CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPATMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 16, 2013

TO: NDA 203284 CMC Review # 1

FROM: Hamid R. Shafiei, Ph.D., CMC Reviewer
(ONDQA/Division II/Branch IV)

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief
(ONDQA/Division II/Branch IV)

SUBJECT: Final CMC Recommendation

In review # 1 of NDA 203284 for Ravicti Liquid for oral use, this NDA was not recommended for approval from the CMC perspective due to the following reasons:

1) CMC related label/labeling issues were ***not*** resolved
2) An overall recommendation of "Acceptable" from the Office of Compliance regarding the facilities involved in this NDA was ***not*** yet issued

The CMC label/labeling issues have been resolved via the amendments dated December 13, 2012 and December 31, 2012 (see the **Attachment -2**).

The Office of Compliance has also made an overall recommendation of "Acceptable" for the facilities involved in this NDA on January 14, 2013 (see the **Attachment-1**).

Recommendation:

This NDA is now recommended for **approval** from the ONDQA perspective.

Appendix

Attachement-1

EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 203284/000	**Action Goal:**	
Stamp Date:	23-DEC-2011	**District Goal:**	24-NOV-2012
Regulatory:	23-JAN-2013		
Applicant:	HYPERION THERAP INC	**Brand Name:**	Glycerol Phenylbutyrate (HPN-100)
	601 GATEWAY BLVD STE 200	**Estab. Name:**	
	SOUTH SAN FRANCISCO, CA 94080	**Generic Name:**	Glycerol Phenylbutyrate (HPN-100)
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	180	001; LIQUID; GLYCEROL PHENYLBUTYRATE; 25ML 002; LIQUID; GLYCEROL PHENYLBUTYRATE; 120ML 003; LIQUID; GLYCEROL PHENYLBUTYRATE; 450ML	
Application Comment:			

FDA Contacts:	C. TRAN-ZWANETZ	Project Manager		(HFD-800)	3017963877
	H. SHAFIEI	Review Chemist			3017962326
	M. KOWBLANSKY	Team Leader			3017961390

Overall Recommendation:	ACCEPTABLE	on 14-JAN-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 07-FEB-2012	by EES_PROD		
	PENDING	on 07-FEB-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment:

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				(b) (4)
SUBMITTED TO DO		GMP Inspection			
ASSIGNED INSPECTION TO IB		GMP Inspection			
INSPECTION PERFORMED			(b) (4)		

This Pre-Approval Inspection (PAI) of a microbiological control testing laboratory was conducted in accordance with a request from DFFI/IOB and CDER/OC/DIDQ/ICB2 (International Compliance Branch 2) for a PDUFA Pre-Approval Inspection of the laboratory to evaluate their microbiological testing of the non-sterile liquid drug substance Glycerol Phenylbutyrate (GPB), under new drug application (NDA) 203284/000. The holder of the NDA is Hyperion Therapeutics, Inc., South San Francisco, CA. The manufacturer, packager and final release testing facility for the GPB drug substance is (b) (4)

Coverage for this inspection was conducted under CP 7356.002, Drug Manufacturing Inspections and CP 7346.832, Pre-Approval Inspections.

Previous inspection of this microbiological control testing laboratory was conducted (b) (4) by a team consisting of a CSO and a Microbiologist. The inspection was a PAI covering the finished dosage sterility testing of (b) (4)

The current inspection included coverage of the laboratory's Quality, Facilities & Equipment, and Laboratory systems. Profile class CTL (Control Testing Laboratory) was covered during the inspection. The inspection found that three lots of GPB were sent b

