CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209449Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 7, 2017
From	Joette M. Meyer, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209449
Applicant	Cycle Pharmaceuticals Ltd. Mapi USA, Inc., US Agent
Date of Submission	September 26, 2017
PDUFA Goal Date	July 26, 2017
Proprietary Name / Established (USAN) names	NITYR (nitisinone)
Dosage forms / Strength	Tablets for oral use: 2, 5 and 10 mg
Proposed Indication(s)	Treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine
Recommended:	Approval, pending labeling

EDR Location: \\CDSESUB1\evsprod\NDA209449\209449.enx

1. Introduction

The sponsor (Cycle Pharmaceuticals Ltd.) is submitting a 505(b)(2) NDA for nitisinone tablets (2, 5 and 10 mg), which relies on the FDA's findings of safety and efficacy for Orfadin® (nitisinone) capsules (NDA 021232 approved on January 18, 2002 and subsequent supplements, the last being February 28, 2017).

Orfadin capsules (2, 5, 10 and 20 mg) are unstable at room temperature and require storage under refrigeration. Cycle states that because Orfadin capsules must be refrigerated (2 to 8°C [36 to 46°F]) they are inconvenient for patients as a lifelong treatment. To address this issue, they have developed a nitisinone tablet that is stable at room temperature.

Two pivotal bioavailability/bioequivalence (BA/BE) studies were conducted by the sponsor to bridge the efficacy and safety profile of the reference listed drug, Orfadin capsules, with the tablet formulation. The studies were designed following FDA's guidance in the type C meeting held on June 2, 2015.

2. Background

Hereditary tyrosinemia type 1 (HT-1) is a rare, inherited disorder of tyrosine metabolism caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme in the metabolic pathway of tyrosine. Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-

pyruvate dioxygenase, an enzyme upstream of 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. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for liver and kidney toxicity. Succinylacetone can also inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1.

Nitisinone normalizes the biochemical markers of HT-1, improves clinical symptoms, and has been shown to increase survival. Nitisinone inhibits catabolism of the amino acid tyrosine and can result in elevated plasma levels of tyrosine. Therefore, treatment with nitisinone also requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma concentrations of tyrosine.

For a detailed description of the disease, see Clinical Review by Patroula Smpokou, MD dated June 30, 2017 in DARRTS.

Two pre-IND meetings were held between FDA and the sponsor, a type B meeting on March 4, 2014 and a type C teleconference on June 2, 2015 (PIND 121021). During meetings, clinical pharmacology and CMC considerations relating to a 505(b)(2) NDA application for nitisinone tablets were discussed.

The sponsor submitted a request to FDA for Orphan Drug Designation for nitisinone tablets on August 2, 2016. On December 13, 2016, the Office of Orphan Products Development (OOPD) issued a letter to the sponsor stating orphan drug designation was denied due to the fact that Orfadin (nitisinone) already has orphan designation. Per 21 CFR 316.20(a) a sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan drug designation for the subsequent drug for the same rare disease or condition if it can provide a plausible hypothesis that its drug may be clinically superior to the first drug. The sponsor (Cycle) did not provide a plausible hypothesis, supported by data, that nitisinone tablets are clinically superior (showing greater efficacy, safety or makes a major contribution to patient care) compared to all formulation of nitisinone that have received marketing approval in the US for the treatment of HT-1.

In the original NDA submission, the sponsor requested a waiver of pediatric studies. In the 74-day letter, issued December 9, 2016, the FDA informed the sponsor that the Pediatric Research Equity Act (PREA) was trigged for this application, as it contains a new dosage form, and requested submission of a Pediatric Study Plant (PSP). On December 16, 2016 the sponsor submitted their PSP, which stated that no additional nonclinical and clinical studies are planned in pediatric patients and that by demonstrating bioequivalence between nitisinone tablets and the reference listed drug (Orfadin capsules), they are relying on the FDA's findings of safety and efficacy for Orfadin approved in NDA 021232 on January 18, 2002 and subsequent supplements.

Nitisinone is currently marketed in the US, EU, and Australia by Swedish Orphan Biovitrum (SOBI) under the brand name Orfadin.

