CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209449Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **July 24, 2017**

From: **Hong Cai, Ph.D. on behalf of**
Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 209449**

Subject: Final Recommendation for NDA 209449

At the time when the CMC Review #1 was completed on July 1, 2017, it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

On July 24, 2017, the applicant submitted revised labeling and the CMC sections of the revised labeling were reviewed and found acceptable (**Attachment-1)**.

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from OPQ perspective.
Hong Cai, Ph.D. on behalf of
Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
July 24, 2017

Attachment 1:

Memorandum

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

Date: July 24, 2017

From: Hong Cai, Ph.D.
Drug Product Reviewer,
Branch V Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: Labeling Review #1 of NDA 209449

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (06/29/2017), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. To resolve the outstanding label/labeling issues, the applicant submitted amendments to the NDA that provides the revised package insert in **Attachment-1** (SN0022 on 07/24/2017) as well as the container and carton labels in **Attachment-2** (SN0020 on 07/07/2017**)**. The revised labels/labeling have adequately addressed all the CMC labeling issues.

Additionally, according to drugs@FDA, the storage condition has been updated for the PI of RLD ORFADIN (nitisinone) capsules through NDA021232 supplement 19 (action date February 28 2017). Orfadin capsules is allowed to be stored at room temperature up to 25°C (77°F) for up to 45 days as an alternative storage condition to the refrigeration at 2° to 8°C (36° to 46°F).

Recommendation:

The outstanding CMC label/labeling issues have been resolved, and therefore, this application is now recommended for **approval** from the labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Hong Cai

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Moo Jhong Rhee

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Date: 7/24/2017 05:47:50PM
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Recommendation: As of this review, this 505 (b)(2) NDA is not ready for Approval in its present form per 21 CFR 314.125(b)(6)

NDA 209449
Review #1

Drug Name/Dosage Form	Nitisinone Tablets
Strength	2 mg, 5 mg and 10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Cycle Pharmaceuticals Ltd., Cambridge, UK
US agent, if applicable	Mapi USA, Inc., Lexington, KY

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	9/26/2016	OPQ
Amendment	11/25/2016	ONDP/DB/BBII
Amendment	1/17/2017	OPQ
Amendment	1/23/2017	OPQ/ONDP
Amendment	3/03/2017	OPQ/ONDP/NDAPI
Amendment	3/09/2017	OPQ/ONDP/NDAPI
Amendment	5/30/2017	OPQ/ONDP
Amendment	6/15/2017	ONDP/DB/BBII, ONDP
Amendment	6/20/2017	OPQ/ONDP
Amendment	6/21/2017	OPQ
Amendment	6/23/2017	OPQ/ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Lawrence Perez	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Environmental Analysis (EA)	Hong Cai	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process and Microbiology	Tianhong Tim Zhao	CDER/OPQ/OPF/ DPAIII/PABVIII
Biopharmaceutics	Peng Duan	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Active	N/A	LOA May 10, 2016
	Type III			Active	N/A	LOA April 17, 2016
	Type III			Active	N/A	May 4, 2016

N/A: There is enough data in the application, therefore, the DMF did not need to be reviewed.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NONE	NONE	N/A

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the issues regarding label/labeling have ***not*** been completely resolved yet as of this review. (see the **List of Deficiencies**)

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per 21 CFR 314.125(b)(6) until the label/labeling issues are satisfactorily resolved.

II. Summary of Quality Assessments

A. Product Overview

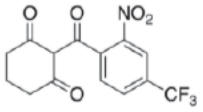
Nitisinone is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase. NITYR (nitisinone) tablets are indicated for the treatment for tyrosinemia type 1 (HT-1). NITYR (nitisinone) tablets are supplied in 2 mg, 5 mg and 10 mg strengths. Currently, nitisinone is marketed as Orfadin Capsules and Orfadin Suspension by Swedish Orphan Biovitrum (SOBI) for the same indications. Both Orfadin Capsules and Orfadin Suspension are required to be refrigerated during storage to avoid degradation. However, NITYR (nitisinone) tablets can be stored at room temperature without affecting their stability.

Proposed Indication(s) including Intended Patient Population	For the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.
Duration of Treatment	As long as needed
Maximum Daily Dose	Recommended adult dose is 0.5 mg/kg taken twice orally
Alternative Methods of Administration	**N/A**

B. Quality Assessment Overview

Drug Substance:

The active pharmaceutical ingredient (API) in the drug product NITYR (nitisinone) tablets is nitisinone. Nitisinone is a 4-hydroxyphenyl-pyruvate dioxygenase (HPPD) inhibitor. It is an achiral, low molecular weight compound with the chemical name of 2-(2-nitro-4-trifluoromethyl benzoyl) cyclohexane-1, 3-dione. It has a molecular formula $C_{14}H_{10}F_3N0_5$ and a molecular weight of 329.23. It is a (b) (4). It is poorly soluble in water but its solubility increases significantly at pH above 6. (b) (4) . It is a Biopharmaceutical Classification System (BCS) Class 1 above pH 6 because of high solubility at pH above 6 and high permeability.



Nitisinone

Nitisinone is manufactured by (b) (4) The drug substance manufacturing process, in-process controls, control of materials, control of critical steps and intermediates as well as the manufacturing process validation information were provided.

The chemical structure of nitisinone has been confirmed by elemental analysis, mass spectroscopy (negative mode) and ^{1}H and ^{13}C NMR spectroscopy.

The quality of the drug substance, nitisinone, is controlled by its specification which includes identity by IR and HPLC, assay by HPLC, impurities by HPLC, residual solvents, water content and particle size distribution. (b) (4) . Therefore, the drug product (b) (4) .

The bulk drug product is (b) (4) Month retest period for nitisinone is proposed and granted.

The CMC information regarding the drug substance, nitisinone, was reviewed by the drug substance reviewer, Dr. Lawrence Perez, and concluded that sufficient information is provided to ensure consistent manufacturing of the drug substance with respect to identity; strength, purity and quality (see the **Drug Substance** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Michael Klapal, has made an "Adequate" recommendation for the drug substance manufacturing and testing facility (see the **Facilities** review).

