CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209449Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # **209449**	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: **Nitisinone** Established/Proper Name: **Nityr** Dosage Form: **Tablets** Strengths: **2 mg, 5 mg and 10 mg**		
Applicant: **Cycle Pharmaceuticals**		
Date of Receipt: **9/26/2016**		
PDUFA Goal Date: **7/26/2017**	Action Goal Date (if different):	
RPM: **Hong Vu**		
Proposed Indication(s): **Treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine**		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 021232 "Orfadin capsules"	**FDA's previous finding of safety and effectiveness for both clinical and nonclinical**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Due to thermal instability at room temperature, ORFADIN® capsules is required to be refrigerated and this is inconvenient for patients as a lifelong treatment. To address the issue, Cycle wishes introduce a thermally stable oral tablet formulation of nitisinone.

Two pivotal bioavailability/bioequivalence studies were conducted by Cycle to bridge the efficacy and safety profile of the reference listed product, ORFADIN® Capsules, with Cycle's tablet formulation.

According to the Clinical Pharmacology review, the pivotal BE study (CT-003) demonstrated bioequivalence between the proposed product (nitisinone tablets) and the listed drug (Orfadin capsules).

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Orfadin (nitisinone) capsules	**NDA 021232**	**Yes**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").
This application provides for a change in dosage form, from capsules to tablets.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

HONG VU
07/20/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: July 12, 2017

To: Hong Vu
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209449
OPDP Comments for draft NITYR (nitisinone) tablets, for oral use, PI and IFU

OPDP has reviewed the proposed draft PI for NITYR (nitisinone) tablets, for oral use and have no additional comments. Comments on the draft IFU will be sent under separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
07/12/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 12, 2017
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	NITYR (nitisinone)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	209449
Applicant:	Mapi USA Inc., U.S. Agent for Cycle Pharmaceuticals Ltd.

1 INTRODUCTION

On September 26, 2016, Mapi USA Inc., U.S. Agent for Cycle Pharmaceuticals Ltd., submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 209449 for NITYR (nitisinone) tablets. The Reference Listed Drug is ORFADIN (nitisinone) capsules NDA 021232. The proposed indication for NITYR (nitisinone) tablets is for the treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. Nitisinone is currently marketed as ORFADIN capsules and ORFADIN suspension NDA 206356. Due to thermal instability at room temperature, ORFADIN is required to be refrigerated, which is inconvenient for patients as a lifelong treatment. To address this issue, Mapi USA Inc., U.S. Agent for Cycle Pharmaceuticals Ltd, is proposing a thermally stable oral tablet formulation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on May 25, 2017 and May 26, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for NITYR (nitisinone) tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming**.**

2 MATERIAL REVIEWED

- Draft NITYR (nitisinone) tablets IFU received on June 15, 2017 and received by DMPP on June 15, 2017.
- Draft NITYR (nitisinone) tablets IFU received on June 15, 2017 and received by OPDP on July 10, 2017.
- Draft NITYR (nitisinone) tablets Prescribing Information (PI) received on June 15, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on July 11, 2017.
- Draft NITYR (nitisinone) tablets Prescribing Information (PI) received on June 15, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on July 12, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
07/12/2017

MEETA N PATEL
07/12/2017

MARCIA B WILLIAMS
07/12/2017

LASHAWN M GRIFFITHS
07/12/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 10, 2017
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209449
Product Name and Strength:	Nityr (nitisinone) tablets, 2 mg, 5 mg and 10 mg
Submission Date:	July 7, 2017
Applicant/Sponsor Name:	Cycle Pharmaceuticals, Ltd.
OSE RCM #:	2017-2227-2
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

This memo reviews the revised carton labeling and container labels (Appendix A) submitted by the Applicant in response to our review, OSE RCM #: 2017-2227-1[a]. Sponsor has accepted all of our recommendations for the carton labeling and container labels and we have no additional comments at this time.

2 CONCLUSION

DMEPA concludes that the container labels and carton labeling are acceptable from a medication error perspective and we have no additional comments at this time.

[a] Abraham.S. Label and Labeling Review for Nityr (NDA 209449). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 06 30. 32 p. OSE RCM No.:2017-2227-1

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/s/

SHERLY ABRAHAM
07/10/2017

SARAH K VEE
07/11/2017

M E M O R A N D U M

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

DATE: July 10, 2017

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products (DGIEP)
Office of Drug Evaluation III
Office of New Drugs

FROM: Srinivas Rao Chennamaneni, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Memo clarifying the authenticity of the RLD (Orfadin 10 mg, SOBI) used in BE Study PXL227430 (CT-003)

Background:

At the request of the Division of Gastroenterology and Inborn Errors Products, the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of the bioequivalence (BE) study below conducted at PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa. This memo provides a summary of the documentation to support that the reference listed drug, Orfadin 10 mg capsules, were procured and used in BE study PXL227430 (CT-003) at PAREXEL, South Africa.

PXL227430 (CT-003): "A Single Center, Single-Dose, Open-Label, Laboratory-Blind, Randomized, Three-Period Crossover Study To Determine The Bioequivalence Of Two Oral Formulations Containing Nitisinone 10 Mg Compared To The Reference Formulation Orfadin® 10 Mg In At

Least 18 Healthy Male And Female Subjects Under Fasting Conditions"

An EIR review with OSIS's recommendation was finalized in DARRTS on April 25, 2017 covering NDA 209449, nitisinone tablets 10 mg, from Cycle Pharmaceuticals Ltd. (Cycle), United Kingdom. On June 8, 2017, the Swedish Orphan Biovitrum (SOBI) contacted the Agency (**Attachment 1**) and stated that they were aware that Cycle was conducting bioequivalence studies comparing nitisinone to Orfadin and they have no record of supplying Cycle or PAREXEL (the clinical site) the US Orfadin product. In addition, SOBI (b) (4) and they were unaware how Cycle could have obtained the US Orfadin product for bioequivalence testing.

PAREXEL, South Africa (Clinical Site):

ORA Investigator James M. Mason audited the clinical portion of Study PXL227430 (CT-003) at PAREXEL Bloemfontein Early Phase Clinical Unit, Bloemfontein, Free State, South Africa. During the inspection, he collected copies of records to support that (b) (4) arranged for the shipment of Orfadin capsules, 10 mg, Batch No. 3041069 from the manufacturer, (b) (4) on March 10, 2016 for BE study PXL227430 (CT-003) (**Attachment 2**). The RLD was shipped under refrigerated conditions (2-8°C), whereas the test article was shipped at ambient conditions.