In addition to a capsule formulation, Orfadin (nitisinone) is also available in the US as an oral suspension (NDA 206356) that is stored refrigerated until first opening, after which it is stored at room temperature for up to 60 days. Orfadin capsules are to be swallowed whole, but for patients who have difficulty swallowing the capsules, and who are intolerant of the oral suspension, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

On February 28, 2017, a CMC labeling supplement was approved that allows for in-use storage of the Orfadin capsules at room temperature for up to 45 days.

Cycle submitted a New Drug Submission to Health Canada for nitisinone tablets on March 31st, 2016 and the product was approved by Health Canada on November 4, 2016. Nitisinone tablets have been marketed in Canada since December 2016 (10 mg as of 12/19/2016; and 2 mg and 5 mg as of 01/13/2017).

(b) (4)

3. CMC/Device

The OPQ Application Technical Lead concludes the following in the application are acceptable from the OPQ perspective, but the NDA is not deemed ready for approval until the label/labeling issues are resolved.

See complete OPQ review by Hitesh Shroff, PhD, dated July 1, 2017 in Panorama. See also Section 12 Labeling of this review.

- Sufficient information is provided to ensure consistent manufacturing of the drug substance with respect to identity; strength, purity and quality (as per the Drug Substance review).

- The proposed limit for each of the impurities in the drug product is compliant with the ICH Q3A and Q3B qualification thresholds. However, in consultation with the Pharmacology/Toxicology reviewer, the acceptance criterion for total impurities in the drug product was further reduced.

See Section 4 Nonclinical Pharmacology/Toxicology of this review.

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

- The Office of Process and Facilities (OPF) reviewer has made an "Adequate" recommendation for both the drug substance and drug product manufacturing and testing facilities (as per the Facilities review).

- The drug product manufacturing process and microbiology assessment were reviewed by and were found to be acceptable (as per the Process review).

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

- The dissolution method and acceptance criteria are acceptable. The sponsor conducted a bioequivalence (BE) study with the 10 mg tablet strength, which is acceptable according to the Clinical Pharmacology reviewer. The dissolution profiles of the two lower tablet strengths (2 mg and 5 mg) are similar to the dissolution profile of the 10 mg tablet strength. The formulation of the different strengths of the proposed drug product is (b) (4) (b) (4) The results of comparative dissolution profile data showed similar dissolution characteristics (f2 being >50); therefore, the biowaiver request for the two lower strengths is acceptable. An additional *in vivo* BE bridging study is not needed from the Biopharmaceutics perspective (as per the Biopharmaceutics review).

- (b) (4)

(b) (4)

The review team discussed the results with the sponsor and the sponsor agreed to perform additional *in vitro* studies. On June 15, 2017 the sponsor submitted a "Nitisinone Syringe Administration" study report that evaluated a new dosing method in which one to two intact tablets were added directly to a 5 mL oral syringe and disintegrated in water without the need (b) (4) The report provided detailed dosing procedures, including the amount of water to be used in the syringe; the time required for complete disintegration; and specific preparation and rinsing procedures for maximum recovery. Based on the following obtained recovery and relative standard deviation (RSD), the proposed dosing of the disintegrated tablet suspension with 5 mL syringes using either (b) (4) mL water for one tablet (b) (4) mL initially followed by 2 mL rinse) or 7 mL water (5 mL initially and 2 mL rinse) for two tablets was deemed acceptable by the Drug Product reviewer:

- 2 mg: 91% and 5.4% RSD;
- 10 mg: 94.6% and 2.5% RSD;
- 2x10 mg: 99.4% and 0.7% RSD

(b) (4)

(b) (4)

(b) (4) Those concerns were conveyed to the sponsor who proposed to revise the storage and handing time for both dosing procedures to "within 2 hours" and committed to provide the assay results to cover the proposed handling and storage period after approval as a postmarketing commitment (PMC). This proposal was acceptable from microbiology perspective (email from Dr. Bryan Riley dated June 28, 2017). These assessments and PMC were also deemed acceptable by the Drug Product reviewer.

See complete Section 13 Recommendations/Risk Benefit Assessment of this review for a description of the PMC.

4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology, pharmacokinetic, or toxicology studies were performed with nitisinone tablets.

Below is a summary of the nonclinical findings.