Nitisinone is manufactured and controlled according to the procedure described in Sec. 3.2.S.2 [redacted] (b) (4) and conforms to the requirements (specification) for drug product formulation of Nitisinone Tablets.

Drug Product:

NITYR (nitisinone) tablets are indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. NITYR (nitisinone) tablets are white to off-white, round, flat tablets debossed with the "strength" on one side and "L" on the other side. Each tablet contains 2, 5 or 10 mg of nitisinone and the following inactive ingredients: glyceryl dibehenate, and lactose monohydrate. NITYR (nitisinone) tablets are packed in high-density polyethylene (HDPE) square bottles with child-resistant tamper-evident polypropylene (PP) screw caps. Each bottle contains 60 Nitisinone tablets.

NITYR (nitisinone) tablets are manufactured by Rivopharm SA, Switzerland. The [redacted] (b) (4) . . The drug product manufacturing process and microbiology assessment were reviewed by Dr. Tianhong Tim Zhou and were found to be acceptable (see the **Process** review).

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, identity, assay, impurities, [redacted] (b) (4), content uniformity, dissolution, and microbial purity.

Based on the drug product stability data assuring the identity, strength, purity, and quality, the proposed **24-month of expiration dating period** is granted when stored at room temperature in the proposed container closure system, according to drug product reviewer, Dr. Hong Cai (see the **Drug Product** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Michael Klapal, has made an "Adequate" recommendation for the drug product manufacturing and testing facilities (see the **Facility** review).

The applicant provided a claim for a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b) and a statement of no extraordinary circumstances existed was included. The claim was reviewed and found to be acceptable.

The applicant relied on FDA's efficacy and safety findings of the previously approved Orfadin (nitisinone) Capsules (NDA 021232) for the same indications as the proposed drug product. A pivotal BE study of Nitisinone tablets, 10 mg and Orfadin capsules, 10 mg were carried out. The PK of 10 mg Nitisinone tablets was bioequivalent to 10 mg Orfadin capsules so 10 mg Nitisinone tablets were deemed bioequivalent by the clinical pharmacological reviewer, Dr. Li Shen, dated June 28, 2017.

The dissolution method and acceptance criteria for 2 mg and 5 mg Nitisinone tablets were reviewed by the biopharmaceutics reviewer, Dr. Peng Duan. The results of Nitisinone tablets and Orfadin capsules comparative dissolution profiles showed similar dissolution characteristics (f2 >50) so the biowaiver request for the 2 mg and 5 mg Nitisinone tablets was accepted. Therefore, additional in vivo bioequivalence (BE) bridging study is not needed from Biopharmacology perspective. (see the **Biopharmaceutics** review)

The proposed labels and labeling are under review and they are not deemed adequate from the CMC perspective according to Dr. Hong Cai (see **Labels/ Labeling** review) because the labels and labeling issues have not been completely resolved as of this review (see the **List of Deficiencies**).

Post-Approval Commitments

The applicant has committed, within two months post approval, to conduct assay and provide the results to assure the strength of the proposed preparation during the use period (2 hours) for the crushed tablets mixed with the apple (b) (4) and the aqueous suspension in syringe at room temperature (Amendments submitted on June 23 and 28, 2017, SN0017 and SN0018).

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies:

A. Regarding PI

1. The product proprietary name and established name should be included in the section #11.
   Revise the following:
   (b) (4)
   "NITYR (nitisinone) tablets are white to off white, round, flat tablets debossed with the "strength" on one side and "L" on the other side."
2. Revise the description of the tablet (b) (4) to "debossed" in Sections #3, #11 and #16.
3. Add "Dispense in tight and light resistant container as defined in USP" to Section #16.
4. The storage and handling period for the two pediatric preparations (the crushed tablet mixed with apple (b) (4) and the suspension of the whole tablet in water stored in the oral syringe) should be revised to up to 2 hours based on the amendment dated June 28, 2017 (SN0018) in Section #16.

B. Regarding the Container/Carton Labels:

5. Include the proposed proprietary name, NITYR, in product title presentation of the container labels and carton labeling. The product title presentation should be revised from "Nitisinone Tablets" to "NITYR (nitisinone) tablets"
6. Add the statement "Dispense in tight and light resistant container as defined in USP" to the container labels and carton labeling.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II

Hitesh N. Shroff -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
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LABELING

I. PI

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NITYR safely and effectively. See full prescribing information for NITYR.

NITYR (nitisinone) tablets, for oral use
Initial U.S. Approval: 2002

----------**DOSAGE FORMS AND STRENGTHS**----------
Tablets: 2 mg, 5 mg, 10 mg. (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	NITYR (nitisinone) tablets	Satisfactory
Dosage form, route of administration	NITYR (nitisinone) tablets, for oral use	Satisfactory
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	Tablets: 2 mg, 5 mg, 10 mg. (3)	Satisfactory

II. FULL PRESCRIBING INFORMATION

2. Dosage AND ADMINISTRATION

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended starting dosage of NITYR is (b) (4) mg/kg administered orally. Titrate the dose for individual patients, as needed based on biochemical and/or clinical response. (b) (4) (b) (4) Monitor plasma and/or urine succinylacetone concentrations, liver function parameters and alpha-fetoprotein levels. If succinylacetone is still detectable one month after the start of nitisinone treatment, increase the nitisinone dosage to (b) (4) mg/kg (b) (4) daily. A maximum dosage of (b) (4) mg/kg orally (b) (4) daily may be needed based on the evaluation of all biochemical parameters.

If the biochemical response is satisfactory, the dosage should be adjusted only according to body weight gain.

(b) (4) during the initiation of therapy or if there is a deterioration in the patient's condition, it may be necessary to follow all available biochemical parameters more closely (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).

2.2 Administration

- Maintain dietary restriction of tyrosine and phenylalanine when taking NITYR.
- NITYR tablets may be taken with or without food. For patients who have difficulty swallowing the tablets, (b) (4)

(b) (4)

Administration of NITYR tablets with a syringe:

An oral syringe (b) (4) with a cap will be provided by a pharmacist.

