Medical Officer/Division Director Summary Review for Regulatory Action

Date	August 21, 2020
From	Anita Zaidi, MD, Medical Officer Lisa Soule, MD, Associate Director
Subject	Medical Officer/Division Director Summary Review
NDA/BLA # and Supplement #	NDA 209449/S-005
Applicant	Cycle Pharmaceuticals Ltd.
Date of Submission	7/2/20
PDUFA Goal Date	9/2/20
Proprietary Name	NITYR
Established or Proper Name	nitisinone
Dosage Form(s)	Oral tablets
Applicant Proposed Indication(s)/Population(s)	Treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	Treatment of hereditary tyrosinemia type 1 (HT-1) in adult and pediatric patients combination with dietary restriction of tyrosine and phenylalanine

1. Benefit-Risk Assessment

NITYR® (nitisinone) tablets was approved July 26, 2017 under 505(b)(2) for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine, relying on the FDA's previous findings of safety and effectiveness for the listed drug (LD) Orfadin® (nitisinone) capsules (NDA 021232).

No new clinical data were submitted in the current supplement. See the CDTL review for the original NDA (209449; dated July 7, 2017) for a discussion of HT-1 disease, a serious, rare inherited disorder.

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.

Orfadin and NITYR are the only approved treatments for HT-1 disease. NITYR is an alternative dosage formulation of nitisinone but has not been shown to provide a direct

efficacy or safety advantage over Orfadin. NITYR allows for more prolonged storage at room temperature, compared to Orfadin, but the applicant has not shown that more flexible storage conditions lead to improved patient adherence to treatment, such that there would be an improvement in serious outcomes from the disease.

In this efficacy supplement, the applicant (Cycle Pharmaceuticals) is requesting final approval of S-005 to add information on the option of once-daily dosing for pediatric patients 5 years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone, in addition to the currently labeled twice-daily dosing regimen. The applicant relied on the information found in the Orfadin Prescribing Information (PI) which had been approved on September 1, 2017 (sNDA 021232/S-20). A NITYR supplement proposing the same additional dosing regimen received tentative approval on December 6, 2018 (see the CDTL/Division Director review dated 12/6/18). Due to the 3-year exclusivity received by Orfadin for the new once-daily dosage regimen on September 1, 2017, the new dosing regimen sought for NITYR was blocked and full approval could not be granted at that time.

The Agency advised the applicant to submit an amendment two or six months prior to the expiration of the exclusivity protection, identifying any changes in the conditions under which the product was tentatively approved. The applicant has since identified changes to the warnings and precautions, drug interactions and clinical pharmacology sections that have been approved for the prescribing information for the LD (Orfadin NDA 21232). These changes are a consequence of a new safety signal of asymptomatic keratopathies identified post-marketing as well as results of in vivo and in vitro drug interactions studies. Since Orfadin is NITYR's LD, the applicant has incorporated these safety changes in the proposed prescribing information.

2. Background

On July 2, 2020, the applicant submitted supplement S-005 with updated safety labeling changes. As the 3-year exclusivity for Orfadin will expire on September 1, 2020, the applicant is requesting full approval of the new dosing regimen. Due to the applicant's request for a new dosing regimen for NITYR, PREA was triggered, (b) (4)

The applicant has proposed labeling changes affecting sections 5, 7, and 12.3 of the Prescribing Information (PI) regarding two new safety signals that were identified from the PI for the LD (Orfadin). The first safety signal was asymptomatic keratopathies, based on findings from an ongoing clinical study, SONIA2, in a non-HT-1 population; alkaptonuria (AKU), without dietary restriction with high levels of tyrosine. The second safety signal was moderate CYP2C9 inhibition by nitisinone based on results from the completed Sobi.NTBC-006 clinical drug-drug interaction study in healthy subjects.

The proposed changes that were tentatively approved on December 6, 2018 were to the PI in sections 2.1, 8.4, 12.1, 12.2, and 14. The changes in Sections 2.1 and 12.2 primarily involve revising the dosing regimen to add the option of once-daily dosing for patients 5 years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone, in addition to the currently labeled twice-daily dosing regimen. Changes in the other sections (8.4, 12.1 and 14) were made to align with Orfadin, as well.