Cycle Pharmaceuticals Response to IR:

On June 20, 2017, the Agency sent an Information Request to Cycle requesting clarification on whether the applicant contracted directly with the manufacturer or a third party to procure Orfadin for Study PXL227430 (CT-003).

Cycle responded on June 22, 2017 and provided documentation to support that they sourced Orfadin capsules, 10 mg, Batch number 3041069 indirectly from the manufacturer (b) (4) through a third-party supplier named (b) (4) successfully procured the RLD from SOBI's licensed (b) (4) distributor for Cycle. The RLD was shipped refrigerated (2-8°C) directly from (b) (4) whereas the test article was shipped at ambient conditions from manufacturer, (b) (4)

Division of Pharmaceutical Analysis (DPA), FDA:

Bioequivalence Study PXL227430 (CT-003) is subject to 21 CFR 320.38, which requires the clinical site conducting the study to randomly select and retain reserve samples of the test article and reference standard from each shipment sent to the clinical site. This helps ensure that the test article and the reference standard are representative of the products used in the BE study.

The ORA investigator collected reserve samples of test and reference products at PARXEL, South Africa during the inspection on March 28, 2017 (**Attachment 4**). An affidavit signed by Chris Sutherland, Senior Director, PARXEL, South Africa supports that the reserve samples are representative of the test and reference products used in the BE study (**Attachment 5**).

The Division of Pharmaceutical Analysis (DPA), St. Louis, MO provided pictures of the test and reference products received for analysis, which were shipped by the ORA investigator from PAREXEL, South Africa (**Figure 1 and Figure 2**). The pictures support the authenticity of the test and reference products used in the study.

(b) (4)

(b) (4)

Conclusion:

The documentation collected during the FDA inspection of PAREXEL, South Africa and those submitted by the applicant in response to the Information Request support that Cycle contracted with (b) (4) to procure Orfadin capsules, 10 mg, Batch number 3041069 for BE Study PXL227430 (CT-003) conducted at PAREXEL, South Africa.

The pictures from (b) (4) clarify that the test product (tablet) is visually discernable from the RLD (capsule). Therefore, OSIS reaffirms that PAREXEL, South Africa used Orfadin capsules, 10 mg, in BE Study PXL227430 (CT-003).

Srinivas R. Chennamaneni, Ph.D.
DNDBE Branch, OSIS, OTS

CC:
OTS/OSIS/Kassim/Choe/Taylor/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au
OND/ODEIII/DGIEP/Vu/Bashaw/Griebel
ORA/PHI-DO/Mason/Karnick

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ PAREXEL Bloemfontein Early Phase Clinical Unit, Bloemfontein, South Africa/NDA 209449_Nitisinone Tab, 10 mg
Draft: SRC 7/8/2017
Edit: CRB 7/10/2017
BE File: 7328
FACTS: 11706081

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/s/

SRINIVAS RAO N CHENNAMANENI
07/11/2017

CHARLES R BONAPACE
07/11/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Labeling Review

Date: June 26, 2017 **Date consulted:** November 30, 2016

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: NITYR (nitisinone) Tablets

NDA: 209449

Applicant: Cycle Pharmaceuticals Ltd.

Subject: Pregnancy and Lactation Labeling

Indications: Treatment of Hereditary Tyrosinemia Type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Materials Reviewed:

- Applicant's submission, dated September 30, 2015
  - Proposed annotated label
  - Clinical Overview Addendum, module 2.5
  - Response to filing issues identified
  - Four month safety update
- Orfadin oral solution, NDA 206356:
  - Labeling approved August 30, 2016
  - Division of Pediatric and Maternal Health Labeling Review, by L. Sahin, March 16, 2016 (DARRTS Reference ID: 3903475)
- Orfadin oral capsule, NDA 021232:
  - Labeling approved June 13, 2016

- Pediatric and Maternal Health Staff Labeling Review, by M. Dinatale, March 25, 2014 (DARRTS Reference ID: 3476767)

Consult Question: DGIEP requests input regarding proposed PLLR labeling

INTRODUCTION

On September 26, 2016, the applicant submitted a 505(b)(2) NDA for nitisinone tablets, using Orfadin capsules (NDA 021232) as the reference listed product (RLD). Orfadin capsules were approved in the U.S. in 2002 for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input regarding compliance of the proposed labeling with the Pregnancy and Lactation Labeling Rule (PLLR).

BACKGROUND

Drug Characteristics

The applicant proposes to introduce a thermally stable oral tablet formulation of nitisinone, to be stored at 20°C to 25°C. Storage of Orfadin capsules requires low temperature (2°C to 8°C).

Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of fumarylacetoacetate hydrolase (FAH) in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate, which lead to porphyric crises and liver and kidney toxicity.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,*"[1] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[2] format to include information about the risks and benefits of using these products during pregnancy and lactation.

DATA REVIEW

The applicant reviewed the published literature for nitisinone exposure during pregnancy. The three publications referenced in the submission were previously reviewed by DPMH. No new publications were found.

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[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[2] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,* published in the Federal Register (71 FR 3922; January 24, 2006).

Outcomes of pregnancy cases reported in the literature:

- Segarra et al. 2010[1] – infant with tyrosinemia type I (both parents were carriers of the same mutation), otherwise no adverse outcome
- Vanclooster et al. 2012[2] – healthy infant
- Kassel et al. 2015[3] – healthy infant

Both the applicant and DPMH reviewed the published literature and found no human data available to inform use of nitisinone during lactation. Reproductive (TERIS, ReproTox) and lactation databases (LactMed) provided no additional information.

As this 505(b)2 product has not been marketed yet, the applicant has not collected cases of pregnancy or lactation in a pharmacovigilance database.

There are no animal or human data regarding effects on fertility. There are no labeling recommendations for contraception use or pregnancy testing, therefore, section 8.3 is omitted from the labeling.

CONCLUSIONS

Although the RLD has been marketed for over 15 years, there is sparse published literature to inform safe use of nitisinone in pregnancy and lactation, or to assess the effects of the drug on fertility. There are no new data available since the time of the previous DPMH reviews that would change the safety messaging for nitisinone use in women with HT-1 who are pregnant or lactating. The labeling will remain consistent with the RLD.

