CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209449
Supporting document/s:	1
Applicant's letter date:	9-26-2016
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Product:	Nityr (Nitisinone Tablets)
Indication:	Treatment of hereditary tyrosinemia type 1 (HT-1)
Applicant:	Cycle Pharmaceuticals Ltd.
Review Division:	Gastroenterology and Inborn Errors Products
Reviewer:	Fresnida Ramos, PhD
Supervisor/Team Leader:	David Joseph, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Hong Vu, PharmD, Msc

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1 Executive Summary

1.1 Introduction

The Sponsor, Cycle Pharmaceuticals Ltd., seeks to market Nityr (nitisinone), a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), for the treatment of hereditary tyrosinemia type 1 (HT-1). The Sponsor has developed a new thermal stable tablet formulation that does not require low temperature storage. This NDA for Nityr (Nitisinone Tablets) was submitted as a 505(b)(2) application, with reliance on ORFADIN (nitisinone) capsules as the listed drug (NDA 021232).

1.2 Brief Discussion of Nonclinical Findings

The only nonclinical study submitted was a Quantitative Structure-Activity Relationship ((Q)SAR) analysis for nitisinone and its (b) (4), as part of a mutagenicity risk assessment for potential impurities. Potential impurities for the drug substance and/or drug product included (b) (4) A literature/database search identified (b) (4). (Q)SAR was performed for the structures of nitisinone (b) (4) to assess their risk of mutagenicity. Although nitisinone received positive predictions (b) (4), the predictions were disregarded due to previous negative results in the Ames bacterial mutagenicity test. Thus, the structurally-related potential impurities, (b) (4) were also considered as non-mutagenic. (Q)SAR 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. In addition, the proposed limit for each of the impurities 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)% (Sequence 0010).

1.3 Recommendations

1.3.1 Approvability

From a nonclinical viewpoint, there are no approvability issues.

1.3.2 Additional Nonclinical Recommendations

The acceptance criterion for total impurities should be set at ≤(b) (4)%.

1.3.3 Labeling

Sponsor's Proposed Version:

8.1 Pregnancy

Risk Summary

Limited available data with nitisinone use in pregnant women are insufficient to [(b) (4)] drug-associated risk of adverse [(b) (4)] 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 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 to 4% and 15 to 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 [(b) (4)] 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.

Evaluation:

The proposed labeling text is acceptable.

Sponsor's Proposed Version:

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 development and health benefits of breastfeeding should be considered along with the mother's clinical need for Nitisinone tablets and any potential adverse effects on the breastfed infant from Nitisinone tablets or from the underlying maternal condition.

Evaluation:

The proposed labeling text is acceptable.

Sponsor's Proposed Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of nitisinone. Nitisinone was not genotoxic in the Ames test and the in vivo mouse liver unscheduled DNA synthesis (UDS) test. Nitisinone was mutagenic in the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test and in an in vivo mouse bone marrow micronucleus test.

In a single dose-group study in rats given 100 mg/kg (b) (4) times the recommended initial (b) (4) dose 1 mg/kg per day based on (b) (4) body surface area), reduced litter size, decreased pup weight at birth, and decreased survival of pups after birth was demonstrated.

Evaluation:

The proposed labeling text is acceptable.

2 Drug Information

2.1 Drug

CAS Registry Number: 104206-65-7

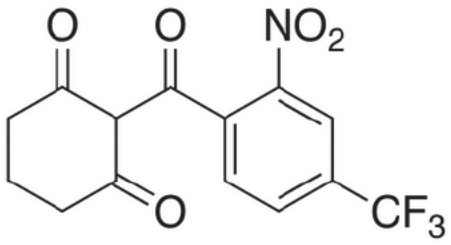
Generic Name: nitisinone

Code Name: N/A

Chemical Name: 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione

Molecular Formula/Molecular Weight: $C_{14}H_{10}F_3NO_5$/329.23

Structure or Biochemical Description:



Pharmacologic Class: 4-hydroxyphenylpyruvate dioxygenase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 121021 (Nitisinone tablets), NDA 021232 (ORFADIN capsules), and NDA 206356 (ORFADIN suspension)

2.3 Drug Formulation

Table 1: Nitisinone Tablets Formulation

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

The maximum daily dose of nitisinone is 2 mg/kg (1 mg/kg BID). Thus, a patient weighing 60 kg would need to ingest 120 mg/day to achieve this dose. For calculation of the number of tablets ingested in a 60-kg patient, it is assumed that the maximum tablet strength (10 mg) will be used. Therefore, safety assessment of the excipient levels is based the amounts ingested with 12 10-mg tablets per day. 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 (see the table below). Therefore, there are no safety concerns about the excipients.

Table 2: Nitisinone Tablets Excipients

Name of Ingredient	CAS no.	Maximum Potency from FDA IIG List	Maximum Daily Dose from Nitisinone Tablets for a 60-kg Adult
Glyceryl Dibehenate	99880645	(b) (4)	
Lactose Monohydrate	64044515		

(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Drug substance impurities:

The acceptance criteria for impurities and the measured levels are summarized in the Sponsor's table below.

Table 3: Drug Substance Impurities

(b) (4)

All the impurities were shown to be below the identification threshold of (b) (4)%. The unknown impurity with RRT (b) (4)%) was shown to be a (b) (4)

(b) (4)

Drug Product Impurities:

Three potential drug-related impurities were identified in Nitisinone tablets: (b) (4) The drug product impurities are summarized in the Sponsor's table below. Batch analyses showed that (b) (4) were below the ICH reporting threshold of (b) (4)%. (b) (4) product of Nitisinone, was thought to be one of the unknown impurities detected (RRT of (b) (4) and was also below the ICH reporting level of (b) (4)%. This unknown impurity was also detected at levels below the ICH reporting level in the accelerated stability study. It was detected at levels of (b) (4)% in the long term stability study for the 2 mg strength tablets at the 9 month time point and then was stable at those levels at the 12 month time point. Since the levels of these three impurities were below the ICH identification threshold of (b) (4)%, they were treated as unknown impurities and their acceptance levels were set to ≤(b) (4)%. The total impurity acceptance level was set to ≤(b) (4)%. However, since the total of the unknown impurities should be ≤(b) (4)% and a range of <(b) (4)% was observed for total impurities in stability studies, it is recommended that the total impurity acceptance level be set to ≤(b) (4)%.

Table 4: Drug Product Impurities

Specification	Acceptance criteria	Nitisinone 2 mg tablet	Nitisinone 5 mg tablet	Nitisinone 10 mg tablet
Related substance (HPLC)	(b) (4)	(b) (4)		

A hazard assessment was performed for (b) (4) by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data. This impurity was found to be non-mutagenic in the Ames test for bacterial mutagenicity.

(b) (4) and was treated as a non-mutagenic impurity (see Sponsor's table below). A computational toxicology assessment was performed using (Q)SAR methodologies to evaluate the mutagenic and carcinogenic potential of nitisinone (b) (4). Based on the results of this study, nitisinone and (b) (4) Since nitisinone (b) (4) a potential impurity that was not detected in the drug substance, (b) (4) nitisinone, they were also given (b) (4) (see Sponsor's table below). The *in silico* study is reviewed in section 7.4.

Table 5: Carcinogenic potential of drug-related impurities

Presence in drug substance	Chemical Name or Code	Structure	Origin	Carcinogenicity classification*
Detected	(b) (4)			
Not detected				
Detected				
Potential, not detected				

*Classification as per ICH M7 step 4

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population includes patients with hereditary tyrosinemia type 1 (HT-1). The recommended starting dosage of Nitisinone tablets is 0.5 mg/kg orally twice daily. The maximum recommended dosage is 1 mg/kg orally twice daily.

2.7 Regulatory Background

The Sponsor, Cycle Pharmaceuticals Ltd., submitted a 505(b)(2) NDA for Nitisinone Tablets, using ORFADIN capsules as the listed drug. The Sponsor relied on the FDA's findings of safety and effectiveness for ORFADIN (NDA 021232).