3. Product Quality

No new CMC-related information was provided in this supplement.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data was provided in this supplement.

5. Clinical Pharmacology

No new clinical pharmacology data was provided in this supplement.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No new clinical efficacy data was provided in this supplement.

8. Safety

No new safety data were provided in this supplement. The sponsor confirmed during the review that no new post marketing adverse reactions have been reported for Nityr. The most recent Periodic Adverse Drug Experience Report (PADER) from May 19, 2020 reported no new safety signals.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

No new pediatric data were provided, and no pediatric review was conducted. Unlike Orfadin, NITYR does not have Orphan Designation. This supplement triggered PREA due to addition of a new dosage regimen.

(b) (4)

The Division met with PeRC on August 18, 2020 and came to an agreement for deferral for the conduct of pediatric (<5 years old) studies and for assessment in pediatrics (≥ 5 years old) for Nityr. Nityr has fulfilled the requirement for pediatric assessment in patients ≥ 5 years of age, based on reliance upon the LD (Orfadin), which submitted data supporting the once-daily dose regimen for patient 5 years and older. Since the Orfadin trial that supported the efficacy of once-daily dosing did not evaluate enough patients <5 years of age, the applicant should provide a plan to study those patients, as once-daily dosing (if effective) may provide improved compliance. However, since Orfadin has a PMC to provide additional data in that age group that is due in September 2020, the applicant may be able to rely on the results of that PMC to fulfill the pediatric requirement.

11. Other Relevant Regulatory Issues

Not applicable

12. Labeling

The following is a summary of the substantive proposed labeling changes to the PI. All the proposed changes are aligned with the Orfadin PI. OPDP, DMEPA and patient labeling have reviewed the proposed labeling and concurred with minor edits that were accepted by the applicant.

Addition = underline; deletion = ~~strikethrough~~

INDICATIONS AND USAGE
The population in whom the drug is approved was added to section (indicated by a double underline in the text below). NITYR is approved for adults and pediatric patients of all ages.

> NITYR™ is indicated for the treatment of adult and pediatric patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Warnings and Precautions

- Obtain slit-lamp examination prior to treatment, and re-examination regularly during treatment; Reexamine patients if symptoms develop or tyrosine levels are > 500 micromol/L. Assess plasma tyrosine levels in patients with an abrupt change in neurologic status. (5.1)

Drug Interactions:

- CYP2C9 Substrates: [redacted] increased systemic exposure of these co-administered drugs, [redacted] reduce the dosage. Additional dosage adjustments may be needed to maintain therapeutic drug concentrations for narrow therapeutic index drugs. (7)
- OAT1/OAT3 Substrates: Increased systemic exposure of these co-administered drugs; monitor for potential adverse reactions. (7)

DOSAGE AND ADMINISTRATION

2.1 Dosage

A maintenance regimen was added for once-daily dosing in select pediatric patients:

> Maintenance Regimen
> In patients 5 years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone, the total daily dose of NITYR may be given once daily (e.g., 1 to 2 mg/kg once daily) *[see Clinical Pharmacology (12.2)]*.

In the dosage titration subsection, information about monitoring biochemical response was revised for clarity. In addition, information was added to emphasize the role of restriction in dietary tyrosine and phenylalanine intake in the treatment of HT-1.

5.1 Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques

Nitisinone is an inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme in the tyrosine metabolic pathway *[see Clinical Pharmacology (12.1)]*. Therefore, treatment with NITYR may cause an increase in plasma tyrosine levels in patients with HT-1. Maintain concomitant reduction in dietary tyrosine and phenylalanine while on NITYR treatment. Do not adjust NITYR dosage in order to lower the plasma tyrosine concentration. Maintain plasma tyrosine levels below 500 micromol/L. Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine levels and levels greater than 500 micromol/L may lead to the following:

- Ocular signs and symptoms including corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia have been reported in patients treated with nitisinone *[see Adverse Reactions (6.1)]*. In a clinical study in a non HT-1 population without dietary restriction and reported tyrosine levels >500 micromol/l both symptomatic and asymptomatic keratopathies have been observed. Therefore, perform a baseline ophthalmologic examination including slit-lamp examination [redacted] prior to initiating NITYR treatment and regularly thereafter [redacted]. Patients who develop photophobia, eye pain, or signs of inflammation such as redness, swelling, or burning of the eyes or tyrosine levels > 500 micromol/L during treatment with NITYR should undergo slit-lamp reexamination and immediate measurement of the plasma tyrosine concentration.