DO RECOMMENDATION	(b) (4)	ACCEPTABLE INSPECTION	(b) (4)
OC RECOMMENDATION	(b) (4)	ACCEPTABLE DISTRICT RECOMMENDATION	(b) (4)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: PROVIDES FOR MANUFACTURING, QA/QC TESTING AND RELEASE, PACKAGING, STABILITY TESTING (GLYCEROL PHENYLBUTYRATE, DSM)
(b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				(b) (4)
SUBMITTED TO DO		GMP Inspection			
WILL BE OVER 3 YEARS AT TIME OF PDUFA OTHER FIRMS PENDING INSPECTION REQUESTS FOR THIS NDA					
ASSIGNED INSPECTION TO IB	(b) (4)	GMP Inspection			
INSPECTION PERFORMED			(b) (4)		
INSPECTION SCHEDULED					
UNDER REVIEW					
CASE ID (b) (4) IN QUEUE FOR REVIEW; CSO NOT YET ASSIGNED					
DO RECOMMENDATION	(b) (4)			ACCEPTABLE	
				INSPECTION	
OC RECOMMENDATION				ACCEPTABLE	
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: USED FOR STABILITY SAMPLE STORAGE (b) (4)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
REQUEST CANCELLED	(b) (4)			(b) (4) IRRELEVANT FACILITY/PROFILE	
SUBMITTED TO OC				(b) (4)	
OC RECOMMENDATION				ACCEPTABLE BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: USED FOR MANUFACTURING, QA/QC TESTING AND RELEASE, PACKAGING, STABILITY TESTING (b) (4)
(b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				(b) (4)
SUBMITTED TO DO		GMP Inspection			
ASSIGNED INSPECTION TO IB		GMP Inspection			
INSPECTION SCHEDULED			(b) (4)		
INSPECTION PERFORMED					

This inspection of a contract manufacturing site of Active Pharmaceutical Ingredients (APIs) was initiated in response to CDER/HFD-325, Foreign Inspection Request trip No (b) (4) FACTS Assignment ID (b) (4) to conduct a Pre-Approval Inspection (PAI) of NDA (b) (4) . Other products covered include NDA 203284 for Glycerol Phenylbuyrate, (b) (4) Profile class CSN was covered. Firm stated they are not a contract testing lab and profile class CTX was discontinued in FACTS. CTL also does not apply to this firm as stated by firm management..

The previous inspection conducted on (b) (4) did not result in issuance of a FDA 483. One recommendation was made: Drug Master File (DMF) states the method and the details of how many standard injections to inject for system suitability along with the number of sample injection(s) to determine the assay. The EIR noted the firm was conducting (b) (4) .

The current inspection did not result in issuance of an FDA 483. Various records were reviewed for PAI coverage (b) (4) manufacturing. cGMP controls were reviewed for Glycerol Phenylbuyrate, (b) (4). Various elements of Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling and Laboratory Control Systems were covered. The following recommendations were made: list summary of change cont

UNDER REVIEW	(b) (4)		(b) (4)
CSO NOT YET ASSIGNED			
DO RECOMMENDATION		ACCEPTABLE	
		INSPECTION	
OC RECOMMENDATION		ACCEPTABLE	
		DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1224701 **FEI:** 1000513191

LYNE LABORATORIES INC

10 BURKE DR
BROCKTON, MA 02301

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: USED FOR MANUFACTURING, QA/AC TESTING AND RELEASE, PACKAGING, STABILITY TESTING AND STORAGE (on 17-JAN-2012 by C. TRAN-ZWANETZ (HFD-800) 3017963877)
PER DARRTS - LYNE LABS IS FD MANUFACTURER AND PRODUCT IS ORALLY ADMINSTERED LIQUID - PROFILE CHANGED FROM CSN TO LIQ (on 15-MAR-2012 by D. SMITH (HFD-323) 3017965321)