One Tablet

1. Remove the plunger from the syringe and insert the tablet.
2. (b) (4)
3.
4.

5. Uncap the syringe and administer the suspension into the patient's mouth. To facilitate full administration, avoid depressing the plunger to the end of the syringe and leave a gap between the plunger and the syringe. The remaining drug in the syringe will be recovered by rinse as described in step 6.
6. Rinse the syringe by drawing up (b) (4) 2 mL of water. Cap the syringe and (b) (4) to suspend any remaining particles.
7. Uncap the syringe and administer the suspension into the patient's mouth. This time (b) (4)

Two Tablets

(b) (4)

1. Remove the plunger from the syringe and insert two tablets.
2. Replace the plunger and draw up 5 mL of water at room temperature. (b) (4)
3. (b) (4)

(b) (4)

Preparation and administration of (b) (4) NITYR (b) (4), in apple (b) (4).

1. Measure around (b) (4) of apple (b) (4) (1 (b) (4) teaspoon) and transfer it into a clean container (e.g clean glass).
2. Always crush one tablet at a time. Position the tablet between two teaspoons and apply light pressure on the top spoon.
3. Press and rotate the two teaspoons against each other repeatedly (b) (4).
4. (b) (4)
5. Carefully transfer the resulting powder (b) (4) the apple (b) (4) container ensuring all the powder is transferred, and no powder residues remains on the teaspoons.
6. If more than one tablet is needed (b) (4), repeat the procedure starting from (b) (4) 2 and collect all the resulting powders together in the apple (b) (4) container.
7. Mix the powder (b) (4) the apple (b) (4) until the powder is well dispersed.
8. Administer the mixture to the patient's mouth using a teaspoon.
9. To assure that any leftover mixture from the container is recovered, add around (b) (4) (1 (b) (4) teaspoon) of apple (b) (4) to the same container and mix the fresh apple (b) (4) with the remaining mixture.
10. Administer the additional mixture to the patient's mouth using a teaspoon.
11. (b) (4).

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	See information above	**Not Satisfactory** Infant dosing preparation and procedure should be revised properly to ensure the recovery and stability.

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg, 5 mg, and 10 mg white to off white, round, flat tablets (b) (4) with "L" on one side and the strength ("2" mg, "5" mg, or "10" mg), on the other side.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Tablets	Satisfactory
Strengths: in metric system	2mg, 5 mg, and 10 mg	Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to off white, round, flat tablets (b) (4) with "L" on one side and the strength ("2" mg, "5" mg, or "10" mg), on the other side.	**Not Satisfactory** Revise (b) (4) to "embossed"

4. *Section 11 Description*

11 DESCRIPTION

NITYR contains nitisinone, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

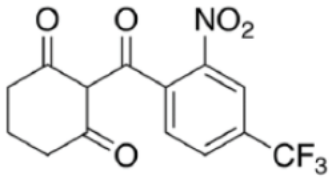
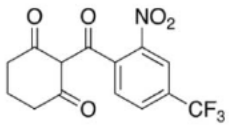


Figure 1. The molecular formula is $C_{14}H_{10}NO_5F_3$ and with a relative mass of 329.23.

(b) (4)

(b) (4) Each tablet contains 2, 5 or 10 mg of nitisinone. Inactive ingredients are: glyceryl dibehenate, and lactose monohydrate. NITYR tablets are intended for oral administration.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4)	**Not Satisfactory** Both proprietary name and established name should be included. Revise to (b) (4)
Dosage form and route of administration	Each tablet contains 2, 5 or 10 mg of nitisinone	Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	N/A	N/A
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients are: glyceryl dibehenate, and lactose monohydrate.	Satisfactory
Statement of being sterile (if applicable)	N/A	N/A

Pharmacological/ therapeutic class	NITYR contains nitisinone, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).	Satisfactory
Chemical name, structural formula, molecular weight	Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:  **Figure 1. The molecular formula is $C_{14}H_{10}NO_5F_3$ and with a relative mas**	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.	Satisfactory

5. *Section 16 How Supplied/Storage and Handling*

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets: White to off white, round, flat tablets (b) (4) with the "strength" on one side and "L" on the other side. Each tablet contains 2, 5 or 10 mg nitisinone. NITYR tablets are packed in High-density polyethylene (HDPE) square bottles with a child-resistant tamper-evident Polypropylene (PP) screw cap. Each bottle contains 60 tablets.

2 mg tablets: From white to off white, round, flat tablets (b) (4) "2" on one side and "L" on the other side, NDC 70709-002-60

5 mg tablets: From white to off white, round, flat tablets (b) (4) "5" on one side and "L" on the other side, NDC 70709-005-60

10 mg tablets: From white to off white, round, flat tablets (b) (4) "10" on one side and "L" on the other side, NDC 70709-000-60

Store NITYR tablets at 20° to 25° (68° to 77°F). (b) (4) excursions between 15° and 30° (59° and 86°F). (b) (4)

Manufactured by:
Rivopharm SA,
Centro Insema,
6928 Manno Switzerland

Marketed by:
Cycle Pharmaceuticals Ltd.
Bailey Grundy Barrett Building
Little St Mary's Lane,
CB2 1RR, Cambridge, United Kingdom

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	Each tablet contains 2, 5 or 10 mg nitisinone.	Satisfactory
Available units (e.g., bottles of 100 tablets)	Each bottle contains 60 tablets.	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	2 mg tablets: From white to off white, round, flat tablets (b) (4) "2" on one side and "L" on the other side, NDC 70709-002-60 5 mg tablets: From white to off white, round, flat tablets (b) (4) "5" on one side and "L" on the other side, NDC 70709-005-60 10 mg tablets: From white to off white, round, flat tablets (b) (4) "10" on one side and "L" on the other side, NDC 70709-000-60	**Not Satisfactory.** Revise (b) (4) " to "embossed"
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	(b) (4)	**Not Satisfactory** Revise (b) (4) . " to "Dispense in tight and light resistant container as defined in USP."
Storage conditions	Store Nitisinone tablets at 20° to 25° (68° to 77°F), allows for excursions between 15° and 30° (59° and 86°F).	Satisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	**Manufactured by**: Rivopharm SA, Centro Insema, 6928 Manno Switzerland **Marketed by**: Cycle Pharmaceuticals Ltd. Bailey Grundy Barrett Building Little St Mary's Lane,	Satisfactory