7 Drug Interactions

[redacted]

Nitisinone is a moderate CYP2C9 inhibitor, a weak CYP2E1 inducer and an inhibitor of OAT1/OAT3. TABLE 2 includes drugs with clinically important drug interactions when administered concomitantly with NITYR and instructions for preventing or managing them.

TABLE 2 Clinically Relevant Interactions Affecting Co-Administered Drugs	
Sensitive CYP2C9 Substrates (e.g., celecoxib, tolbutamide) or CYP2C9 Substrates with a Narrow Therapeutic Index(e.g., phenytoin, warfarin)	
Clinical Impact	Increased exposure of the co-administered drugs metabolized by CYP2C9. *[see Clinical Pharmacology (12.3)]*
Intervention	Reduce the dosage of the co-administered drugs metabolized by CYP2C9 drug by half. Additional dosage adjustments may be needed to maintain therapeutic drug concentrations for narrow therapeutic index drugs. See prescribing information for those drugs.
OAT1/OAT3 Substrates (e.g., adefovir, ganciclovir, methotrexate)	
Clinical Impact	Increased exposure of the interacting drug [*see Clinical Pharmacology (12.3)*]
Intervention	Monitor for potential adverse reactions related to the co-administered drug.

USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The wording was revised to follow the recommended wording for an approved pediatric indication ("safety and effectiveness have been established") and a summary of the data that supported the indication was added.

> The safety and effectiveness of NITYR have been established in pediatric patients for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine. Use of NITYR in pediatric patients is supported by evidence from one open-label, uncontrolled clinical study conducted with another oral formulation of nitisinone in 207 patients with HT-1 ages 0 to 22 years (median age 9 months) *[see Clinical Studies (14)]*.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

A statement about the importance of dietary restriction of tyrosine and phenylalanine intake to prevent tyrosine toxicity was removed from this section as it does not pertain to the mechanism of action and was relocated in Section 12.2 Pharmacodynamics.

> ~~Nitisinone inhibits catabolism of the amino acid tyrosine and can result in elevated plasma levels of tyrosine. Therefore, treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine [*see Warnings and Precautions (5.1)*].~~

12.2 Pharmacodynamics

Information on succinylacetone concentrations in urine and plasma, as measured in a clinical efficacy and safety study, was moved here from Section 14 Clinical Studies, as it describes the biomarker response to treatment. Biomarker response in another study that supported the once daily dosing regimen was added. As noted above, a statement about restriction of dietary intake of tyrosine and phenylalanine to prevent tyrosine toxicity was moved here from Section 12.1.

> In a clinical study, patients with HT-1 were diagnosed by the presence of succinylacetone in urine or plasma and treated with another oral formulation of nitisinone *[see Clinical Studies (14)]*. In all 186 patients whose urine succinylacetone was measured, the urinary succinylacetone concentration

decreased to less than 1 mmol/mol creatinine, the lower limit of quantitation. The median time to normalization of urine succinylacetone was 0.3 months. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 micromol/L (95% confidence interval: 23, 51 micromol/L). In 87% (150/172) of patients whose plasma succinylacetone was measured, the plasma succinylacetone concentration decreased to less than 0.1 micromol/L, the lower limit of quantitation. The median time to normalization of plasma succinylacetone was 3.9 months.

In another study, comparing two dosing regimens of another oral formulation of nitisinone, succinylacetone was measured in urine and/or blood in 16 patients with HT-1 aged 5 years to 24 years. All study patients were on a stable nitisinone daily dosage (0.4 mg/kg/day to 1 mg/kg/day) during both study dosing regimens. After at least 4 weeks of twice daily dosing with nitisinone, both the urine and/or blood succinylacetone concentrations were below the limit of quantitation for the assay. Patients were then switched to once daily dosing with the same total daily dosage of nitisinone and blood and/or urine succinylacetone concentrations remained undetectable when measured following at least 4 weeks of treatment with once daily dosing.