Profile: NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-FEB-2012				TRANZWANETZC
SUBMITTED TO DO	15-MAR-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION	25-MAR-2012			ACCEPTABLE	DEMERSON
THE FIRM WAS LAST INSPECTED 3/9-3/25/11. THE INSPECTION WAS CLASSIFIED VAI. THE INSPECTION COVERED LIQUID PRODUCTS. THE FIRM HAS MANUFACTURED LIQUID PRODUCTS IN THE PAST, BASED ON FILE REVIEW AND PREVIOUS EIR, THE DISTRICT RECOMMENDS APPROVAL OF THE FACILITY FOR THIS APPLICATION. THE DISTRICT WILL COVER THIS PRODUCT DURING THE NEXT GMP AT THIS FACILITY.				BASED ON FILE REVIEW	
OC RECOMMENDATION	26-MAR-2012			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE OTHER TESTER
Establishment Comment: UASED FOR MICROBIOLOGICAL TESTING (b) (4)
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				(b) (4)
SUBMITTED TO DO		10-Day Letter			
JUST A DOUBLE CHECK TO THE DO FOR MICRO TESTING					
DO RECOMMENDATION	(b) (4)			ACCEPTABLE	
THE FIRM WAS LAST INSPECTED (b) (4) INSPECTION WAS CLASSIFIED VAI. CORRECTIVE ACTIONS TO ISSUED 483 WERE REVIEWED AND DETERMINED TO BE APPROPRIATE. FIRM HAS APPROPRIATE COMPLIANCE HISTORY. DISTRICT RECOMMENDS APPROVAL OF THIS SITE FOR THIS APPLICATION BASED ON THE PREVIOUS INSPECTION RESULTS.				BASED ON FILE REV	
OC RECOMMENDATION	(b) (4)			ACCEPTABLE	
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: USED FOR MICROBIOLOGICAL TESTING (GLYCEROL PHENYLBUTYRATE, (b) (4) (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				(b) (4)
SUBMITTED TO DO		GMP Inspection			
MICRO TESTING OF DRUG SUBSTANCE					
ASSIGNED INSPECTION TO IB	(b) (4)	GMP Inspection			
INSPECTION PERFORMED			(b) (4)		
INSPECTION PERFORMED					
INSPECTION SCHEDULED					
DO RECOMMENDATION				ACCEPTABLE	
REPRESENTATIVE COVERAGE OF TESTING RESPONSIBILITIES PROVIDED DURING INSPECTION ENDING ON (b) (4). INSPECTION WAS CLASSIFIED NAI.				BASED ON FILE RE	
OC RECOMMENDATION	(b			ACCEPTABLE	
				DISTRICT RECOMMENDATION	

Attachment-2

1) Final labeling: The applicant has submitted an interim labeling on December 31 2012 addressing all CMC labeling issues that were documented in CMC review #1 of this NDA.

HIGH LIGHTS **ACCEPTABLE**

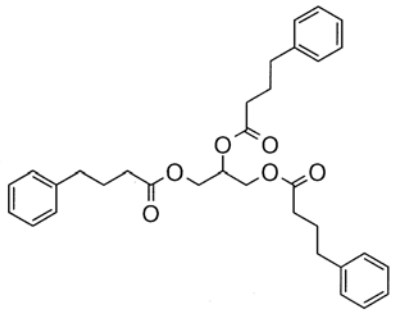
Dosage Form and Strength: Liquid. Each mL of Ravicti contains 1.1 grams of glycerol phenylbutyrate.

- 25 mL multidose glass bottle

FULL PRESCRIBING INFORMATION **ACCEPTABLE**

Description: Ravicti (glycerol phenylbutyrate) is a clear, colorless to pale yellow liquid, for oral administration. It is insoluble in water and most organic solvents, and it is soluble in dimethylsulfoxide (DMSO) and > 65% acetonitrile.

Glycerol phenylbutyrate is a nitrogen binding agent. It is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone, the chemical name of which is benzenebutanoic acid, 1', 1' ' –(1,2,3-propanetriyl) ester with a molecular weight of 530.67. It has a molecular formula of C33H38O6. The structural formula is:



How Supplied: Ravicti (glycerol phenylbutyrate) liquid 1.1 g/mL is supplied in multi-use, 25 mL, glass bottles. The bottles are supplied in the following configurations:

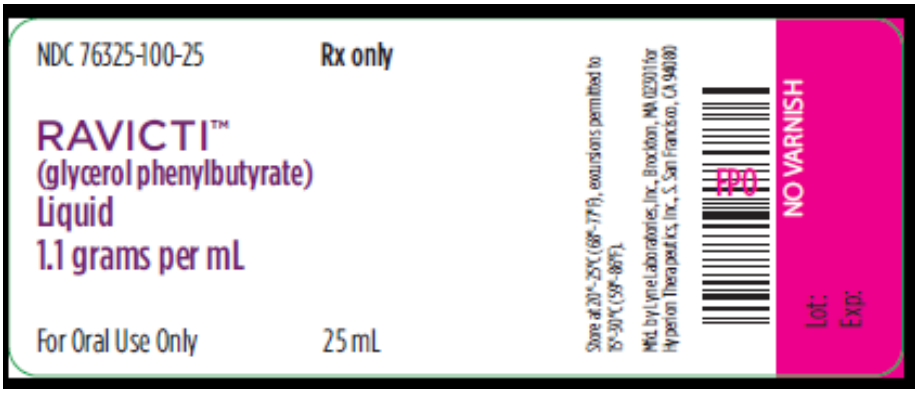
- NDC 76325-100-25: Single 25 mL bottle per Carton
- NDC 76325-100-04: Four 25 mL bottles per Carton

