Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	January 6, 2025
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Product Name:	Nityr (nitisinone)
Pediatric Labeling Approval Dates:	July 26, 2017 and September 2, 2020
Application Type/Number:	NDA 209449
Applicant:	Cycle Pharmaceuticals Ltd.
TTT Record ID:	2024-11983

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Nityr (nitisinone) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with nitisinone in pediatric patients.

Orfadin (nitisinone) capsule is a hydroxy-phenylpyruvate dioxygenase inhibitor and was initially approved in the U.S. on January 18, 2002. Orfadin (nitisinone) oral suspension was approved on April 22, 2016. Nityr (nitisinone) was approved on July 26, 2017 as new dosage form of oral tablets. Nitisinone is currently indicated for 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.

This pediatric postmarketing safety review was stimulated by two Nityr pediatric labeling changes:

- Pediatric labeling at approval on July 26, 2017, that included the indication for the treatment of pediatric patients aged birth to 17 years old for the treatment of HT-1. This product also represented a new formulation and administration for pediatric patients (i.e., tablet that can disintegrate in water and be administered via oral syringe for patients, including pediatric patients, who have difficulty swallowing intact tablets).
- Pediatric labeling change on September 2, 2020, that approved a new dosage 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.

DPV reviewed all U.S. serious FAERS reports with nitisinone in pediatric patients less than 18 years of age through October 1, 2024, and identified 73 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with nitisinone in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for nitisinone at this time and will continue routine pharmacovigilance monitoring for nitisinone.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Nityr (nitisinone) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with nitisinone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Orfadin (nitisinone) capsule is a hydroxy-phenylpyruvate dioxygenase inhibitor and was initially approved in the U.S. on January 18, 2002.[1] Orfadin (nitisinone) oral suspension was approved on April 22, 2016.[2] Nityr (nitisinone) was approved on July 26, 2017 as new dosage form of oral tablets. Nityr is available as 2, 5, and 10 mg tablets. Nitisinone is currently indicated for 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.[3]

This pediatric postmarketing safety review was stimulated by two Nityr pediatric labeling changes:

- Pediatric labeling at approval on July 26, 2017, that included the indication for the treatment of pediatric patients aged birth to 17 years old for the treatment of HT-1. This product also represented a new formulation and administration for pediatric patients (i.e., tablet that can disintegrate in water and be administered via oral syringe for patients, including pediatric patients, who have difficulty swallowing intact tablets).[4]
- Pediatric labeling change on September 2, 2020, that approved a new dosage 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.[5]

A pediatric safety review for nitisinone has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

1.2.1 Nityr labeling

The Nityr labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[3] For additional Nityr labeling information, please refer to the full prescribing information.

> ----------**CONTRAINDICATIONS**----------
> None.(4)
>
> ----------**WARNINGS AND PRECAUTIONS**----------
> *Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques Due To Elevated Plasma Tyrosine Levels:* Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine

and levels above 500 micromol/L may lead to ocular signs and symptoms, intellectual disability and developmental delay, or painful hyperkeratotic plaques on the soles and palms. (5.1)

- Do not adjust NITYR dosage in order to lower the plasma tyrosine concentration. (5.1)
- Obtain slit-lamp examination prior to treatment and regularly thereafter. 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)

Leukopenia and Severe Thrombocytopenia: Monitor platelet and white blood cell counts. (5.2)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (>1%) are elevated tyrosine levels, thrombocytopenia, leukopenia, conjunctivitis, corneal opacity, keratitis, photophobia, eye pain, blepharitis, cataracts, granulocytopenia, epistaxis, pruritus, exfoliative dermatitis, dry skin, maculopapular rash and alopecia. (6.1)

8.4 Pediatric Use

The safety and effectiveness of nitisinone have been established for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine in pediatric patients. Use of NITYR for this indication 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)].

1.2.2 Orfadin Labeling

The Orfadin labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[6] For additional Orfadin labeling information, please refer to the full prescribing information.

----------**CONTRAINDICATIONS**----------

None.(4)

----------**WARNINGS AND PRECAUTIONS**----------

•Elevated Plasma Tyrosine Levels, Ocular Symptoms, Developmental Delay and Hyperkeratotic Plaques: Inadequate restriction of tyrosine and phenylalanine intake can lead to elevations in plasma tyrosine, which at levels above 500 micromol/L can result in symptoms, intellectual disability and developmental delay or painful hyperkeratotic plaques on the soles and palms; do not adjust ORFADIN dosage in order to lower the plasma tyrosine concentration. Obtain slit-lamp examination prior to treatment, 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)
•Leukopenia and Severe Thrombocytopenia: Monitor platelet and white blood cell counts. (5.2)
•Risk of Adverse Reactions Due to Glycerol Content of ORFADIN Oral Suspension: Doses of 20 mL of ORFADIN oral suspension may cause headache, upset stomach and diarrhea due to the glycerol content. Consider switching patients to ORFADIN capsules. (5.3)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (>1%) are elevated tyrosine levels, thrombocytopenia, leukopenia, conjunctivitis, corneal opacity, keratitis, photophobia, eye pain, blepharitis, cataracts, granulocytopenia, epistaxis, pruritus, exfoliative dermatitis, dry skin, maculopapular rash and alopecia. (6.1)

