol UP 1204-003?

Agency Response:

Please see response to clinical question 1.

3. The first 3 UCD patients in UP 1204-003 safely converted from Buphenyl to HPN-100 [redacted] (b) (4) Thus, Hyperion is proposing to amend protocol UP 1204-003 to allow [redacted] (b) (4) Does the Agency agree with this proposal?

Agency Response:

No. You have not provided adequate information to justify this change. The three UCD patients treated to date were all (b) (4) To date, you have not collected any information on the safety of (b) (4) You should collect data on patients in whom the (b) (4) and who will undergo (b) (4) conversion from Buphenyl to HTN-100 as stated in the existing protocol.

<u>Additional Discussion for Questions 1, 2, and 3:</u>

Hyperion requested consideration of three proposed protocol amendments to Study UP 1204-003 (adult Phase 1 PK/PD study) as follows:

1. ***Instead of having patients (b) (4) Hyperion felt that this would improve enrollment and patient convenience.***

2. ***Convert patients from Buphenyl to HPN-100 in a single step, (b) (4) manner as currently delineated in the study protocol. Hyperion is concerned about possible adverse events due to HPN-100 and Buphenyl interactions, and believes that single-step conversion from Buphenyl to HPN-100 is justified based on the clinical experience obtained to date with HPN-100 in normal volunteers and UCD patients.***

3. ***(b) (4) Buphenyl dose should be permitted in this study, instead of (b) (4) as currently delineated in the study protocol based on the clinical experience obtained to date with HPN-100 in normal volunteers and UCD patients.***

   Hyperion presented two slides of summary PK/PD results for HPN-100 versus Buphenyl in normal human volunteers and UCD patients (n = 3) in support of the request for (b) (4) (see attachment following meeting minutes).

The Agency responded that there is not enough clinical experience to date in UCD patients to justify single-step conversion or (b) (4), and information available to the Agency at this time shows that HPN-100 PK/PD parameters in UCD patients do not appear to be similar to those obtained in normal volunteers. The Agency reiterated that additional PK/PD information in UCD patients needs to be obtained and submitted for our review prior to any consideration of single-step conversion or (b) (4) with HPN-100.

The Agency stated that (b) (4) could be considered provided an adequate safety plan is proposed that is consistent with the known PK/PD and toxicity profile of HPN-100. The sponsor should submit their proposal in writing for our review, and further discussion as to the acceptability of this proposal can occur after the proposal is submitted.

4. The proposed amendment to study UP 1204-003 allows the UCD patients to be dosed with HPN-100 for a total of (b) (4). This duration of exposure is supported by the 13-week repeated dose toxicity studies in mice, rats, and primates, and by recommendations defined in ICH M3 Guidance titled "Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals." Does the Agency agree?

Agency Response:

Nonclinical studies support the duration of the clinical trial for up to 13 weeks of treatment with HTN-100. However, we do not agree with changing the protocol at this time based on the limited information available in only three patients. See responses to clinical questions 1 through 3.

5. Hyperion is planning to initiate a Phase 2 PK/PD study in the coming months to evaluate HPN-100 in pediatric UCD patients ranging between the ages of 2 and (b) (4) years (refer to Section 12, and Appendix 0). The design is similar to UP 1204-003 (with the proposed modifications); initially patients will be treated with HPN-100 at a Buphenyl® (b) (4) dose. After a week on this dose of HPN-100, patients will return to clinic (b) (4) To minimize blood draws, patients will have PK/PD assessments on Day 1 with sparse-sampling draws on subsequent visits. Proposed sampling design includes Day 1; pre-dose, 1, 4, 6, 12, and 24 hours. On subsequent visits, blood draws pre-dose (trough level) to the first dose of the day and 2 hours after the second dose of the day will be the sparse sampling. Accumulated pediatric PK/PD data will be included in the current PK/PD dataset to update the PK/PD model and determine if age-related exposure-response exists for HPN-100. Does the Agency find this study design and approach to PK sampling and analysis acceptable?