Store at 20°–25°C (68°–77°F) with excursion permitted to 15°–30°C (59°–86°F).

2) Final immediate container/carton label
The applicant has provided a labeling amendment on December 31, 2012 that provides the immediate container as well carton labels Ravicti (glycerol phenylbutyrate) Liquid for oral use.

The figure below is the immediate container and carton labels, respectively for Ravicti packaged in 25-mL glass bottles.

ACCEPTABLE



ACCEPTABLE


RAVICTI™
(glycerol phenylbutyrate)
Liquid, 1.1 grams per mL
NDC 76325-100-25
Rx only
RAVICTI™
(glycerol phenylbutyrate)
Liquid
1.1 grams per mL
25 mL
For Oral Use Only
Pharmacist: Dispense the enclosed Medication Guide to patient and/or caregiver.
Lot:
Exp:
For Oral Use Only
Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F).
Manufactured by:
Lyne Laboratories, Inc.
Brockton, MA 02301
Manufactured for:
Hyperion Therapeutics, Inc.
601 Gateway Blvd, Suite 200
South San Francisco, CA 94080
HYPERION
THERAPEUTICS
NDC 76325-100-25
Rx only
RAVICTI™
(glycerol phenylbutyrate)
Liquid
1.1 grams per mL
25 mL
For Oral Use Only
Pharmacist: Dispense the enclosed Medication Guide to patient and/or caregiver.
Usual dosage: See Prescribing Information.
Each mL of RAVICTI contains 1.1 grams of glycerol phenylbutyrate and delivers 1.02 grams of phenylbutyrate.
Keep out of reach of children.
Pharmacist: Dispense with a measuring device appropriate for the prescribed dose.

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/s/

HAMID R SHAFIEI
01/16/2013

MOO JHONG RHEE
01/16/2013
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Hamid R. Shafiei, Ph.D., CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: hamid.shafiei@fda.hhs.gov
Phone: (301)-796-2326
Fax: (301)-796-9745

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: 203-284

Name of Product: Ravicti (glycerol phenylbutyrate)

Applicant: Ucyclyd Pharma, Inc.

Applicant's Contact Person: Klara Dickinson, Sr. VP Regulatory Affairs

Address: 7720 N. Dobson Road, Scottsdale, AZ 85256

Telephone: (480) 291-5953 Fax: (480) 302-6333

Date Methods Validation Consult Request Form Received by DPA: 4/27/12

Date Methods Validation Package Received by DPA: 4/27/12

Date Samples Received by DPA: 5/16/12

Date Analytical Completed by DPA: 8/9/12

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments:
See attached memo

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3866

Date: July 30, 2012

To: Hamid R. Shafiei, Ph.D., CMC Reviewer
Marie Kowblanski, Ph.D., CMC Lead

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis

From: Jamie D. Dunn, Chemist

Subject: Methods Validation for NDA 203284
Ravicti (Glycerol Phenylbutyrate) Oral Liquid
Hyperion Therapeutics, Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. LA6-0179 revision 2 "HPLC Assay for (b) (4) in Glycerol Phenylbutyrate and HPN-100 (glycerol phenylbutyrate) Oral Liquid"
2. LA6-0174 revision 3 "HPLC Assay for the Determination of (b) (4) Impurities in Glycerol Phenylbutyrate (GPB) and HPN-100 (glycerol phenylbutyrate)"

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods.