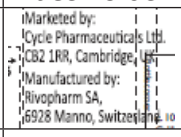
	CB2 1RR, Cambridge, United Kingdom	

II. Labels:

1. Immediate Container Label

(b) (4)

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	**Not Satisfactory** Revise to "NITYR (nitisinone) tablets"
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	2mg 5mg 10mg	Satisfactory
Net contents	60 tablets	Satisfactory
"Rx only" displayed prominently on the main panel	Rx only	Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	2mg: NDC-70709-002-60 5mg: NDC-70709-005-60 10mg: NDC-70709-000-60	Satisfactory
Lot number and expiration date (21 CFR 201.17)	Lot Number: Exp. Date:	Satisfactory
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".		**Not Satisfactory** Add the statement "Dispense in tight and light resistant container as defined in USP".
Bar code (21CFR 201.25)	Place holder	Satisfactory
Name of manufacturer/distributor		Satisfactory
And others, if space is available		

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4)	**Not Satisfactory** Revise to "NITYR (nitisinone) tablets"
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	2 mg 5 mg 10 mg	Satisfactory
Net quantity of dosage form	60 tablets	Satisfactory
"Rx only" displayed prominently on the main panel	Rx only	Satisfactory
Lot number and expiration date	Lot : VARNISH FREE AREA EXP: MMM YYYY	Satisfactory
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20°-25°C (68°-77°F)	**Not Satisfactory** Add in the statement of "Dispense in tight and light resistant container as defined in USP"
Bar code (21CFR 201.25)	Place holder	Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	2mg: NDC-70709-002-60 5mg: NDC-70709-005-60 10mg: NDC-70709-000-60	Satisfactory
Manufacturer/distributor's name	Marketed by: Cycle Pharmaceuticals Ltd. CB2 1RR, Cambridge, UK Manufactured by: Rivopharm SA, 6928 Manno, Switzerland Distributed by: XXX XXXX	Satisfactory
Quantitative ingredient information (injectables)	Inactive Ingredients: glyceryl dibehenate and lactose monohydrate.	N/A
Statement of being sterile (if applicable)	N/A	
"See package insert for dosage information"	(b) (4) For use and (b) (4) see prescribing information.	Satisfactory
"Keep out of reach of children" (Required for OTC in CFR.	Keep out of the reach and sight of children.	Satisfactory

Optional for Rx drugs)		

List of Deficiencies:

1. The product proprietary name and established name should be included In Description (section #11) of PI.

   Revise the following

   [redacted]

   to

   "NITYR (nitisinone) tablets are white to off white, round, flat tablets debossed with the "strength" on one side and "L" on the other side."

2. Revise the description of the tablet [redacted] to "debossed" in Section 3, 11 and 16 of PI.
3. Add "Dispense in tight and light resistant container as defined in USP" to section 16 of PI.
4. The storage and handling period for the two pediatric preparations (the crushed tablet mixed with apple [redacted] and the suspension of the whole tablet in water stored in the oral syringe) should be revised to up to 2 hours based on the amendment dated June 28, 2017 (SN0018).
5. Include the proposed proprietary name, NITYR, in product title presentation of the container labels and carton labeling. The product title presentation should be revised from "Nitisinone Tablets" to "NITYR (nitisinone) tablets"
6. Add the statement "Dispense in tight and light resistant container as defined in USP" to the container labels and carton labeling.

Overall Assessment and Recommendation:

The following materials related to labeling/label have been reviewed (updated PI was submitted on June 15, 2017 and container/carton labels submitted on September 26, 2016:

- Highlights of Prescribing Information: Names and Dosage Forms and Strengths.
- Full Prescribing Information: Sections: #3 DOSAGE FORMS AND STENGTHS; #11 (DESCRIPTION) and #16 (HOW SUPPLIED/STORAGE AND HANDLING)

- Container and carton labels for 2mg, 5mg and 10mg strength tablets.

From the ONDP perspective, this application is not recommended for approval per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Cai's assessment of the labels/labeling, and concur with her statement that this application is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Hong Cai

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Moo Jhong Rhee

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BIOPHARMACEUTICS

Product Background:

NDA: 209449

Drug Product Name / Strength: Nitisinone (2 mg, 5 mg and 10 mg) Immediate Release (IR) Tablets

Route of Administration: Oral

Applicant Name: Cycle Pharmaceuticals Ltd.

Indication: Treatment of hereditary tyrosinemia type 1 (HT-1) patients

Review Summary:

The Applicant submitted NDA 209449 for nitisinone immediate release (IR) tablets, 2, 5, and 10 mg) on 09/26/2016 as a 505(b)(2) submission referencing ORFADIN capsules (NDA 021232) and expects to bridge and rely on FDA's previous finding on efficacy and safety of this reference drug to support the approval of the proposed drug product. ORFADIN capsules (NDA 021232) is approved on MM/DD/YY and indicated for treatment of hereditary tyrosinemia type 1 (HT-1) patients.

The composition of the proposed drug product is shown in Table 1.

Table 1: Composition of Nitisinone tablets

Tablets Strength Name of Ingredient and Quality Standard	Function	2 mg tablets (amount / tablet)		5 mg tablets (amount / tablet)		10 mg tablets (amount / tablet)	
Nitisinone, In-house	Active ingredient	2 mg	(b) (4)	5 mg	(b) (4)	10 mg	(b) (4)
Glyceryl Dibehenate (b) (4)							(b) (4)
Lactose Monohydrate (b) (4							
Tablet weight		120 mg	100.0%	120 mg	100.0%	120 mg	100%

A pivotal bioequivalence study (CT-003) was carried out with Nitisinone tablets 10 mg and ORFADIN capsules 10 mg. Additionally a food effect study (CT-002) was conducted with Nitisinone tablets 10 mg to investigate the food effect on the bioavailability of Nitisinone tablets. These studies will be reviewed by the OCP (Office of Clinical Pharmacology). The Biopharm review will focus on the evaluation of biowaiver request for the two lower strengths, 2 mg and 5 mg tablets, and proposed dissolution method as well as dissolution acceptance criterion.