Agency Response:

The pediatric study should not be initiated until the study in adult patients has been completed, and the results have been analyzed.

Your proposed Phase 2 PK/PD protocol for pediatric patients needs revision. It is not clear to us if a TID dosing regimen or a single-dose administration is planned for pediatric patients, since you proposed blood sampling on Day 1 at pre-dose, and at 4, 6, 12, and 24 hours post-dose at the clinic visit.

Sparse sampling for population PK (PPK) analysis is acceptable for Day 1 blood drawing. If TID dosing is planned for pediatric patients, we recommend that blood samples be drawn at pre-dose, and at 2 and 6 hours post-dose in half of the pediatric patients, and at 1, 4, and 8 hours post-dose in the other half of patients during a dosing interval (between 0 and 8 hours) at steady state. If single-dose administration is planned on Day 1, for each individual pediatric patient, four blood samples should be drawn randomly, i.e., one from each of the four time periods (0-4, 4-8, 8-12, and 12-24 hours post-dose).

Additional Discussion:

Hyperion stated that they will complete and analyze the results of the adult Phase 1 PK/PD study prior to initiating any studies in pediatric patients.

6. Hyperion is proposing to include all UCD patients that are (b) (4) years of age in the Phase 3 study. Due to the challenging PK/PD sampling issues involved in studying neonates and infants, Hyperion intends to (b) (4) Would the Agency consider such (b) (4) If not, would a (b) (4)? What type of data would the Agency require in (b) (4) ?

Agency Response:

(b) (4)

(b) (4)

Of note, if a pediatric population is excluded from drug studies for safety reasons, this information must be included in the drug labeling.

If efficacy is demonstrated in children, adolescents, and/or adults, we may consider if it would be appropriate to extrapolate efficacy down to infants and neonates. However, if it is determined that extrapolation is inappropriate, efficacy studies in neonates and infants also would be required (b) (4)

Please note that nonclinical juvenile and/or neonatal studies are required prior to the initiation of any pediatric trial.

Additional Discussion:

(b) (4)

7.

Agency Response:

(b) (4)

(b) (4)

[redacted]

We additionally note that should your drug be submitted for an NDA and be approved, we will only be able to label your drug for the populations studied in your clinical development program. Since it is anticipated that pediatric patients would use HTN-100 post-approval, consideration should be given to including pediatric patients as early in your program as possible.

8. Hyperion is initiating a 6 month rat, and a 12 month primate study to fulfill the chronic toxicology study guidelines defined by ICH. The 12 month primate study is due to begin in April 2008. Currently, Hyperion is proposing to conduct an interim 6 month data analysis to support the dosing of Phase 3 study patients up to 6 months duration. The 6 month data will be available prior to initiating the Phase 3 study. The 12 month data will not be available at study initiation, but will be available prior to extending exposures beyond 6 months. Will this provide sufficient data to support the initiation of the Phase 3 clinical trial?

Agency Response:

Your proposed six-month interim rodent and non-rodent toxicology data will support clinical trials up to six months. However, the six-month interim report must include analysis of all toxicology parameters including histopathology.

9. In addition to the chronic toxicology studies, ADME studies in the primate, and the Segment I and II reproduction and development toxicity studies will be completed prior to initiation of the Phase 3 study, will these studies be sufficient to support the

continuation of clinical development plan as described in this meeting package including the initiation of the Phase 3 study?

Agency Response:

Yes.

10. Throughout the communications regarding the clinical hold on IND 73,480, there were several communications regarding non-clinical hold issues regarding the ICH S7A and S7B. Hyperion would like to confirm that the Agency has agreed with the non-clinical proposal that Ucyclyd presented for addressing the issue including the following studies:

- *in vitro* hERG assay (complete, study IPST-501209-1),
- *in vivo* cardiac telemetry in Primate study (complete, UCY-004),
- *in vitro* study in isolated cardiac myocytes using voltage clamp technique to determine the effect of GT4P on ionic currents (complete IPST-700109-1), and
- *in vivo* study in simulated pathological conditions and arrhythmias (Carlson Model) (to be conducted)

Do these studies address the nonclinical assessment on cardiovascular pharmacology?