1. LA6-0179 revision 2 "HPLC Assay for (b) (4) in Glycerol Phenylbutyrate and HPN-100 (glycerol phenylbutyrate) Oral Liquid"

(b) (4)

2. LA6-0174 revision 3 "HPLC Assay for the Determination of (b) (4) Impurities in Glycerol Phenylbutyrate (GPB) and HPN-100 (glycerol phenylbutyrate)"

   - Typographical error in the Title on pages 1-15 needs to be corrected. Change phenlybutyrate to phenylbutyrate on all pages.

(b) (4)

1. LA6-0179 revision 2 "HPLC Assay for [redacted] (b) (4) in Glycerol Phenylbutyrate and HPN-100 (glycerol phenylbutyrate) Oral Liquid"

Sample	Result	Specification	PASS/FAIL
% Assay	[redacted] (b) (4)	[redacted] %	PASS

2. LA6-0174 revision 3 "HPLC Assay for the Determination of [redacted] (b) (4) Impurities in Glycerol Phenylbutyrate (GPB) and HPN-100 (glycerol phenylbutyrate)"

Impurity	Result	Specification	PASS/FAIL
[redacted] (b) (4)			PASS
			PASS
			PASS
			PASS
			PASS
Total impurities	[redacted] (b) (4)	[redacted]	PASS

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

/s/

MICHAEL L TREHY
08/09/2012

BENJAMIN J WESTENBERGER
08/10/2012

NDA 203284

Ravicti
(glycerol phenylbutyrate)
25mL

Ucyclyd Pharma, Inc.

Hamid R. Shafiei, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC REVIEW
For the Division of Gastroenterology and Inborn Errors Products

Table of Contents

CMC Review Data Sheet

1. NDA 203284

2. REVIEW #: 1

3. REVIEW DATE: 15-July-2012

4. REVIEWER: Hamid R. Shafiei, Ph.D.

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	12/23/2011
Correspondence (C)	
Amendment (BC)	07/02/2012
Amendment (BC)	N/A

7. NAME & ADDRESS OF APPLICANT:

Name:	Hyperion Therapeutics
Address:	601 Gateway Blvd, Suite 200 South San Francisco, CA 94080
Representative:	Karla A Dickinson
Telephone:	(650) 745-7820

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ravicti
b) Non-Proprietary Name: Glycerol Phenylbutyrate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Adjunctive Therapy for Chronic Management of Urea Cycle Disorder in Patients $\geq$ 6 years of age

CMC Review Data Sheet

11. DOSAGE FORM: Liquid for Oral Administration

12. STRENGTH/POTENCY: 25mL of [redacted] (b) (4) Active Ingredient (glycerol phenylbutyrate)

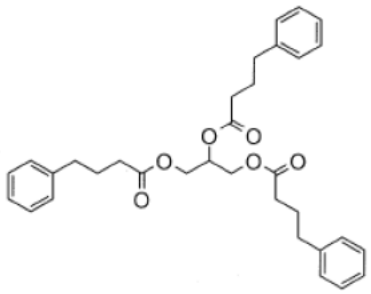
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__√__ Not a SPOTS product

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



USAN and INN: Glycerol Phenylbutyrate
IUPAC: Propane-1,2,3-tryl tris(4-phenylbutanoate)
Empirical formula: $C_{33}H_{38}O_6$
Molecular Mass: 530.67
CAS Number: 611168-24-2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	
NDA	N/A	

CMC Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS			
EA	Categorical exclusion (see review)		
Microbiology	N/A		

The CMC Review for NDA 203-284

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product, Ravicti liquid for oral administration.

However, the Office of Compliance has ***not*** made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.

Also label/labeling issues identified have ***not*** been satisfactorily resolved.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for approval in its present form, per 21 CFR 314.125(b)(6) & (13).

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

Not applicable.

II. Summary of CMC Assessments

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

(1) Drug Substance

The Drug substance, glycerol phenylbutyrate is intended for the treatment of patients 6 years of age or older with urine cycle disorder and is a prodrug consisting of three phenylbutyrate linked together by glycerol. The mechanism of action for this drug is that if swallowed it is expected to break down to phenylbutyrate in the gut. Phenylbutyrate is converted to phenyl acetate in the body. Phenyl acetate reacts with the amino acid glutamine, a nitrogen containing amino acid and forms a substance that can be removed from the body by kidneys. Removal of the nitrogen containing glutamine from the body leads to the reduction in the production of ammonia.