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Therefore, the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 90 min is considered acceptable.

In-Vitro Soft-food Interaction Study

Reviewer's Assessment:

In the draft label from the Applicant, it was stated that:

(b) (4)

The Applicant evaluated the feasibility of infant administration for nitisinone tablets in a simulated clinical setting. Nitisinone tablets were crushed between two spoons, mixed with the specified vehicles, and administrated by the specified delivery method as follows:

1. Apple sauce study

The crushed tablets were mixed with applesauce and administrated with spoon, and the assay (uniformity) and stability of nitisinone tablets were assessed.

(b) (4)

3. Syringe study

The crushed Nitisinone Tablets were mixed with (b) (4) water (at both 25°C and 40°C) and administered with syringes (2.5 mL and 5 mL). The recovery (assay in delivered liquid) and stability (related substances of nitisinone in vehicle at 0, 30 and 60 minutes after preparation) of nitisinone were assessed.

The results for assessment on the administration of nitisinone tablets with apple sauce, or administration (b) (4) with syringe were shown in Table 10, respectively.

Table 10A. Assessment on the administration of Nitisinone Tablets with apple sauce

Test		Target value	Result			
			1	2	3	Mean
Uniformity in apple sauce (n=10)		Acceptance value ≤ (b) (4)	6.0			
Stability in apple sauce (assay %)	0 minutes (n=3)	(b) (4) %	104.4	103.4	103.8	103.9
	30 minutes (n=3)		102.5	93.1	103.8	99.8
	60 minutes (n=3)		105.3	105.3	105.3	105.3
Related substance in apple sauce	0 hours (n=1)	< (b) (4) (individual) % (total)	Not detected (see appendix 1)			
	4 hours (n=1)					

While nitisinone tablets was administrated by mixing with applesauce, as shown in Table 10A, the average recovery of nitisinone when administrated with spoon could reach 103.9%, and a satisfied stability up to 60 min was observed. However, in the original submission, the Applicant didn't specify the pH or the brand for the applesauce.

Table 10B - Assessment on the administration of Nitisinone Tablets with (b) (4)

(b) (4)

(b) (4)

Table 10C - Assessment on the administration of Nitisinone Tablets with syringe

Test		Target value	Result			
			1	2	3	Mean
Recovery						
2.5 mL syringe	Water (25°C, n=3)	(b) (4)%	53.9%	55.7%	46.4%	52.0%
	Water (40°C, n=3)		32.0%	36.7%	56.0%	41.6%
	(b) (4)					(b) (4)
5 mL syringe	Water (25°C, n=3)		74.6%	64.1%	82.8%	73.8%

Test		Target value	Result			
			1	2	3	Mean
	Water (40°C, n=3)		72.8%	75.8%	75.9%	74.8%
	(b) (4)					(b) (4)
Stability (Related substances in 2.5 mL of vehicle)						
Vehicle	Time point	Sample temperature	Target value	Individual impurity		Total impurity
Water	0 minutes	36.8°C	(b) (4)% (individual) (b) (4)% (total)	< 0.05%		< 0.05%
	30 minutes	21.8°C		< 0.05%		< 0.05%
	60 minutes	22.0°C		< 0.05%		< 0.05%
(b) (4)						(b) (4)

While nitisinone tablets was administrated with syringe with 2.5 mL or 5.0 mL of water (b) (4) at 25 °C or 40 °C (Table 10C), the recovery of nitisinone was lower in water (42%-82%) (b) (4). The Applicant proposed a (b) (4)% target value for the recovery, and stated that over (b) (4) of nitisinone tablets can delivered via 5 mL syringe in water (b) (4). For the low target recovery of (b) (4)%, the Applicant justified that nitisinone was dosed by titration, and patients administrating crushed tablets via syringe can adjust dose if necessary based on closely monitoring. However, the (b) (4)% target recovery rate is not acceptable by the Division of Biopharmaceutics and also not acceptable either according to clinical team.

On February 10, 2017, a combined information request (IR) from Biopharm and Drug product reviewers was conveyed to the Applicant as follows:

For crushed tablets administration, we have the following comments that request your responses:

1. Provide a specific dosing instruction as to how the crushed tablets in the applesauce can be delivered to the infant assuring the target dose value. In addition, the crushed tablets should be administered within one hour after being mixed with the apple sauce.

2. Provide the brand and the pH value of the apple sauce you used in your in vitro study for infant administration.

3. When crushing the tablets with two spoons, provide the justification that the tablet can be crushed in a consistent manner regardless of the tablet hardness during the shelf life, and provide crushing comparison data for the three strengths, 2 mg, 5 mg and 10 mg, at their release and stability.

Also, we have some concerns about the potential choking hazards to the infant if the crushed tablet particle sizes are too big. Provide detailed instructions of how the tablets are to be crushed with two spoons to ensure the consistent production of the fine powders.

4. Regarding the (b) (4) tablets which are mixed with 5 ml water (b) (4) and dosed with the syringes:

a. The proposed (b) (4)% target value of the delivered dose with the data variability shown in the Table 4 (Infant Administration Study Report) is not deemed acceptable for the dose accuracy and consistency. In addition, we believe it is not practical to dose the infant with the syringe at 40°C, although the dose delivered at that temperature appears to be better comparing that at 25°C. You need to study the root cause of the low delivered dose and modify the dosing procedures with supporting data to demonstrate improved and consistently delivered dose for our review. One possible procedure is to (b) (4) the (b) (4) tablets with 3mL water or (b) (4) (b) (4) for delivery first, and then following with a rinsing step with additional 2mL water or (b) (4) to recover any leftover suspension from the vessel and the syringe.

b. Alternatively, you may consider reformulating your pediatric drug formulation if you could not further improve the delivered dose.