See the complete nonclinical pharmacology/toxicology review by Fresnida Ramos, PhD dated June 15, 2017 in DARRTS.

- There are no novel excipients. The maximum daily intake of excipients from the drug product does not exceed the maximum potency listed for oral tablets in the FDA inactive ingredient (IIG) database. Therefore, there are no safety concerns about the excipients.

- An *in silico* toxicology study to investigate the genotoxicity and carcinogenicity potential of nitisinone and the degradant oxotetrahydroxanthone was conducted. Although nitisinone received positive predictions for mutagenicity due to (b) (4) in its structure, the predictions were disregarded due to previous negative results in the Ames bacterial mutagenicity test. The structurally related potential impurities, (b) (4) were also considered as non-mutagenic. Analysis of (b) (4) resulted in negative predictions for mutagenicity. Thus, the genotoxicity assessment of the potential impurities determined that they were either reported to be non-mutagenic or should be considered as non-mutagenic.

  The results of the *in silico* analysis were not considered appropriate for inclusion in product labeling because the Agency only accepts *in silico* analyses as a preliminary genotoxicity risk assessment for impurities, to determine the appropriate control measures for the impurities.

- The proposed limit for each of the impurities in the drug product is compliant with the ICH Q3A and Q3B qualification thresholds. However, the proposed acceptance criterion of ≤ (b) (4)% for total impurities in the drug product was deemed as unacceptable since the total of the unknown impurities is estimated to be ≤ (b) (4)%, and the actual range of total impurities observed in stability studies was < (b) (4)% to (b) (4)%. The sponsor agreed to the Agency's request (dated February 10, 2017) to reduce the acceptance criterion for total impurities in drug product to ≤ (b) (4)%.

5. Clinical Pharmacology/Biopharmaceutics

The reviewer concludes the application is acceptable from the Clinical Pharmacology standpoint, proving agreement can be reached on labeling.

See complete Clinical Pharmacology review by Shen Li, PhD, dated June 28, 2017 in DARRTS.

The following points were made in the review:

- The sponsor proposes a new tablet formulation with 2 mg, 5 mg and 10 mg strengths. The sponsor does not propose a 20 mg strength tablet. Orfadin capsules are available in 2 mg, 5 mg, 10 mg, and 20 mg strengths.

- To bridge the proposed product (nitisinone 10 mg tablet) to the listed drug (Orfadin 10 mg capsule), the sponsor conducted a pivotal relative BA/BE study (Study CT-003) to demonstrate bioequivalence between the two products under fasted conditions. In the same study, the sponsor also compared the bioavailability between (b) (4) nitisinone tablets stored at 40°C/75% RH for 6 months to Orfadin 10 mg capsules to investigate the effect of prolonged *in vitro* dissolution time of (b) (4) nitisinone tablets on bioavailability. The tablet formulation was designed to exhibit *in vitro* dissolution release profiles as similar as possible to the Orfadin capsule. However, as noted in the OPQ Drug Product review, the (b) (4) nitisinone tablet was found to have a prolonged *in vitro* dissolution time. The 90% confidence intervals for both nitisinone 10 mg tablet/Orfadin 10 mg capsule ratios and nitisinone 10 mg tablet (stored for 6 months at 40°C/75% RH)/Orfadin 10 mg capsule ratios under fasting conditions were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

- No relative BA/BE studies were conducted for two lower tablet strengths, 5 mg and 2 mg. This approach is acceptable to the clinical pharmacology reviewer since the three proposed tablets strengths (2 mg, 5mg and 10 mg) are considered proportionally similar. The difference in inactive ingredients between the highest (10 mg) and the lowest (2 mg) tablet strengths (b) (4) The biowaiver request was considered acceptable by the Biopharmaceutics reviewer.

See discussion of the biowaiver in Section 3 CMC/Device of this review.