LABELING RECOMMENDATIONS

DPMH made minor revisions to subsections 8.1 and 8.2 of the labeling for compliance with the PLLR. DPMH labeling recommendations are below with changes tracked. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

TABLE OF CONTENTS

[1]Garcia Segarra N, Roche S, Imbard A, Benoist JF, Grenèche MO, Davit-Spraul A, Ogier de Baulny H. Maternal and fetal tyrosinemia type I. J Inherit Metab Dis. 2010 Dec;33 Suppl 3:S507-10.

[2] Vanclooster A1, Devlieger R, Meersseman W, Spraul A, Kerckhove KV, Vermeersch P, Meulemans A, Allegaert K, Cassiman D. Pregnancy during nitisinone treatment for tyrosinaemia type I: first human experience. JIMD Rep. 2012;5:27-33.

[3] Kassel R, Sprietsma L, Rudnick D. Pregnancy in an NTBC-Treated Patient With Hereditary Tyrosinemia Type I. J Pediatr Gastroenterol Nutr. 2015 Jan; 60(1):e5-7.

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
Limited data on nitisinone use in pregnant women are not sufficient to determine a (b) (4) drug associated risk of adverse developmental outcomes. Animal reproduction studies have been conducted for nitisinone. In these studies, nitisinone was administered to mice and rabbits during organogenesis with oral doses of nitisinone up to 20 and 8 times respectively, the recommended (b) (4) dose. In mice, nitisinone caused incomplete skeletal ossification of fetal bones and decreased pup survival at doses 0.4 times the recommended (b) (4) dose, and increased gestational length at doses 4 times the recommended (b) (4) dose. In rabbits, nitisinone caused maternal toxicity and incomplete skeletal ossification of fetal bones at doses 1.6 times the recommended (b) (4) dose *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Reproduction studies have been performed in mice at oral doses of about 0.4, 4 and 20 times the recommended (b) (4) dose (1 mg/kg/day) and in rabbits at oral doses of about 1.6, 4 and 8 times the recommended (b) (4) dose based on the body surface area. In mice, nitisinone has been shown to cause incomplete skeletal ossification of fetal bones at 0.4, 4 and 20 times the recommended (b) (4) dose, increased gestational length at 4 and 20 times the recommended human dose, and decreased pup survival at 0.4 times the recommended (b) (4) dose based on the body surface area. In rabbits, nitisinone caused incomplete skeletal ossification of fetal bones at 1.6, 4 and 8 times the recommended (b) (4) dose based on the body surface area.

8.2 Lactation

Risk Summary

There are no data on the presence of nitisinone in human milk, the effects on the breastfed infant, or the effects on milk production. Data suggest that nitisinone is present in rat milk due to findings of ocular toxicity and lower body weight seen in drug naive nursing rat pups. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for nitisinone and any potential adverse effects on the breastfed infant from nitisinone or from the underlying maternal condition.

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/s/

TAMARA N JOHNSON
07/07/2017

LYNNE P YAO
07/10/2017

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # NDA 209449
Product Name: NITYR (nitisinone) tablets

PMC #1 Description: To conduct assays of two pediatric preparations and report the assay results within two months post approval.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	09/19/2017
Final Report Submission:	09/26/2017
Other:	MM/DD/YYYY

PMC #2 Description:

PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY
Other:	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☒ Only feasible to conduct post-approval
   ☐ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

Two pediatric dosing procedures with nitisinone tablets are proposed for the patients who have difficulty in swallowing the tablets. The applicant proposed a storage and handling period of 2 hours following room temperature preparation of 1) crushed tablets in the apple (b) (4) and 2) a suspension produced from disintegrating the tablets in water stored in the medical syringes, but did not provide supporting assay data for each procedure. The PDUFA goal date is 07/26/2017 and the proposed study may not finish before the action date.

2. Describe the particular review issue and the goal of the study.

Review issue: In the absence of the assay results to cover the proposed dosing and storage period of the crushed tablets in apple (b) (4) and the suspension obtained by disintegrating the whole tablets in water with 5 mL medical syringes (2 hours) , the applicant has not provided justification for the proposed storage and handling periods.

Goal of the study: To ensure the proposed storage and handling periods for the two pediatric dosing procedures do not compromise the strength of the drug administered.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

Within two months post approval, the applicant will conduct assays for the two pediatric preparations, crushed tablets in apple (b) (4) and the suspension obtained from disintegrated tablets in the medical syringes with water, to justify the proposed storage and handling periods.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs? Yes.
- ☒ Are the objectives clear from the description of the PMC? Yes.
- ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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/s/

HONG CAI
07/07/2017

MOO JHONG RHEE
07/07/2017
Chief, Branch V

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 3, 2017
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209449
Product Name and Strength:	Nityr (nitisinone) tablets, 2 mg, 5 mg and 10 mg
Submission Date:	June 29, 2017
Applicant/Sponsor Name:	Cycle Pharmaceuticals, Ltd.
OSE RCM #:	2017-2227-1
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader (Acting):	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

This memo reviews the revised carton labeling and container labels (Appendix A) submitted by the sponsor in response to our review, OSE RCM #: 2017-2227[a]. Sponsor has accepted all of our recommendations for the carton labeling and container labels. We identified additional areas in the container labels and carton labeling that can be improved to increase the readability and the clarity of information to promote the safe use of the product. We note that the established name is not at least half the size of the proprietary name and we are requesting the Applicant to revise. We also reviewed the updated instructions for use (IFU) that was submitted on June15, 2017 that outlines the steps for administering the tablets via an oral syringe and

[a] Abraham.S. Label and Labeling Review for Nityr (NDA 209449). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 06 19. 32 p. OSE RCM No.:2017-2227

crushed in apple sauce for patients who cannot swallow the tablets whole. We provided recommendations for the IFU to DGIEP.

We provide letter-ready recommendations for the Applicant in Section 2.1.

2 CONCLUSION

DMEPA concludes that the container labels and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations for the Applicant in Section 2.1 below:

2.1 Recommendations to Cycle Pharmaceuticals

1. The established name is not at least half the size of the proprietary name. Thus, we request you to revise the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Move the manufacturer symbol (circle with cycle) to the side panel or reduce the size as it competes with the proprietary name for prominence and takes readers' attention away from important information such as proprietary and proper names and strength.

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/s/

SHERLY ABRAHAM
07/03/2017

SARAH K VEE
07/05/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation Research
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health

10903 New Hampshire Avenue
Silver Spring, MD 20993
Telephone 301.796.2200
Fax 301.796.9744

MEMORANDUM: PEDIATRIC REVIEW

From: Melanie E. Bhatnagar, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Acting Pediatric Team Leader
John J. Alexander, MD, MPH, Deputy Director
DPMH/ODEIV/OND

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: NITYR (nitisinone) tablets (2 milligram [mg], 5 mg, and 10 mg)

NDA: 209449

Applicant: Cycle Pharmaceuticals

Proposed Indication: NITYR is a 4-hydroxyphenylpyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine.