The drug substance, glycerol phenylbutyrate is a colorless to pale yellow liquid with a molecular formula of $C_{33}H_{38}O_6$, a molecular mass of 530.67g/mole, and a density of 1.1g/mL. This drug substance is soluble in dimethylsulfoxide and > 65% acetonitrile-water, freely soluble in toluene and acetone, sparingly soluble in isopropyl alcohol, and insoluble in water. Glycerol phenylbutyrate decomposes at 160ºC, and therefore, boiling point for this drug substance could not be determined. Furthermore, due to lack of any ionizable moiety in this molecular entity, the pH of this API could not be determined.

Glycerol phenylbutyrate is manufactured and supplied by two different manufacturers, (b) (4). The manufacturing process used (b) (4) Both API manufacturers have proposed and utilized adequate in-process testing procedures for controlling the manufacturing steps identified as critical. The API manufacturing information provided in this application clearly illustrates that drug substance manufactured (b) (4)

The proposed API release and stability specification includes testing and acceptance criteria for appearance, identification, assay, related substances (related impurities), water content, residue on ignition, heavy metals, and residual solvents. The proposed specification is deemed adequate to assure the identity, strength, purity, and quality of the API, glycerol phenylbutyrate. Furthermore, the drug substance manufacturers have provided sufficient release and stability data to support the proposed API re-test period.

(2) Drug Product

The drug product Ravicti is (b) (4) Although the photostability data provided indicates that this drug

product may not be sensitive to light, nevertheless, the outer cartons provide adequate protection from exposure to light.

The in-process testing of the drug product entails (b) (4)

The proposed drug product release and stability specification includes testing and acceptance criteria for appearance, identity, assay, related substances (related impurities), and (b) (4) is omitted from the drug product release and stability testing since these impurities are controlled during the testing and release of the drug substance. The proposed drug product specification is deemed adequate to assure the identity, strength, purity, and quality of the drug product, Ravicti.

Based on the 6-month accelerated, 24-month long-term real-time stability data and statistical treatment of the stability data, an expiration dating period of 36 months is proposed. The proposed expiration dating period is considered acceptable.

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

The drug product Ravicti is (b) (4) This drug product is intended for oral use in the treatment of patients with the rare disease of urine cycle disorder. Based on very small population of patients diagnosed with this disorder, this drug product has been given an orphan drug status.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(13)

- The final "Acceptable" recommendation from the Office of Compliance is still "Pending".

21 CFR 314.125 (b)(6)

- Label/labeling issues has not been resolved.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Hamid R. Shafiei, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA

C. CC Block: entered electronically in DFS

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/s/

HAMID R SHAFIEI
11/13/2012

MOO JHONG RHEE
11/13/2012
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Hamid R. Shafiei, Ph.D., CMC Reviewer
Marie Kowblanski, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: hamid.shafiei@fda.hhs.gov
Phone: (301)-796-2326
Fax.: (301)-796-9745

Through: Moo Jhong Rhee, Ph.D., Branch Chief, Branch IV, Division II
Phone: (301)-796-1440

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203-284

Name of Product: Ravicti (gylcerol phenylbutyrate), Liquid Drug Substance

Applicant: Ucyclyd Pharma, Inc.

Applicant's Contact Person: Klara Dickinson, Sr. VP Regulatory Affairs

Address: 7720 N. Dobson Road, Scottsdale, AZ 85256

Telephone: 480-291-5953 Fax: 480-302-6333

Date NDA Received by CDER: **12/23/2012**

Date of Amendment(s) containing the MVP: **12/23/2012**

DATE of Request: **March 30, 2012**

Requested Completion Date: **8/1/2012**

PDUFA User Fee Goal Date: **10/23/2012**

Submission Classification/Chemical Class: 0

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA #

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	N/A
Specifications/Methods for New Drug Substance(s)	NDA 203-284 Module 3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)	NDA 203-284 Module 3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.	NDA 203-284 Module 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms	
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
LA6-0174 Revision 3	Drug Product Impurity	NDA 203-284	**0**	
LA6-0179 Revision 2	Drug Product Assay	NDA 203-284	**0**	
			0	
			0	
			0	