- Two additional clinical pharmacology studies were conducted.
  - A comparative bioavailability study (Study CT-001) evaluated the effect of a change the content of one of the excipients, a (b) (4) in the nitisinone tablet in support of the formulation development: (b) (4) glyceryl dibehenate (b) (4), in the final to-be-marked formulation vs. (b) (4) in the interim formulation. The results showed that both formulations of nitisinone tablets were bioequivalent with Orfadin capsules under fasted conditions.
  - A food effect study (Study CT-002) demonstrated no effect of food (a high fat, high calorie meal consisting of approximately 800 to 1000 calories with approximately 50% of total calories from fat) on the bioavailability of nitisinone tablets.
    - The 90% confidence intervals of nitisinone 10 mg tablet fed/fasting ratios were contained entirely within the range of 0.80 to 1.25 with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

- The high fat meal delayed the median T_{max} by 3 hours to 6 hours compared to that without food; however, nitisinone has a long half-life (54 hours) and no acute effect is expected with a delay in T_{max}.
- Therefore, the tablets can be taken without regard to food.
- Orfadin capsules are to be taken at least one hour before, or two hours after a meal, since the food effect on Orfadin capsules is unknown.

See discussion of dosing and administration in Section 12 Labeling of this review.

- The Office of Study Integrity and Surveillance (OSIS) inspection reports recommend that the clinical and bioanalytical data for the pivotal BE study (CT-003) be accepted for review. OSIS recommends accepting bioanalytical data without an on-site inspection based on the recent favorable inspection results of the bioanalytical study site (b) (4) OSIS also asked whether the calibration range for nitisinone concentrations was representative of study sample concentrations. The calibration standard curve was established at concentrations from 19.53 to 2500 ng/mL in human plasma. The reported plasma concentrations reported ranged from 20.02 to 1884 ng/mL in Study CT-003. As such, the clinical pharmacology reviewer's analysis indicates that the calibration curves were representative of study sample concentrations.

See OSIS bioanalytical inspection report by Shila Nkah, PhD, dated February 24, 2017 appended to the Clinical Pharmacology review.

- In addition to swallowing the whole tablets, the sponsor proposes dosing methods of either administration of crushed tablets mixed with apple (b) (4) or tablets suspended in water using an oral syringe. Bioequivalence was only evaluated for the whole, intact tablets and not for the crushed tablets or tablets suspended in water. (b) (4) but no significant effects on bioavailability were anticipated, as the differences in the dissolution time between nitisinone tablets and (b) (4) nitisinone tablets did not result in a significant difference in the *in vivo* bioavailability of nitisinone in Study CT-003. (b) (4)

See discussion of the in vitro dissolution acceptability in Section 3 CMC/Device of this review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No clinical efficacy trials were conducted. The sponsor is relying on FDA's findings of safety and efficacy for Orfadin capsules (NDA 021232).

8. Safety

The clinical review focused on the safety data submitted from the three BA/BE studies conducted in healthy adult subjects with nitisinone tablets.

The adverse events reported during Studies CT-001, CT-002 and CT-003 are summarized below. There were no serious adverse events. All the reported adverse events were reported as mild intensity. Two subjects (one in Study CT-001 and the other in CT-003) were withdrawn from the study after vomiting.

Summary of Adverse Events in Study CT-001

Preferred Term	Orfadin Capsule 10 mg (reference) (N=24)	Nitisinone Tablet 10 mg (to-be marketed formulation) (N=23)	Nitisinone Tablet 10 mg ((b) (4) formulation) (N=23)
Headache	1*	1	1*
Rash	1*	1*	1*
Pruritus	--	--	1*
Pre-syncope	1	--	--
Cough	--	--	1
Myalgia	--	1	--
Nausea	1*	--	--
Vomiting	1*	--	--
Influenza	1	--	--
Dry lip	1*	--	--

* Considered possibly related by the investigator
Source: Adapted from Tables 3 and 4 in the sponsor's Clinical Overview

Summary of Adverse Events in Study CT-002

Preferred Term	Nitisinone Tablet 10 mg Fasted (N=20)	Nitisinone Tablet 10 mg Fed (N=19)
Dizziness	--	1*
Throat Irritation	--	1*

* Considered possibly related by the investigator
Source: Adapted from Tables 5 and 6 in the sponsor's Clinical Overview

Summary of Adverse Events in Study CT-003

Preferred Term	Orfadin Capsule 10 mg (reference) (N=24)	Nitisinone Tablet 10 mg (N=23)	Nitisinone Tablet 10 mg (b) (4) (N=23)
Vomiting	1	--	--
Fatigue	--	1*	--
Influenza	--	--	1
Upper respiratory infection	--	1	--
Headache	--	1*	--

* Considered possibly related by the investigator
Source: Adapted from Tables 5 and 6 in the sponsor's Clinical Overview

No adverse events related to laboratory parameters were reported in any of the studies.