Nitisinone inhibits catabolism of the amino acid tyrosine and can result in elevated plasma levels of tyrosine. Therefore, treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine [*see Warnings and Precautions (5.1)*].

CLINICAL STUDIES

As noted above the information on biomarker response was moved to Section 12.2 Pharmacodynamics.

(b) (4)

12.3 Pharmacokinetics

For NITYR, the arithmetic mean (SD) terminal half-life of nitisinone is 59.3 (8.9) hours in healthy subjects (n=23).

Metabolism: In vitro studies have shown that nitisinone is relatively stable in human liver microsomes with minor metabolism possibly mediated by CYP3A4 enzyme.

Excretion: Renal elimination of nitisinone is of minor importance, since the mean of the fraction of dose excreted as unchanged nitisinone in the urine (fe(%)) was 3.0% (n=3) following multiple oral doses of 80 mg daily in healthy subjects. The estimated mean (CV%) renal clearance of nitisinone was 0.003 L/h (25%).

Drug Interaction Studies

(b) (4)

Nitisinone does not inhibit CYP2D6. Nitisinone is a moderate inhibitor of CYP2C9, and a weak inducer of CYP2E1 (TABLE 4). Nitisinone is an inhibitor of OAT1/3 (TABLE 4).

TABLE 4 Percent Change in $AUC_{0-\infty}$ and C_{max} for Co-administered Drugs in the Presence of nitisinone in 18 Healthy Subjects			
Co-administered Drug [a]	Dose of Co-administered Drug (Route of Administration)	Effect of Nitisinone on the Pharmacokinetics of Co-administered Drug [b]	
		$AUC_{0-\infty}$	C_{max}
CYP2C9 Substrate Tolbutamide [c]	500 mg (oral)	131% ↑	16% ↑
CYP2E1 Substrate Chlorzoxazone	250 mg (oral)	27% ↓	18% ↓
OAT1/3 Substrate Furosemide	20 mg (intravenous)	72% ↑	12% ↑

↑ = Increased; ↓ = Decreased

[a] The interacting drug was administered alone on Day 1 and together with nitisinone on Day 17.

[b] Multiple doses of 80 mg nitisinone were administered daily alone from Day 3 to Day 16.

[c] 16 subjects in Period 2 received nitisinone and tolbutamide while 18 subjects in Period 1 received nitisinone alone.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically
In vitro studies showed that nitisinone does not inhibit CYP1A2, 2C19, or 3A4. Nitisinone does not induce CYP1A2, 2B6 or 3A4/5. Nitisinone does not inhibit P-gp, BCRP, OATP1B1, OATP1B3 and OCT2-mediated transports at therapeutically relevant concentrations.

13. Postmarketing

Due to PREA requirements, the applicant should conduct a study to provide PK and PD evidence supporting use of a once-daily dosing regimen in pediatric patients aged < 5.

PMR # 1:

Collect observational data in HT-1 patients to characterize the pharmacodynamic response (urine and blood succinylacetone), pharmacokinetics (plasma nitisinone concentration), tolerability, and safety of Nityr treatment given under a once-daily dosing regimen. Measurements of succinylacetone (urine and blood) and nitisinone concentration (blood) can follow routine clinical practice. The duration of such study should be at least 6 months to enable characterization of the tolerability and safety of the once-daily dosage regimen and to provide repeated measures of succinylacetone levels and nitisinone concentrations on once-daily dosage regimen over an extended period of time. The patient population should include patients of any age diagnosed with HT-1 (biochemically, molecularly, or both) and, especially, include a sufficient number of patients younger than 5 years old. To the extent feasible, the study should provide PD and PK data from treatment-naïve patients of any age who are initiated on Nityr treatment under a once-daily dosing regimen.

a. Final Protocol Submission: 09/2021
b. Study Completion: 11/2022
c. Final Report Submission: 11/2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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