Materials Reviewed:

- Documents available in DARRTS under NDA 209449
  - DPMH consult request dated 12/13/16
  - Pediatric Waiver Request dated 9/26/16
  - Pediatric Study Plan and associated Expert Statement dated 12/16/16
  - General Advice email correspondence dated 4/25/17 and 5/2/17 (includes applicant's response)
  - Information Requests (IRs) dated 11/23/16, 2/9/17, 5/22/17 and applicant's associated responses dated 11/25/16, 3/3/17, and 6/15/17, respectively
  - Applicant's annotated draft labeling dated 1/17/17 and 6/20/17
- Documents associated with the reference listed drug (Orfadin)
  - Orfadin labeling revised August 2016 (accessed from FDA Label on 6/26/17)
  - Approval Letter dated 1/18/02 accessed from DARRTS under NDA 021232
  - Approval Letter dated 4/22/16 accessed from DARRTS under NDA 206356

Consult Request

DGIEP consulted DPMH to ensure the applicant is in compliance with the Pediatric Research Equity Act (PREA) for the current 505(b)(2) NDA submission. Additionally, DGIEP requested DPMH's input regarding safety considerations for the youngest pediatric patients, who are unable to swallow intact tablets, if the tablet is crushed but not fully dissolved prior to administration.

Regulatory History

On September 26, 2016, Cycle Pharmaceuticals submitted NDA 209449 through the 505(b)(2) pathway for NITYR, an oral tablet formulation of nitisinone. The applicant intends to rely on the safety and efficacy of Orfadin (nitisinone) as an approved listed drug and provides data to support bioequivalence of the nitisinone tablets to the Orfadin capsules. Orfadin oral capsules and oral suspension are approved for adults and pediatric patients of all ages for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.[1] The original NDA submission for Orfadin contained a full pediatric assessment.[2] Cycle Pharmaceuticals is seeking the same indication as Orfadin and has not conducted any additional non-clinical or clinical studies.

On December 13, 2016, DGIEP consulted DPMH to ensure the applicant is in compliance with PREA. The applicant applied for orphan designation on August 3, 2016 and because they anticipated receiving orphan status, an agreed initial Pediatric Study Plan (PSP) was not included in the NDA submission.[3] The applicant's request for orphan designation was not granted, so the new tablet dosage form triggers the requirement for a pediatric assessment under PREA. DPMH recommended that DGIEP advise the applicant to submit a PSP which states the applicant intends to provide a full pediatric assessment in this NDA by establishing bioequivalence to the reference listed drug. The applicant submitted the PSP on December 16, 2016.[4]

Introduction

Hereditary tyrosinemia type 1 (HT-1) results from a deficiency of fumarylacetoacetate hydrolase, the last enzyme in the tyrosine degradation pathway.[5] Nitisinone blocks 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme which acts earlier in the pathway, thereby preventing build-up of intermediates which are toxic to the liver and kidneys.[6] In the clinical study conducted with Orfadin, survival probability increased for patients treated with nitisinone in combination with dietary restriction compared to historical controls treated with dietary restriction alone.[2]

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[1] Nitisinone was originally approved as Orfadin oral capsules on January 18, 2002 under NDA 021232. Subsequent approval for Orfadin oral suspension was granted on April 22, 2016 under NDA 206356 through the same applicant, Swedish Orphan Biovitrum. Approval letters accessed from DARRTS under the respective NDAs.
[2] The efficacy and safety of Orfadin was assessed in an open-label, uncontrolled study of 207 patients with HT-1 from birth to 22 years (median age 9 months) [Orfadin labeling accessed from FDA Label 6/6/17].
[3] Cover Letter dated 9/26/16 accessed from DARRTS under NDA 209449
[4] Pediatric Development Plan dated 12/16/16 accessed from DARRTS under NDA 209449
[5] C de Laet, et al, 2013, Recommendations for the management of tyrosinaemia type 1, Orphanet J Rare Dis, 8(8)
[6] Section 12 Clinical Pharmacology of Orfadin labeling (accessed from FDA Label 6/6/17)

According to one source, use of nitisinone in addition to dietary restrictions has since become the mainstay of HT-1 management.[5] Nitisinone is the only FDA approved drug product for treatment of HT-1 and is currently available only as Orfadin.

HT-1 most commonly presents in early infancy and requires lifelong daily treatment.[5] To address the youngest pediatric patients, the applicant provided the following instructions in subsection 2.2 Dosage and Administration of their proposed labeling for nitisinone tablets:

> *For patients who have difficulty swallowing the tablets, such as pediatric patients, tablets* (b) (4) *can be administered using a syringe. Crushed tablets may also be mixed with* (b) (4) *apple sauce* (b) (4).

In support of this labeling statement, the applicant provided data for the recovery and stability of (b) (4) nitisinone tablets using water, (b) (4) and applesauce as administration vehicles.[7] Upon reviewing the data, DGIEP concluded that drug recovery using water was inadequate and, although recovery was adequate using (b) (4), use of this vehicle resulted in an unknown impurity in excess of allowed limits.

DGIEP encouraged the applicant to evaluate strategies for improving drug recovery of (b) (4) tablets in a liquid vehicle. DGIEP also asked the applicant to address whether or not inadvertent administration of large particle sizes, which may result from inadequate tablet crushing, could present a choking hazard to the youngest pediatric patients.[8] In response, the applicant reported that the information requested by DGIEP is not available and cited the FDA Health Hazard Evaluation Board which notes that foreign objects less than 7 mm in maximum dimension rarely cause serious injury, except in special risk groups such as infants.[9] (b) (4) The applicant suggested keeping instructions for crushing tablets for administration in applesauce, stating that pediatric patients who have been introduced to solid food may have a lower risk for choking on incompletely crushed tablet particles.