120-Day Safety Update
The sponsor noted that nitisinone tablets were approved by Health Canada on November 4, 2016, but the product was not yet available on the Canadian market at the time of the safety update. Therefore, no post-marketing safety data are available. In addition, there are no new or ongoing clinical studies since the NDA was submitted.

The clinical reviewer concluded that no new safety signals were identified and the product was generally well-tolerated by adult healthy subjects.

See Clinical Review by Patroula Smpokou, MD dated June 30, 2017 in DARRTS.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The applicant applied for orphan designation on August 2, 2016 and because they anticipated receiving orphan drug designation, an agreed initial Pediatric Study Plan (iPSP) was not included in the original NDA submission of September 26, 2017. On December 13, 2016, OOPD denied the request for orphan designation. The new tablet dosage form triggers the requirement for a pediatric assessment under PREA. The Division of Pediatric and Maternal Health (DPMH) recommended the sponsor to submit a PSP that states they intend to provide a full pediatric assessment in this NDA by establishing bioequivalence to the listed drug, Orfadin capsules. Orfadin capsules are approved for adults and pediatric patients of all ages for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine. The original NDA submission for Orfadin capsules contained a full pediatric assessment. Cycle Pharmaceuticals is seeking the same indication as Orfadin and has not conducted any additional nonclinical or clinical studies.

The PSP was submitted on December 16, 2016.

The application will be discussed at an upcoming meeting of the Pediatric Review Committee (PeRC) on July 19, 2017.

To address administration of the tablets in the youngest pediatric patients, the sponsor conducted *in vitro* studies and provided instructions in the Dosage and Administration section of the Prescribing Information (PI) to allow the tablets to be crushed between two spoons (b) (4) rushed tablets may also be mixed with (b) (4) apple (b) (4) for oral administration.

As discussed above, the drug recovery in water was considered inadequate by the review team and use of (b) (4) resulted in an unknown impurity. Following discussion with the review team on how to evaluate and improve drug recovery of (b) (4) tablets in a liquid vehicle, the sponsor performed additional *in vitro* studies in water. They did not pursue the use of (b) (4)

The Pediatric reviewer discussed the risk of the tablets causing choking in pediatric patients less than 3 years of age, which is due, in part, to their immature swallowing coordination and small airway size. Considerations on how to mitigate the risk in labeling were provided.

See complete Pediatric Review by Melanie Bhatnagar, MD, dated June 30, 2017 in DARRTS.

See also Section 12 Labeling of this review.

11. Other Relevant Regulatory Issues

The inspection report by the Office of Study Integrity and Surveillance (OSIS) determined that the clinical data submitted for the pivotal BE study CT-003 are acceptable for FDA review (clinical site: PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa, inspected March 27-30, 2017) and recommended accepting the bioanalytical data without an on-site inspection based on the recent favorable inspection results.

See OSIS clinical inspection report by Srinivas Chennamaneni, PhD, dated April 25, 2017 in DARRTS.

In addition, during the NDA review cycle, OSIS confirmed the identity of the listed drug used in Study CT-003 as the Orfadin 10 mg capsule.

12. Labeling

Prescribing Information

The Prescribing Information (PI) for nitisinone tablets follows that of the listed drug, Orfadin capsules, in all sections except for those described below.

Highlights
The sponsor's proposed proprietary name, NITYR was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

See DMEPA review by Sherly Abraham, RPh dated May 26, 2017 and the letter to the sponsor dated June 6, 2017 in DARRTS.

Therefore, the Product Title line in Highlights is written as:

NITYR (nitisinone) tablets, for oral use

2 DOSAGE AND ADMINISTRATION
2.1 Dosage

In this section, the information regarding the recommended starting dosage, dosage titration and, drug monitoring were reorganized for clarity. The only substantive change from Orfadin is that new information was added that the administered dose should be rounded up from the calculated body weight (mg/kg) dose and administered using the available tablet strengths of 2 mg, 5 mg and 10 mg.