(b) (4)

On 3/9/2017, the Applicant responded that:

1. They proposed detailed instruction for preparation and administration of crushed nitisinone tablets in apple sauce as the followings, which now include additional rinse steps:

Preparation and administration of crushed Nitisinone tablets in apple (b) (4):

1). Crush one tablet at a time. Position the tablet between two teaspoons and apply light pressure on the top spoon. The two teaspoons should overlap each other to (b) (4) form a fine powder.

2). Press the two teaspoons against each other repeatedly (b) (4) .

3). (b) (4)

4). Carefully transfer the resulting powder into a clean container (e.g clean glass) ensuring all the powder is transferred, and no residue remains on the teaspoons.

5). If more than one tablet is needed (b) (4), repeat the procedure starting from (b) (4) and collect all the resulting powders together in the container.

6). Measure around (b) (4) of apple (b) (4) (1 full teaspoon) and transfer it into the container.

7). Mix the powder with the apple (b) (4) until the powder is well dispersed.

8). Administer the mixture to the patient's mouth using a teaspoon.

9). To assure that any leftover mixture from the container is recovered, additiona (b) (4) (1 full teaspoon) of apple (b) (4) can be added to the container and mixed with the remaining mixture. Administered the additional mixture to the patient's mouth using a teaspoon.

10). The crushed tablets should be administered within one hour after being mixed with the apple (b) (4)

2. Regarding the pH or brand for apple sauce used in infant administration study, the Applicant responded that:

The apple (b) (4) used in Cycle's study is Ella's Kitchen Apples Apples Apples Super Smooth Puree. The pH has been measured by Cycle to be 3.8, which is in line with the pH range of apple juice (3.35 – 4.00) and that of apple sauce (3.10 – 3.60). This response is acceptable.

3. Regarding the question 3 in FDA IR as above, the Applicant responded that:

Currently there is no data available. The Applicant commits to providing data showing that the crushing method described produces a consistent powder regardless of tablet hardness and tablet age. Cycle expects that this data will be available by Q3, 2017.

4. Regarding the question 4 in FDA IR as above, the Applicant responded that:

Based on the Agency comments, Cycle would like to withdraw the proposed syringe administration method until the challenges outlined by the Agency are addressed. Therefore, the proposed USPI has been revised to reflect this change i.e., (b) (4) has been removed.

Since the Applicant withdrew the proposed syringe administration, the current draft labeling by the Applicant is as follows:

(b) (4)

However, on 6/15/2017, the Applicant reconducted the study for nitisinone with syringe administration to address Agency's previous concern on syringe administration, and proposed to put the syringe administration method back to the label.

In the study report, the Applicant improved the previous low recovery issue on syringe administration by the addition of rinse step. They concluded that:

1. When a 10 mg tablet was placed in an oral dosing syringe with 2.5 mL of water at ambient temperature, the tablet would fully disintegrate within (b) (4) min, and reached (b) (4) % of mean recovery with a rinse volume of 2 mL of water.

2. A mean recovery of (b) (4) % and (b) (4) % was achieved in two separate studies when a single 2 mg tablet was allowed to disintegrate in an oral dosing syringe for (b) (4) minutes in 2.5 ml of water at ambient temperature with a rinse volume of 2 ml of water.

3. However, a lower mean recovery of (b) (4) % and (b) (4) % was found when a 10 mg tablet was crushed and administered in 2.5 ml of water via an oral dosing syringe where a single or duplicate rinse of 2.5 ml of water was carried out respectively.

4. The Nitisinone tablet suspension is stable for up to (b) (4) hours after the introduction of water into the oral dosing syringe.

Based on Drug Product reviewer Dr. Cai Hong's comments and the Applicant's response to IR dated 06/15/2017, the above study report was reviewed and found acceptable, and the Applicant proposed that tablet disintegration within the syringe is another viable option for infant administration for NITYR (in addition to administration with apple sauce). In particular, for patient with difficulty swallowing the tablets, up to two tablets may be inserted into an empty oral syringe followed by water at room temperature to allow for disintegration prior to administration.

For patients who are able to swallow semi-solid food, such as pediatric patients above weaning age, tablets may be crushed between two spoons and mixed with (b) (4) apple (b) (4) for administration. Furthermore, based on response to IR from the Applicant dated on 06/22/2017, the Applicant commits to providing the assay results at (b) (4) hours for the crushed tablets mixed with the apple (b) (4) for the suspension in syringe within two months post approval. Dr. Cai Hong would review syringe adminisatration and negotiate the labeling with the Applicant. Please refer to Dr. Cai Hong's review for details.

Overall, from the Biopharmaceutics perspective, the Applicant's response and proposal of administrating by spoon with apple (b) (4) is overall acceptable. The drug product reviewer and clinical team would determine the feasibility and (b) (4) and labeling instruction for the administration (b) (4) for pediatric patients (semi-solid food such as apple sauce may not be appropriate for certain ages of pediatric patients (e.g. < 6 months).

Bridging of Formulations

Reviewer's Assessment:

One batch of Nitisinone 10 mg tablets (batch RX501203.ML2) and one batch of Nitisinone 2 mg (batch RX501203.ML3) tablets were manufactured for formulation development purpose. The formulations of development batches are identical to the commercial formulations (Table 11), and the manufacturing processes are fairly similar, as the manufacturing process involves (b) (4) No major modification was made to the manufacturing process between the scale-up and process validation batches, except for some fine adjustments to the (b) (4) .

The batch size for the validation batches is (b) (4) tablets, which is the same as the batch size for the commercial batch. The size of the scale-up batch is (b) (4) tablets, which is within the 5 fold difference in batch size compared to the commercial batch.

Overall, there is no issue for bridging of formulations.