On April 3, 2017, DGIEP held a teleconference with the applicant to discuss a plan for the applicant to address how to evaluate and improve drug recovery of (b) (4) nitisinone tablets in a liquid vehicle. In response, the applicant performed additional studies assessing drug recovery in water using two methods.[10] First, the applicant modified the recovery studies previously conducted by incorporating a rinsing step. The recovery rate continued to be sub-optimal at less than 90%. Next, the applicant dissolved one or two nitisinone tablets (2 mg and 10 mg, fresh and 24 month-old) directly in a water-filled syringe (2.5 mL or 5 mL, respectively) and found the tablets fully disintegrate within 50 minutes. Greater than 90% drug recovery is achieved if the syringe is rinsed with 2.5 mL water following administration. The applicant did not pursue further investigation (b) (4)

[7] Infant administration study report for nitisinone tablets dated 1/6/17 (accessed from DARRTS under NDA 209449)
[8] Information Request dated 2/9/17 (accessed from DARRTS under NDA 209449)
[9] Applicant's 3/3/17 response to IR (accessed from DARRTS under NDA 209449)
[10] Applicant's 6/15/17 response to IR (accessed from DARRTS under NDA 209449)

using this method. Ultimately, DGIEP agreed drug recovery was adequate for crushed tablets delivered in applesauce and dissolved tablets delivered in water, each including a rinsing step after administration.

Discussion

(b) (4)

DPMH's literature search retrieved regulatory guidelines and published literature that acknowledge prescribers may resort to crushing tablets for pediatric patients when an age-appropriate formulation is not available.[13, 14, 15] These resources focus primarily on the potential consequences on bioavailability and efficacy and lack detailed advice related to potential choking hazards with this method.

There appears to be a lack of evidence to support a specific age or developmental stage at which solid oral dosage forms can be comfortably and safely ingested.[16] The acceptance of tablet swallowing by pediatric patients varies with age, developmental stage, and the individual patient's tolerability, as well as the size and shape of the tablet.[17]

(b) (4)

[12] Synthroid (levothyroxine sodium) tablet labeling revised June 2017 (accessed from FDA Label on 6/15/17)
[13] Addendum to ICH E11 dated 8/25/16 accessed 6/19/17 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf
[14] F Liu, 2014, Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations, Drugs 74:1871-1889
[15] A Ali, et al, 2014, Pediatric drug development: formulation considerations, Drug Dev Ind Pharm, 40(10): 1283-99
[16] Report of the informal expert meeting on dosage forms of medicines for children, 2008, 17th meeting of the Expert Committee on Selection and Use of Essential Medicines (accessed 4/19/17 from http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf)
[17] R Sockolow and A Solomon, 2013, The jelly bean test: a novel technique to help children swallow medications, Pediatric Drug Development: Concepts and Applications, 2nd Edition, 583-587, Ed. A Mulberg, et al.

The International Conference on Harmonisation (ICH) acknowledges the need for pediatric formulations which permit accurate dosing, enhance patient compliance, and consider acceptability parameters such as tablet size.[13, 18] Although PREA requires pediatric assessments be conducted using an age-appropriate formulation, FDA's guidance to industry on this topic does not specify how these formulations should be developed.[19] The 2013 European Medicines Agency (EMA) guideline for pediatric drug development is the only regulatory source identified by this reviewer with detailed information regarding pediatric drug formulation considerations.[20] The guideline states that the risk of choking should be discussed in relation to the age of pediatric patients intended to use the product and the size and shape of the product, but notes there is limited available data to describe the influence of size and shape on acceptability in different pediatric age groups.[20] The ICH E11 addendum notes that alternative dosing strategies, such as crushing and administration with food or liquid, may need to be considered for pediatric populations.[13] The addendum does not elaborate on potential safety concerns, but states "understanding real-world use behaviors in administering pediatric dosage forms and the mitigation of associated risks will contribute to the development of a formulation that allows for safe dose administration."[13]

A WHO publication for promoting the safety of medicines for children cites four deaths in pediatric patients less than 3 years of age resulting from choking on albendazole tablets in 2007 in Ethiopia.[21] Although cases of children dying from choking on large pills available over-the-counter have been the subject of newspaper articles in the United States,[22, 23] these events seem to be rare as no literature evaluating the risk was retrieved by this reviewer through a PubMed search. The rarity of these reported events may be related to the limited use of these dosage forms in pediatric patients or to under-reporting.

The American Academy of Pediatrics (AAP) considers children less than 3 years of age to have the highest risk for choking because of the following factors: (1) insufficient chewing due to lack of molars, (2) immature swallowing coordination, (3) small airway sizes, and (4) behavioral factors such as distractibility and high activity levels while eating.[24] The AAP notes the choking risk in children less than 3 years of age is associated with ingestion of hard, small, round foods such as hot dogs, nuts, and whole grapes. The United States Consumer Product Safety Commission (CPSF) defines a "small part" which may present a choking risk as any object that fits completely into a cylinder measuring 2.25 inches (57.15 millimeters [mm]) long by 1.25 inches (31.75 mm) wide, thought to approximate the size of the throat of a child under 3 years of

[18] ICH E11 dated 7/20/00 (accessed 6/19/17 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf)
[19] FDA Guidance for Industry, 2000, E11 Clinical Investigation of Medicinal Products in the Pediatric Population accessed 6/19/17 from https://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073143.pdf
[20] 2013 EMA Guideline on pharmaceutical development of medicines for pediatric use (accessed 4/17/17 from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf)
[21] WHO, 2007, Promoting safety of medicines for children (accessed 6/21/17 from http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf)
[22] https://www.washingtonpost.com/archive/local/1999/04/23/boy-chokes-on-vitamin-while-mother-seeks-help/3b66224b-8fa8-4c72-b9d0-cf1ffbbdbb0d/?utm_term=.51f2e86fe4fb
[23] http://nypost.com/2006/02/17/4-year-old-tribeca-boy-chokes-to-death-on-pill/
[24] AAP Policy Statement – Prevention of Choking Among Children, 2010, Pediatrics 125 (3): 601-607

age.[25] In a 2006 study, airway cross-sectional area was evaluated in 125 pediatric patients less than 10 years of age (median 2 years) referred for bronchoscopy for chronic cough.[26] Digital images were obtained at specified locations during bronchoscopy and airway diameter was measured. The cross-sectional area at the level of the cricoid for age 2.5 years (n=72) was 34.71 ± 8.48 mm^2 and for ages 2.5 years to 5 years (n=28) was 36.89 ± 7.94 mm^2.[26]

The choking considerations described by the AAP and CPSF are applicable to the proposed nitisinone tablet formulation because nitisinone tablets are small, hard, and round with a 7 mm diameter (38.48 mm^2 cross-sectional area) which approximates the size of the average airway of pediatric patients less than 6 years of age. Therefore, ingestion of the intact tablet could present a potential choking hazard, particularly for pediatric patients less than 3 years of age who have the smallest airways and the most immature swallowing coordination. Although neurologic crises occur in patients with poorly controlled HT-1, persistent neurologic dysfunction and intellectual disability are not features of the disease, so these factors are unlikely to play a role in swallowing ability for these patients.