2.2 Administration

This section was written to follow the step-by-step procedures that the sponsor used in their *in vitro* studies for disintegration of the tablets in water for administration in an oral syringe and crushing the tablets for administration in applesauce which demonstrated acceptable drug recovery. Reviewers from OPQ Drug Product, Clinical, DMEPA, DMPP and Pediatrics all provided input on this section.

CDTL Comment: The review team felt that for the purposes of labeling, it would be acceptable to use the term "applesauce" instead of "apple (b) (4)

It is stated that NITYR can be taken with or without food, per the results of the food effect study (CT-002). Orfadin capsules were not studied with food, so the instructions for that product say to administer at least one hour before or two hours after a meal.

The preparation and administration instructions for patients who have difficulty swallowing the intact tablets, is preceded by a statement that administration of NITYR with liquids other than water and foods other than applesauce has not been studied and is not recommended.

Disintegration with Water in an Oral Syringe
The instructions emphasize that only one or two tablets can be prepared in a 5 mL oral syringe at a time. If more tablets are needed to achieve the recommended dose, the steps must be repeated using additional oral syringes.

Since it may at least an hour to fully disintegrate the tablets and form an aqueous suspension, the procedure utilized in the sponsor's protocol for disintegration and the maximum storage and handling time of 2 hours is emphasized.

Rinsing the oral syringe with additional water is also included in the steps, in order to maximize drug recovery.

Crushed Tablets in Applesauce
The Pediatrics reviewer recommended that administration of crushed tablets mixed in applesauce should not be limited to a specific age or weight parameter because these parameters lack specificity for the development of swallowing coordination. Instead, the administration in applesauce is limited to patients "who can swallow semi-solid food." To provide additional assurances for safety, the instructions for tablet crushing emphasize that the tablets should be crushed into a powder.

Rather than crushing the tablets between two spoons, as the sponsor recommended, the instructions were revised to allow for crushing the tablets into a powder using a single metal spoon in a clean container, per the DMPP reviewer (who performed ad hoc testing of the procedure, per email communication with the review team). This

method of administration prevents loss of drug on the spoons and upon transfer of the powder to the container.

Rinsing of the container with additional applesauce to maximize drug recovery and the maximum storage and handling time of 2 hours is also emphasized in this section.

3 DOSAGE FORMS AND STRENGTHS

Information on the available dosage forms, including strength and identifying characteristics of the tablets is provided.

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

As no clinical safety and efficacy studies were conducted with NITYR, the following statement was added at the beginning of this section, as per best labeling practice for 505(b)(2) drugs:

> The safety of NITYR has been established [redacted] (b) (4) studies of another oral formulation of nitisinone *[see Clinical Studies (14)]*. Below is a display of the adverse reactions of nitisinone in these [redacted] (b) (4) studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Limited available data with nitisinone use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes

11 DESCRIPTION

A description of the tablets, including active and inactive ingredients is included.

> Each tablet contains 2, 5 or 10 mg of nitisinone. Inactive ingredients are: glyceryl dibehenate, and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The pharmacokinetics of nitisinone when administered as a single NITYR 10 mg tablet to healthy subjects in Studies CT-002 (fasted and fed) and CT-003 are provided in this subsection.

Information regarding metabolism and drug interactions is the same as for Orfadin capsules.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

No changes were made in this section that is different from what is stated in this section of the Orfadin capsules PI.

14 CLINICAL STUDIES

As no clinical efficacy studies were conducted with NITYR, the following statement was added at the beginning of this section, per best labeling practice for 505(b)(2) drugs:

> The safety and efficacy of NITYR have been established based on studies of another oral formulation of nitisinone in patients with HT-1. Below is a display of the results of these studies of nitisinone in these conditions.

16 HOW SUPPLIED/STORAGE AND HANDLING

Information on the available dosage forms, including strength and identifying characteristics of the tablets is provided, including NDC numbers and units in which the dosage form is marketed:

> High-density polyethylene (HDPE) square bottles with a child-resistant tamper-evident Polypropylene (PP) screw cap. Each bottle contains 60 tablets.

Storage information is also provided:

> Store NITYR tablets at room temperature between 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]. Dispense in tight and light resistant container as defined in USP.