8.4 Pediatric Use

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

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	October 2, 2024
Time period of search	All reports through October 1, 2024
Search type	RxLogix DPV Surveillance Summary Alert
Product term	Product Active Ingredient: Nitisinone
MedDRA search terms (Version 27.0)	All Preferred Terms
Other search terms†	Case Seriousness: Serious
* See Appendix A for a description of the FAERS database. †For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

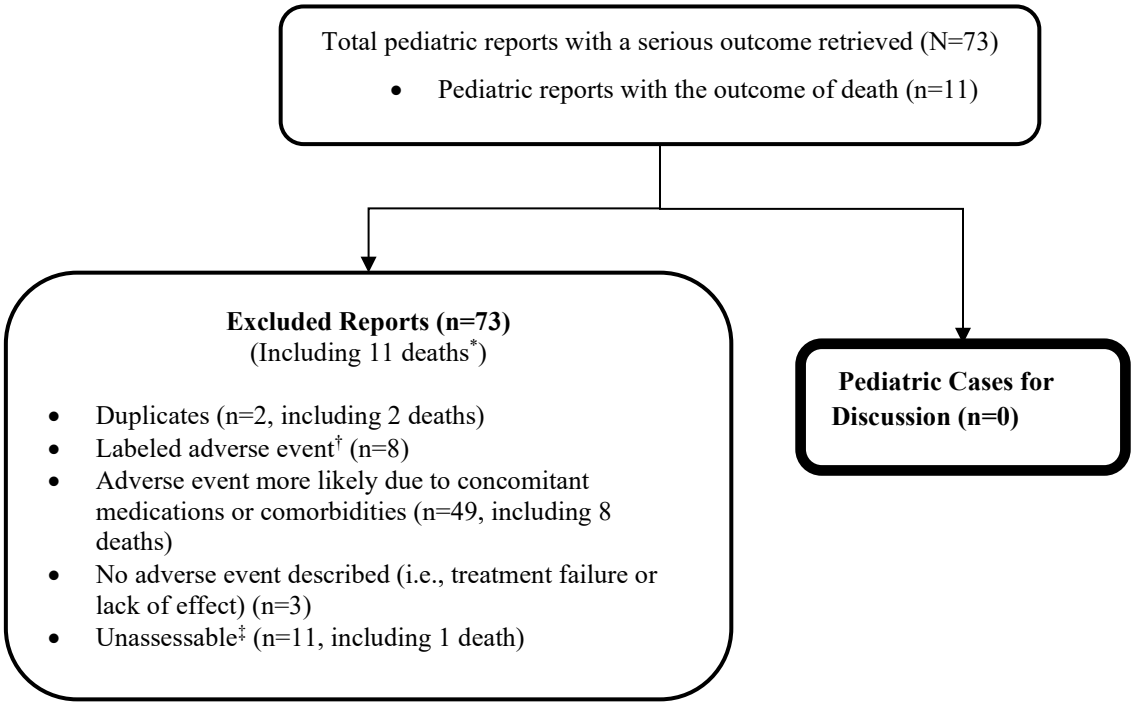
3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 73 U.S. serious pediatric reports for patients less than 18 years old through October 1, 2024.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 73 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

[a] Includes one pediatric report that was identified among reports not coded with an age.

Figure 1. Selection of U.S. Serious Pediatric Cases With Nitisinone



* Eleven excluded U.S. FAERS reports with a serious outcome described fatal outcomes. After accounting for duplicate reports (n=2), we identified nine unique cases describing fatal outcomes. None of the deaths were determined to be attributed to nitisinone. Eight cases described death secondary to complications from primary disease or other medical conditions (liver failure associated with HT-1, n=6; stage IV metastatic neuroblastoma, n=1; and severe infection and pulmonary hemorrhage, n=1). One death case lacked sufficient clinical information to understand events that led to death or perform a causality assessment with nitisinone.

† Labeled adverse event does not represent increased severity.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with nitisinone in pediatric patients less than 18 years of age through October 1, 2024, and identified 73 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with nitisinone in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for nitisinone at this time and will continue routine pharmacovigilance monitoring for nitisinone.

6 REFERENCES

1. U.S. Food and Drug Administration. Initial Approval Letter for NDA 021232, Orfadin (nitisinone); oral capsules. January 18, 2002. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/21232ltr.pdf (Accessed November 26, 2024).
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6. Orfadin® (nitisinone) capsules and oral suspension, for oral use [Prescribing Information]. Apotek Produktion & Laboratorier AB, Sweden: Swedish Orphan Biovitrum AB May 2019.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.