For pediatric patients with HT-1 who are unable to tolerate tablet swallowing, crushing the nitisinone tablet is an alternative means of administration. There is some published evidence that pediatric patients as young as neonates can tolerate small solid oral dosage forms such as miniature tablets and beads for sprinkling, but tolerability in these cases is likely to be formulation-dependent. In an open-label, randomized, prospective cross-over study in Germany, the acceptability and swallowability of a dissolvable 2 mm uncoated mini-tablet was compared to 0.5 mL of syrup in pre-term (n=11) and term (n= 140) neonates (age 2-28 days; median 4 days).[27] The neonates received the two drug-free oral formulations sequentially within 10 minutes; randomization determined which formulation was received first. The neonates were monitored to assess swallowability, which was defined as everything swallowed, without residual content in the mouth, without choking, coughing, or inhaling. The authors report that none of the neonates inhaled, coughed, or choked on either formulation. A similar study was conducted by the same authors comparing 2 mm mini-tablets to 3 mL syrup in 306 patients age 6 months to 5 years (n = 306 divided evenly throughout the age range).[28] Two of the patients in the age group of 6 months to 1 year coughed as a direct result of ingestion of the coated mini-tablet. There were no serious adverse events and no episodes of cough, inhalation, or choking in the remaining patients.

Although incomplete crushing of the nitisinone tablet may result in particle sizes similar to those described above for mini-tablets, formulation-dependent characteristics may play a role in the tolerability and safety. For example, the nitisinone tablet is not rapidly dissolvable[29] and the crushed particles may have sharp edges, which could influence swallowability or put the pediatric patient at risk for injury. With regard to choking risk, this reviewer considers the

[25] 16 CFR 1501.4
[26] I Masters, et al, 2006, Airway sizes and proportions in children quantified by a video-bronchoscopic technique, BMC Pulm Med, 6(5)
[27] V Klingmann, et al, 2015, Acceptability of uncoated mini-tablets in neonates – a randomized controlled trial, J Pediatr, 167: 893-6
[28] V Klingmann, et al, 2013, Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children, J Pediatr, 163: 1728-32
[29] According to the sponsor's IR response on 6/15/17, nitisinone tablets fully disintegrate in water within 50 minutes

particle sizes resulting from an incompletely crushed tablet unlikely to occlude the pediatric airway. For example, if the nitisinone tablet is crushed into three equal parts, each particle would measure approximately 2.3 mm (4.15 mm^2). Furthermore, limiting administration of crushed tablets to pediatric patients tolerating semi-solid food ensures only patients who have demonstrated development of early swallowing coordination are exposed to crushed tablets, which may help mitigate any potential choking risk.

Conclusions

Pediatric patients less than 3 years of age are at the highest theoretical risk for choking with use of intact NITYR tablets due, in part, to their immature swallowing coordination and small airway size. This concern can be addressed in product labeling by specifying how to correctly dissolve the product for use in younger pediatric patients who are not yet tolerating solid foods. Resources identified in this review do not address theoretical concerns related to improper crushing technique or the potential for choking due to inadvertent ingestion of large particle sizes resulting from incomplete tablet crushing. Crushed tablet particle sizes of approximately 2 mm or less are unlikely to occlude the pediatric airway, though the risk may be mitigated by limiting administration of crushed tablets to pediatric patients tolerating semi-solid food, thereby ensuring only patients who have demonstrated development of early swallowing coordination are exposed.

DPMH Recommendations for Labeling

DPMH recommends including tablet crushing instructions in NITYR labeling for pediatric patients who are able to tolerate the applesauce vehicle. Administration of crushed tablets should not be limited to a specific age or weight parameter because these parameters lack specificity for the development of swallowing coordination. To provide additional assurances for safety, the instructions for tablet crushing should emphasize that the crushed product is intended to be a fine powder. For pediatric patients unable to tolerate the applesauce vehicle, DPMH recommends including tablet dissolution instructions in NITYR labeling based on the methods studied by the applicant which resulted in adequate drug recovery.

DPMH recommends including labeling language to emphasize that only intact tablets should be used for crushing or dissolving. In a study conducted by FDA, the impact of tablet splitting was evaluated.[30] The results suggest certain physical characteristics, including unscored, round, small tablets, such as with NITYR, result in higher variability of drug content when the tablets are split. DPMH also recommends labeling clearly state that administration of NITYR with vehicles other than water or applesauce has not been studied and is not recommended.

Excerpts from the applicant's proposed labeling dated June 20, 2017 for Section 2 (Dosage and Administration) are copied below with recommended edits from the DPMH Pediatric Team. The DPMH Pediatric Team will convey recommendations for the remaining sections of labeling in a labeling review of the reference drug, Orfadin. Labeling additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text. DPMH's labeling

[30] A Ciavarella, et al, 2016, Dose uniformity of scored and unscored tablets: application of the FDA tablet scoring guidance for industry, Parenteral Drug Association Journal of Pharmaceutical Science and Technology: 70: 523-532

recommendations were discussed with DGIEP at an internal meeting held on June 26, 2017. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested in this review.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Starting Dosage

The recommended starting dosage of NITYR is 0.5 mg/kg orally twice daily. Round to the nearest dosage that can be administered using the available tablet strengths *[see Dosage Forms and Strengths (3)]*.

Titrate the dose for individual patients, as needed based on biochemical and/or clinical response. (b) (4)

Dosage Titration

- 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 0.75 mg/kg twice daily. A maximum dosage of 1 mg/kg orally twice 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 (b) (4) may be taken with or without food.
- For patients who have difficulty swallowing (b) (4) intact tablets, including pediatric patients, NITYR can be disintegrated in water and administered using an oral syringe. (b) (4) If patients can swallow semi-solid foods, (b) (4) NITYR can also be crushed (b) (4) and mixed with (b) (4) applesauce (b) (4) *Administration of NITYR with other liquids or foods has not been studied and is not recommended.*

Preparation and Administration of NITYR [redacted] with Water in an Oral Syringe:

A [redacted] 5 mL oral syringe [redacted] with a cap will be provided by a pharmacist. Follow the instructions below for one or two intact tablets, depending on the number of tablets needed to achieve the patient's individual dosage. No more than two tablets can be prepared at once within the same oral syringe. If more tablets are needed to achieve the patient's dosage, repeat the steps below using multiple oral syringes to achieve the required dose.