Table 11. Formulation comparison between development batch and commercial batch

Tablet Strength	Development Tablet Formulation		Commercial Tablet Formulation		
Batch number	RX501203.ML3	RX501203.ML2	151150 151151 151152	151153 151154 151155	151156 151158 151159
Nitisinone, API	(b) (4)				
Glycerol dibehenate					
(b) (4)					
Lactose monohydrate					
(b) (4)					
Total tablet weight	120 mg	120 mg	120 mg	120 mg	120 mg

Biowaiver Request

Reviewer's Assessment:

The Applicant conducted a BE study (CT-003) between nitisinone tablets 10 mg and ORFADIN capsules 10 mg. As shown in Table 12, the PK of 10 mg nitisinone tablets was bioequivalent to

10 mg reference drug. The acceptability of CT-003 will be determined by the reviewer in Office of Clinical Pharmacology.

Table 12. PK parameters and BE analysis from the Applicant

Table 14.2.1.5: Statistical analyses of nitisinone PK parameters (ANOVA) (pharmacokinetic population) – (b) (4)

Comparison	Paremeter (unit)	N	LSMeans Test1	LSMeans Test2	LSMeans Reference	% Ratio (Test/ Reference)	90% Confidence interval of ratio	Intra CV%
Test1 versus Reference	AUC0_120 (h*ng/mL)	46	78040.865	NA	78149.092	99.86	96.34 ; 103.51	7.0
	AUC0_72 (h*ng/mL)	46	57948.259	NA	58646.164	98.81	95.63 ; 102.09	6.4
	Cmax (ng/mL)	46	1278.828	NA	1333.510	95.90	91.66 ; 100.34	8.9
	Lambda_z (1/h)	46	0.012	NA	0.012	0.01	-0.07 ; 0.10	
	Tmax (h)	46	3.154	NA	2.941	21.35	-69.61 ; 112.31	
Test2 versus Reference	AUC0_120 (h*ng/mL)	46	NA	77187.852	78090.254	98.84	94.75 ; 103.11	8.3
	AUC0_72 (h*ng/mL)	46	NA	57455.264	58600.801	98.05	93.98 ; 102.28	8.3
	Cmax (ng/mL)	46	NA	1273.675	1332.941	95.55	91.14 ; 100.19	9.3
	Lambda_z (1/h)	46	NA	0.012	0.012	-0.03	-0.11 ; 0.06	
	Tmax (h)	46	NA	4.193	2.914	127.91	33.04 ; 222.77	

- N: number of observations; NA: not applicable.
- Reference: Orfadin® 10 mg hard capsule.
- Test1: Nitisinone 10 mg tablet.
- Test2: Nitisinone 10 mg tablet (6 months @ 40°C/75% RH).
- Subject number 09 discontinued and all samples are BLQ.
- For Tmax (hr) and λz (1/hr) untransformed data is used for analysis, for rest three parameters Cmax (ng/mL), AUC(0-120) (hr*ng/mL) and AUC(0-72)(hr*ng/mL) lntransformed data is used for analysis

Based on the result of CT-003, the Applicant requested a biowaiver for the two lower strengths of nitisinone tablets, 2 mg and 5 mg. As Table 1 shows, the formulation of different strengths of the proposed drug product is (b) (4) . However, the only difference among the three strengths is the inactive ingredient, lactose monohydrate (b) (4) % between the highest and the lowest strengths which is considered as a Level 2 change according to the SUPAC IR Guidance. Thus, a Case B dissolution testing was conducted.

The Applicant compared dissolution profiles of three different strengths of drug product in dissolution media with three different pHs (pH 4.5, pH 5.5, and pH 6.8) (Table 13). However, to support biowaiver request for the lower strengths, only dissolution comparison in QC dissolution medium (pH 6.8 phosphate buffer) is required (Figure 7). As mean dissolution shown in Table 13, the f2 between 2 mg strength and 10 mg strength calculated by the reviewer is 53.8. For 5 mg strength and 10 mg strength, the dissolution reached more than 85% within 15 min, and thus f2 calculation is not necessary to demonstrate their dissolution

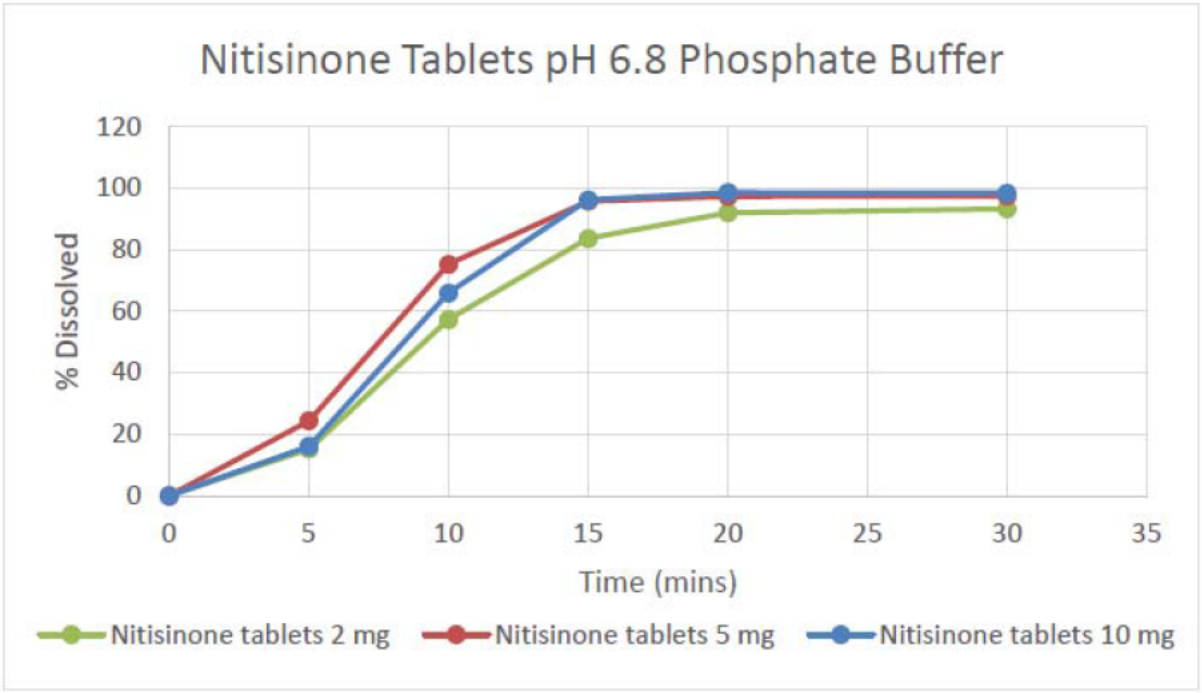
similarity. It is noticed that the variability of dissolution of all strengths at 5 min is high (>~15%), and CV% is more than 20% for 2 mg strength. The f2 between 2 mg and 10 mg strength calculated by the reviewer without the 5 min time point is 51. According to the ***Guidance for industry: dissolution test method for immediate release tablets***, a multiple variance analysis (MVA) on dissolution similarity was also conducted for dissolution comparison between 2 mg and 10 mg strength with all-time points included because of the high variability at 5 min. Based on reviewer's MVA analysis, the dissolution profiles of 2 mg and 10 mg strengths are also similar if 5 min time point is included. Therefore, the dissolution profiles of different strengths of nitisinone tablets are similar.