Additional Comments: **None**

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

CATHERINE A TRAN-ZWANETZ
04/11/2012

HAMID R SHAFIEI
04/11/2012

MOO JHONG RHEE
04/11/2012
Chief, Branch IV

MICHAEL M FOLKENDT
04/11/2012
For Jeannie David

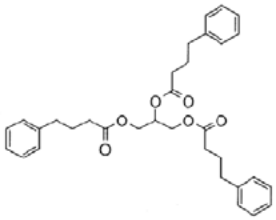
Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division:	Division of Gastroenterology Products
NDA:	203-284
Applicant:	Ucyclyd Pharma (subsidiary of Medicis Pharmaceuticals)
Stamp Date:	12/23/2011
Review Date:	2/22/2012
PDUFA Date:	10/23/2012
Filing Meeting:	2/1/2012
Proposed Trademark:	Ravicti
Established Name:	glycerol phenylbutyrate
Dosage Form:	liquid
Route of Administration:	oral
Indication:	management of urea cycle disorders
CMC Lead:	Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	☒	
Comments for 74-Day Letter		☒

A. Summary

Ravicti (glycerol phenylbutyrate) Liquid is intended for oral administration for chronic management of patients with urea cycle disorders. The drug substance, glycerol phenylbutyrate, is a triglyceride containing three phenylbutyrate (PBA) groups linked via ester linkages to a glycerol backbone



It is a prodrug of PBA which further converts to phenylacetate (PAA) in the digestive tract; PAA is the active moiety. Dosing is on a patient weight basis, but the daily dose may not exceed 17.5 mL (19.3 g).

Glycerol phenylbutyrate, which is a liquid, is manufactured by [redacted] (b) (4)
It is produced [redacted] (b) (4)

The specifications include [redacted] (b) (4)
Although the specified levels of these impurities appear high, particularly in view of the large daily dose, they are likely acceptable since [redacted] (b) (4)

The firm claims categorical exclusion from providing an environmental assessment of Ravicti™ (glycerol phenylbutyrate) in accordance with 21 CFR 25.31 (b). Action on this NDA will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Since this is a new molecular entity this issue has been consulted to the environmental assessment staff for evaluation.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES.

Established name: The established name for this product is glycerol phenylbutyrate. Glycerol phenylbutyrate is a USAN name and consequently is acceptable.

The full CMC review of this NDA will be done by Dr. Hamid Shafiei.

B. Critical issues for review

This is a fairly uncomplicated product both with regard to composition and manufacturing process. The NDA submission is also relatively straightforward, but the following issues should be given some additional consideration:

-- There does not appear to be a delivery device copackaged with the product. Since different doses will be delivered to different people, it is important to determine how the required doses will be delivered and how its accuracy will be assured.

-- The application indicates that under some circumstances reworking will be allowed. The conditions allowing reworking will need to be clearly defined.

-- The application lists ”liquid” as the dosage form. A determination should be made whether “liquid” is in conformance with the CDER standards manual for this type of product, or if some other name such as “oral liquid” is more appropriate.

-- As indicated above, a determination should be made whether the proposed impurity limits are acceptable, given the high daily dose of this product. The toxicology reviewer may need to be consulted.

C. Comments for 74-Day Letter -- None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

2/27/2012
Date

Moo-Jhong Rhee, PhD
Branch Chief

FILING CHECKLIST

NDA Number:	Supplement Number and Type:	Established/Proper Name:
203-284	original	Ravicti (glycerol phenylbutyrate)
Applicant:	**Letter Date:**	**Stamp Date:**
Ucyclyd Pharma, Inc.	December 23, 2011	

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Not applicable

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	√		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			Not applicable. This product is (b) (4)
23.	Have any biowaivers been requested?			Not applicable
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		Container closure DMFs referenced.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			No issues for inclusion in the 74-day letter

{See appended electronic signature page}

Hamid R. Shafiei, Ph.D.
CMC Reviewer, Branch IV
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

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

Date

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/s/

MARIE KOWBLANSKY
02/28/2012

MOO JHONG RHEE
02/28/2012
Chief, Branch IV