One Tablet

1. Remove the plunger from the oral syringe and insert [redacted] a single, intact tablet.
2. Replace the plunger and draw up 2 [redacted] mL of water at room temperature. [redacted]
3. Cap the oral syringe and leave it for at least [redacted] and use within 2 hours of preparation.
4. [redacted] oral syringe for one minute [redacted] The dose must be administered to the patient within 2 hours of when the water was added to the syringe. [redacted]
5. Uncap the oral 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 oral syringe. [redacted]
6. Rinse the syringe by drawing up a further 2 mL of water. [redacted] oral syringe [redacted] to suspend any remaining particles.
7. Uncap the oral syringe and administer the suspension into the patient's mouth, [redacted] this time fully depressing the plunger and ensuring the syringe [redacted] is empty.

Two Tablets

[redacted]

1. Remove the plunger from the syringe and insert two intact tablets.
2. Replace the plunger and draw up 5 mL of water at room temperature. [redacted]
3. [redacted]

[redacted]

[redacted]

Preparation and [redacted] dministration of [redacted] NITYR [redacted] Mixed in [redacted] Applesauce [redacted]
For patients who can swallow semi-solid food, NITYR can be crushed and mixed with applesauce:

1. ~~Measure around~~ Place approximately [redacted] of applesauce [redacted] ~~(1~~ [redacted] ~~teaspoon) and transfer it~~ into a clean container ~~(e.g., clean glass)~~.
2. ~~Always crush one tablet at a time.~~ Place one intact tablet on a teaspoon, holding it over the container with the applesauce.
3. ~~Position the tablet between two teaspoons and a~~Apply light pressure to the tablet using the back of another teaspoon ~~on the top spoon~~. Press and rotate the two teaspoons against each other repeatedly until the tablet has been crushed to a fine powder [redacted]
4. [redacted]
5. ~~Carefully t~~Transfer the resulting powder [redacted] the applesauce [redacted] container ensuring all the powder is transferred, and no powder residues remain on the teaspoons.
6. If more than one tablet is needed [redacted], repeat steps 2 and 3 for each tablet, ~~the procedure starting from~~ [redacted] ~~2 and~~ collecting all the resulting powders together in the applesauce [redacted] container.
7. Mix the powder [redacted] the applesauce [redacted] ~~until the powder is well dispersed~~.
8. ~~Administer~~ Consume all of the applesauce mixture immediately ~~to the patient's mouth using a teaspoon~~.
9. ~~To assure that any leftover mixture from the container is recovered, a~~Add another ~~around~~ [redacted] ~~(1~~ [redacted] ~~teaspoon)~~ of applesauce [redacted] to the same container and mix with any ~~the fresh~~ applesauce [redacted] ~~with the remaining~~ mixture remaining in the container.
10. ~~Administer~~ Consume all the additional applesauce mixture immediately ~~to the patient's mouth using a teaspoon~~.
11. If the applesauce mixture cannot be administered immediately, it can be stored at room temperature for up to [redacted] 2 hours ~~after~~ [redacted] Discard after 2 hours.

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/s/

MELANIE E BHATNAGAR
06/30/2017

JOHN J ALEXANDER
06/30/2017

M E M O R A N D U M

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

DATE: April 24, 2017

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Surveillance Inspection of PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of study PXL227430 (CT-003) conducted at PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa. At the conclusion of the inspection, no significant deficiencies were observed and no Form FDA 483 was issued. The final classification is No Action Indicated (NAI). After review of the establishment inspection report (EIR) and the inspectional findings, I found the clinical data from the audited study to be reliable. Therefore, I recommend that the data from the clinical portion of Study PXL227430 (CT-003) submitted to NDA 209449 be accepted for further agency review.

Audited Study

NDA 209449
Study Number#: PXL227430 (CT-003)

Study Title: "A Single Center, Single-Dose, Open-Label, Laboratory-Blind, Randomized, Three-Period Crossover Study To Determine The Bioequivalence Of Two Oral Formulations Containing Nitisinone 10 Mg Compared To The Reference Formulation Orfadin® 10 Mg In At Least 18 Healthy Male And Female Subjects Under Fasting Conditions"

Study Dates: March 15 – May 25, 2016

The ORA investigator James M. Mason (PHI-DO) audited the clinical portion of the in vivo bioequivalence study at PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa from March 27-30, 2017.

The inspection included a review of the study protocol, IRB submissions and approvals, informed consent forms (ICFs), case report forms, source documents, adverse event reporting, drug accountability, employee training, and interviews and discussions with the firm's management and staff. No significant deficiencies were observed and no Form FDA 483 was issued at the conclusion of the inspection. Reserve samples were collected and sent to CDER-DPA, St. Louis, MO for analysis.

Recommendations:

After review of the EIR and the inspectional findings, the audited study was found to be reliable. Therefore, I recommend that the data from the clinical portion of Study PXL227430 (CT-003) be accepted for further agency review.

Srinivas R. Chennamaneni, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical Site
NAI: PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa (FEI# 3010924245)

CC:
OTS/OSIS/Kassim/Choe/Taylor/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au
OND/ODEIII/DGIEP/Vu/Bashaw/Griebel
ORA/PHI-DO/Mason/Karnick

Draft: SRC 4/21/2017
Edit: GB 4/21/2017; CB 4/23/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ PAREXEL Bloemfontein Early Phase Clinical Unit, Bloemfontein, South Africa/NDA 209449_Nitisinone Tab, 10 mg

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FACTS: 11706081

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/s/

SRINIVAS RAO N CHENNAMANENI
04/24/2017

GOPA BISWAS
04/24/2017

CHARLES R BONAPACE
04/25/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 19, 2017
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209449
Product Name and Strengths:	Nityr (nitisinone) tablets, 2 mg, 5 mg, and 10 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Cycle Pharmaceuticals, Ltd.
Submission Date:	September 26, 2016 June 15, 2017
OSE RCM #:	2017-2227
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review the prescribing information (PI), container label, and carton labeling for any areas of vulnerability that may lead to medication errors for NDA 209449, submitted on September 26, 2016.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Cycle Pharmaceuticals submitted a 505(b)(2) NDA for nitisinone (2 mg, 5 mg, and 10 mg) for treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. The reference listed drug (RLD) for this product is Orfadin (nitisone) capsules, NDA 21232 that was approved on January 18, 2012. Cycle Pharma is seeking approval for this product to introduce a thermally stable formulation of oral tablets.