Table 13. Dissolution profiles and similarity factor (f2) of Nitisinone tablets calculated by the Applicant

Dissolution media			Collection Times (minutes)										f2
			0	5	10	15	20	30	45	60	75	90	
Nitisinone tablets 2 mg (n=12) (batch 151152)	pH 1.2	Mean	0		28.9	35.7	42.1	54.9	65.9	78	84	93.6	32
		RSD%	--		13.1%	13.1%	8.4%	9.1%	9.4%	9.0%	9.3%	12.0%	
	pH 4.5	Mean	0		16.1	31.2	46.2	64.4	82	93.9	101.2	106.8	78
		RSD%	--		16.6%	9.8%	6.0%	3.3%	1.8%	2.4%	1.7%	1.9%	
	pH 5.5	Mean	0		35.5	62.6	84.7	99.3	103.4	103.7	103.3	103.1	74
		RSD%	--		8.4%	8.4%	6.1%	3.6%	3.4%	3.3%	3.0%	3.0%	
	pH 6.8	Mean	0	15.2	57.3	83.7	92.1	93.4					56
		RSD%	--	25.7%	12.1%	5.4%	3.6%	3.2%					
Nitisinone tablets 5 mg (n=12) (batch 151155)	pH 1.2	Mean	0		48.8	56	65.9	72.9	88.8	96.2	99.3	105.4	36
		RSD%	--		8.4%	15.4%	16.0%	7.8%	9.0%	5.9%	3.4%	6.9%	
	pH 4.5	Mean	0		18.8	33.9	46.2	62.5	77.9	87.7	93.2	96.6	73
		RSD%	--		12.3%	7.4%	4.7%	2.2%	2.9%	2.4%	1.8%	1.6%	
	pH 5.5	Mean	0		45	75.1	92.4	103.4	107.1	107.4	107.1	106.6	62
		RSD%	--		9.3%	5.6%	3.6%	1.9%	1.5%	1.7%	1.3%	1.3%	
	pH 6.8	Mean	0	24.4	75.3	95.8	97.4	97.5					--*
		RSD%	--	19.8%	6.9%	2.1%	1.9%	2.3%					
Nitisinone tablets 10 mg (n=12) (batch 151155)	pH 1.2	Mean	0		16.9	19.5	23.9	29	38.1	47.3	58.4	63.8	
		RSD%	--		10.6%	9.8%	7.7%	12.9%	7.1%	10.9%	7.3%	9.5%	
	pH 4.5	Mean	0		13.6	28.4	43	61.5	79.7	90.7	98.2	103	
		RSD%	--		16.9%	9.8%	5.5%	4.1%	2.8%	2.0%	1.9%	1.9%	
	pH 5.5	Mean	0		38.1	68.1	86.9	101.3	107.2	105.8	105.8	105.6	
		RSD%	--		18.6%	8.5%	4.0%	2.0%	5.0%	2.2%	2.3%	2.2%	
	pH 6.8	Mean	0	16.1	66	96.3	98.7	98.5					
		RSD%	--	18.0%	11.6%	3.4%	2.2%	1.9%					

*Not necessary to calculate f2 as the release reached >85% dissolution in 15 minutes.

Figure 7. Mean dissolution profiles of 2 mg, 5 mg, and 10 mg nitisinone tablets in QC dissolution medium



Based on communication with clinical pharmacology reviewer, BE study CT-003 was acceptable and the results of comparative dissolution profile data also showed similar dissolution characteristics (f2 being >50) between the two lower strengths and the highest strength, in which a BE study was conducted.

Overall, the biowaiver request for the proposed 2 mg and 5 mg strengths of nitisinone tablets is, therefore, acceptable.

List of Deficiencies:

N/A

From the Biopharmaceutics perspective, NDA 209949 is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date: Peng (Vincent) Duan, Ph.D. 5/12/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur. 06/07/17 06/29/17

Tien-Mien Chen, Ph.D.

Acting Biopharm. Lead

DB/ONDP/OPQ

Peng Duan

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Tien Mien Chen

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Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 209449 Nitisinone tablets, 2mg, 5 mg and 10 mg

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Assay of the the drug substance, nitisinone, is determined by the in-house validated HPLC method. During manufacturing process development critical steps were identified and in process controls (IPC) e.g. (b) (4) were instituted for a robust manufacturing process and to constistantly produce quality DP. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters • Container/closure system	L	The related substances/ impurities are fully characterized and controlled by DS specification. The impurities are also controlled by DP specification at release and on stability. The impurities are assessed by the in-house validated HPLC method.	Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	The particle size of the drug substance is controlled. During manufacturing the DP quality is controlled by IPC including tablet weight, hardness, thickness, friability and disintegration. Dissolution is also controlled by DP specification.	Low to None	None

Hitesh Shroff

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