Agency Response:

Yes.

11. In the preIND meeting minutes, the Division stated that 2-year carcinogenicity studies in mice and rats were required. Hyperion is committed to conducting carcinogenicity studies. (b) (4) ?

Agency Response:

No. Complete carcinogenicity study reports should be submitted in the NDA.

12. In addition to the chronic toxicology studies, Hyperion is also scheduled to complete the following studies, ADME in primates, Segment I, II and III reproduction toxicity studies, and carcinogenicity study (b) (4) Does the Agency agree that the nonclinical data generated to date and proposed testing plan provided in the briefing document is sufficient to support (b) (4) ?

Agency Response:

No. Since you plan to investigate HPN-100 in pediatric UCD patients, you need to conduct repeat-dose toxicology studies in neonatal/juvenile rodent and non-rodent animals prior to initiating pediatric studies.

Additional Discussion:

The Agency clarified that a one-month (four-week) rodent study and a three-month (13-week) study in sexually immature animals in a non-rodent species (e.g., one to two year old monkeys) would support human PK studies in patients six to 16 years of age. The sponsor agreed to provide information on the age of the monkeys used in the toxicology studies. The nonclinical data from these studies are to be submitted for our review prior to initiating pediatric studies.

If the sponsor plans on administering the drug to patients younger than six years of age, they will need to study younger animal. An one-month repeat-dose toxicity study in neonatal rats and a three-month repeat-dose toxicity study in neonatal non-rodents (dogs will be acceptable) will be needed prior to initiation of studies in younger patients.

The sponsor can submit study protocols for these nonclinical studies for the Agency's review and comment prior to initiating the studies.

Hyperion Therapeutics intends to submit HPN-100 in an eCTD format beginning with the IND Annual Report which is due on 10 June 2008. All previous submissions to this application were made in paper and will not be resubmitted. The electronic submission will be prepared in accordance with the following guidance and specifications:

- ICH eCTD Specifications, version 3.2, dated Feb 2004
- eCTD Backbone Files Specification for Module 1, version 1.3, dated Dec 2006
- eCTD Backbone Files Specification for Modules 2 through 5, version 1.1, dated Mar 2004
- eCTD Backbone Files Specifications for Study Tagging Files, version 2.2, dated Aug 2005
- eCTD Table of Contents Headings and Hierarchy, version 1.2, dated July 2005
- Study Data Specifications, version 1.4, dated Aug 2007

Agency Response:

The above Guidance is correct at this time. When you are ready to submit your application, please verify on the eCTD FDA web site[1] that there have been no new updates that may affect your submission.

13. Does the Agency find it acceptable to convert the paper IND 73,480 to an eCTD format as described above?

Agency Response:

Yes.

14. Hyperion will be utilizing the services of [redacted] (b) (4). for the eCTD compilation. [redacted] (b) (4) has previously submitted an eCTD pilot (Ref: [redacted] (b) (4) submitted [redacted] (b) (4)) and we therefore request a waiver for submitting an additional pilot. Will the Agency grant a waiver for submitting an additional pilot?

Agency Response:

[redacted] (b) (4) **had done an eCTD pilot and passed the FDA evaluation. There is no need for Hyperion to submit the eCTD pilot again if they use the services of** [redacted] (b) (4)

ATTACHMENTS/HANDOUTS:

(see attachment below)

2 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Electronic Common Technical Document (eCTD). <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

Linked Applications	Sponsor Name	Drug Name
IND 73480	UCYCLYD PHARMA INC	GLYCERYL TRI (4-PHENYLBUTYRATE) (GT4P)

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/s/

HEE K LIANOS
04/10/2008
meeting with sponsor