DMEPA evaluated the proposed PI, container label, and carton labeling to determine whether there are any vulnerabilities that may lead to medication errors. We identified areas in the PI and Instructions for Use that can be improved and communicated these recommendations directly to DGIEP. DMEPA also identified areas in the container labels and carton labeling that can be improved to increase the readability and the clarity of information to promote the safe use of the product. We provide letter-ready recommendations for the Applicant in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information and container labels and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations for the Applicant in Section 4.1 below:

4.1. RECOMMENDATIONS TO CYCLE PHARMACEUTICALS

A. Container Labels and Carton Labeling:

1. As currently presented, three different colors (blue, yellow and orange) are utilized to represent three different strengths by highlighting the established name, dosage form and box around the strength. Color is typically used to differentiate the different strengths of a product. Since the product name and dosage form are the same across the three strength presentations, we recommend using your color scheme to highlight the different strengths of your product (i.e., use colored fonts for the product strengths).

2. Please submit the revised container labels and carton labeling with the conditionally acceptable proposed proprietary name, Nityr, for review.

B. Carton Label:

1. Revise the usual dosage statement to be consistent with the prescribing information or to state: See Prescribing Information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for nitisone that submitted by Cycle Pharmaceuticals on September 26, 2016 and June 15, 2017.

Table 2. Relevant Product Information for nitisinone tablets and RLD Orfadin capsules		
Products	NDA 209449 (nitisone tablets)	NDA 21232 (Orfadin capsules)
Initial Approval Date	N/A	January 18, 2002
Active Ingredient	Nitisinone	
Indication	Treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine	Treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.
Route of Administration	oral	
Dosage Forms	tablets	capsules
Strengths	2 mg, 5 mg, 10 mg	2 mg, 5 mg, 10 mg, and 20 mg
Dose and Frequency	Recommended dosage is (b) (4) .	The recommended starting dosage is (b) (4) mg/kg (b) (4) daily. Maximum dosage is (b) (4) mg/kg orally (b) (4) daily.
How Supplied	60 count bottles	
Storage	Store nitisinone tablets (b) (4) (b) (4) at 20° to 25° (68° to 77°F), allows for excursions between 15° and 30° (59° and 86°F). (b) (4)	Store refrigerated at 2° C to 8°C (36°F to 46°F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following nitisone labels and labeling submitted by Cycle Pharmaceuticals on September 26, 2016 and June 15, 2017.

- Container label
- Carton labeling
- Prescribing information

G.2

Proposed container labels:

(b) (4)

[redacted]

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/

SHERLY ABRAHAM
06/19/2017

SARAH K VEE
06/20/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # **209449** BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: **Nitisinone** Dosage Form: **Tablets** Strengths: **2mg, 5mg and 10 mg**		
Applicant: **Cycle Pharmaceuticals Ltd.** Agent for Applicant (if applicable): **Patricia Anderson, Mapi USA, Inc.**		
Date of Application: **9/26/2016** Date of Receipt: **9/26/2016** Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: **7/26/2017**	Action Goal Date (if different):	
Filing Goal Date: **11/25/2016**	Date of Filing Meeting: **11/21/2016**	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): **Treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine** (b) (4) (b) (4)		
Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)	
Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): **IND 121021**	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☒	☐		Orfadin® (nitisinone)
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☒	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☒	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	Consult to Maternal Health
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):**	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/21/2016

BACKGROUND: Cycle Pharma submitted the NDA 209449 for nitisinone tablets via the 505(b)(2) pathway to introduce a thermally stable oral tablet formulation of nitisinone for the treatment of hereditary tyrosinemia type 1. The listed drug is Orfadin requires refrigeration, because of its thermal instability at room temperature.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Hong Vu	Yes
	CPMS/TL:	Kevin Bugin	Yes
Cross-Discipline Team Leader (CDTL)	Sue Chih Lee		Yes
Division Director/Deputy/Associate	Donna Griebel, Division Director Dragos Roman, Associate Director		Yes/Yes
Office Director/Deputy	Office Director		N/A
Clinical	Reviewer:	Patroula Smpokou	Yes
	TL:	Laurie Muldowney	Yes
Social Scientist Review (*for OTC products*)	Reviewer:		N/A
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		N/A
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		N/A
	TL:		
Clinical Pharmacology	Reviewer:	Shen (Steven) Li	Yes
	TL:	Sue Chih Lee	Yes
• Genomics	Reviewer:		N/A
• Pharmacometrics	Reviewer:		N/A
Biostatistics	Reviewer:		N/A

	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fresnida Ramos	Yes
	TL:	David Joseph	Yes
Statistics (carcinogenicity)	Reviewer:		N/A
	TL:		
Product Quality (CMC) Review Team:	ATL:	Hitesh Shroff	Yes
	RBPM:	Rabiya Laiq	Yes
• Drug Substance	Reviewer:	Lawrence Perez	Yes
• Drug Product	Reviewer:	Hong Cai	Yes
• Process	Reviewer:	Tianhong Tim Zhou	No
• Microbiology	Reviewer:	Tianhong Tim Zhou	No
• Facility	Reviewer:	Michael Klapal	No
• Biopharmaceutics	Reviewer:	Peng Duan (Primary Reviewer)	Yes
• Immunogenicity	Reviewer:		N/A
• Labeling (BLAs only)	Reviewer:		N/A
• Other (e.g., Branch Chiefs, EA Reviewer)			N/A
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sherly Abraham	Yes
	TL:	Mishale Mistry	No
OSE/DRISK (REMS)	Reviewer:		N/A
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		N/A
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		N/A
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		N/A
	TL:		
Other reviewers/disciplines			
• OSE Safety Project Manager (OSE SRPM)	SRPM:	Nicholas Miles	No
	TL:	Aleksander Winiarski	No
• Pharmacovigilance (DPV)	Reviewer:	Kim Swank	No
	TL:	Ling Y (Eileen) Wu	No
• Epidemiology (DEPI)	Reviewer:	Joel Weissfeld	Yes
	TL:	Sukh Sandhu	No
Other attendees	Joette Meyer, DGIEP Associate Director of Labeling		Yes
	Kathryn O'Connell, CDER Rare Disease Program		Yes

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO To bridge the listed product, the sponsor conducted two BE studies and one food effect study.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☐ YES ☐ NO ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dragos Roman **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): N/A **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

HONG VU
12/20/2016