17 PATIENT COUNSELING INFORMATION

The healthcare provider is instructed to refer the patient/caregiver to the Instructions for Use document for preparation and administration instructions for patients who have difficulty swallowing the intact tablets.

Patient Labeling (Instructions for Use)

Recommended revisions from DMEPA, DMPP and OPDP have not been received at the time of this review. The patient instructions on how to prepare and administer the tablets when disintegrated in water and administered using an oral syringe or crushed and administered

mixed with applesauce will follow the steps outlined in the PI, and the sponsor's study protocol, incorporating further details and figures to facilitate patient/caregiver understanding of the instructions.

Carton/Container Labeling

DMEPA labeling comments were sent to the sponsor on June 20, 2017. The sponsor submitted revised carton/container labeling on June 30, 2017. Additional comments from DMEPA and OPQ were sent on July 5, 2017. A response is pending at the time of this review.

See DMEPA labeling reviews by Sherly Abraham, RPh dated June 19 and July 5, 2017.

13. Recommendations/Risk Benefit Assessment

The review team recommends approval of nitisinone tablets for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine, pending final agreed-upon labeling. I concur.

The NDA for nitisinone tablets (2, 5 and 10 mg) relies on the FDA's findings of safety and efficacy for Orfadin (nitisinone) capsules (NDA 021232 approved on January 18, 2002 and subsequent supplements, the last being February 28, 2017).

Bioequivalence was successfully demonstrated between the 10 mg nitisinone tablet and 10 mg Orfadin capsule (Study CT-003). An additional food effect study demonstrated that there is not an effect of food on nitisinone tablets; therefore, they can be dosed without regard to meals (Study CT-002). The sponsor was granted a biowaiver from conducting *in vivo* BE studies with the 2 mg and 5 mg dose strengths.

The sponsor also conducted *in vitro studies* that allow the crushed tablets to be administered mixed with applesauce or disintegrated in water and administered in an oral syringe for patients who cannot swallow the intact tablet(s).

No clinical safety or efficacy studies were conducted with the nitisinone tablets. No new safety signals were identified in the BA/BE studies conducted in healthy subjects.

The NDA for nitisinone tablets triggered PREA due to the new tablet dosage form. No PREA postmarketing requirements (PMRs) are being issued because the sponsor provided a full pediatric assessment by demonstrating bioequivalence of the new tablet dosage form to the reference listed drug, Orfadin capsules, which are approved for the treatment of HT-1 in all pediatric ages. The review team considers the pediatric assessment to be adequate and supportive of product approval in all pediatric ages.

As of February 2017, Orfadin capsules (2, 5, 10 and 20 mg) are to be stored refrigerated, or alternatively, patients/caregivers may store Orfadin capsules at room temperature for up to 45

days. Orfadin oral suspension must be stored refrigerated prior to first use. After first opening, it can be stored at room temperature for up to 60 days.

The Orfadin oral suspension is appropriate for patients who are unable to swallow the intact capsule. In addition, for patients who have difficulty swallowing the capsules, and who are intolerant of the oral suspension, Orfadin capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

This sponsor (Cycle) states that because Orfadin capsules must be refrigerated (2 to 8°C [36 to 46°F]), they are inconvenient for patients as a lifelong treatment and the availability of a tablet formulation that can be stored at room temperature offers relatively easier handling conditions to ensure drug quality for patients.

While the storage conditions for both Orfadin capsules and oral suspension allow for limited storage at room temperature, the availability of another formulation of nitisinone that is stable for up to 24 months at room temperature offers patients flexibility and an additional source of nitisinone for patients in the event of a drug shortage.

A Risk Evaluation and Management Strategy (REMS) is not required for this application.

There are no postmarketing requirements (PMRs). There is one postmarketing commitment (PMC). The sponsor has committed, within two months post approval, to conduct assays of the two preparations (crushed tablets mixed with the applesauce and the aqueous suspension of the disintegrated tablet in water in an oral syringe) at room temperature to assure the strength of the drug product during the use period (2 hours).

- Study/Trial Completion: 9/19/2017
- Final Report Submission: 9/26/2017

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/s/

JOETTE M MEYER
07/07/2017