3 Studies Submitted

3.1 Studies Reviewed

Toxicological analysis of Nitisinone and [redacted] (b) (4) using Derek Nexus and Leadscope.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

N/A

4 Pharmacology

4.1 Primary Pharmacology

N/A

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

N/A

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

N/A

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

N/A

7.2 *In Vitro* Assays in Mammalian Cells

N/A

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

N/A

7.4 Other Genetic Toxicity Studies

Study title: Toxicological analysis of Nitisinone (b) (4) using Derek Nexus and Leadscope.

A computational toxicology assessment was performed using (Q)SAR methodologies to evaluate the mutagenic and carcinogenic potential of nitisinone and its (b) (4) This was done to fulfil the hazard assessment of impurities as stated in ICH M7. Derek Nexus (rule-based expert system), Leadscope (statistical-based system), and Vega (open-source statistical-based system) were used to analyze nitisinone (b) (4). Multiple endpoints were analyzed by each software system, and the results are reported below. However, bacterial mutagenicity is currently the only endpoint accepted by CDER from *in silico* analysis to support regulatory decisions about impurities.

Methods:

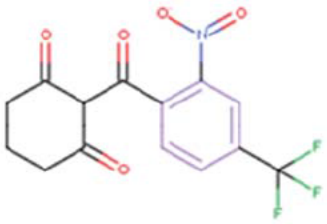
Derek Nexus:	
Knowledge base version:	Derek KB 2014 1.0
Species:	Escherichia coli, Salmonella typhimurium, dog, guinea pig, hamster, human, mammal, monkey, mouse, primate, rabbit, rat and rodent
Endpoints searched:	Carcinogenicity, Genotoxicity (including mutagenicity and chromosome damage)
Processing constraints:	The option to perceive (b) (4) was selected.
System type:	Rule-based expert system; assigns various levels of non-numeric likelihood to its predictions ranging from CERTAIN to CONTRADICTED, via PROBABLE, PLAUSIBLE, EQUIVOCAL, DOUBTED, IMPROBABLE, IMPOSSIBLE and OPEN.

Leadscope:	
Model Applier Version:	1.8.3

Suites applied:	Genetic toxicity (developed by a CRADA with U.S. FDA)
Endpoints:	Clastogenicity in vitro, clastogenicity in vivo, gene mutation.
Processing constraints:	Positive predictivity set to > 0.60, negative predictivity set to <0.40; indeterminate 0.40 to 0.60.
System type:	Statistical-based system; predicts toxicity by comparing the entered structure with empirical data then assigns a probability value based on likelihood of occurrence. Leadscope takes into account both toxifying and detoxifying structures.

Vega:	
Model Applier Version:	2.1.12
Suites applied:	Mutagenicity model (CAESAR)
Endpoints:	Mutagenicity
System type:	Integrates rule-based and statistical-based systems; compares the inputted structure to real data taken from structurally similar compounds.

Figure 1: Structures analyzed by (Q)SAR



Nitisinone

(b) (4)

Results:

Derek Nexus: Three (b) (4) configurations were analyzed for nitisinone and (b) (4) PLAUSIBLE alerts for carcinogenicity, mutagenicity, and hepatotoxicity were triggered (b) (4) The PLAUSIBLE alerts indicated that there was sufficient information in the database to support the prediction. An EQUIVOCAL alert was also triggered for chromosome damage *in vivo* and *in vitro* (b) (4). The EQUIVOCAL alert indicated that there was an equal weight of evidence for and

against the proposition. A PLAUSIBLE alert for skin sensitization was also triggered by the presence of a (b) (4) group in nitisinone and (b) (4) did not trigger any alerts for carcinogenicity, chromosome damage, genotoxicity, or mutagenicity because its structure did not match any structural alerts or examples for mutagenicity in Derek. It was predicted to be INACTIVE in the Ames assay. The Derek Nexus results are summarized in the table below.

Table 6: Derek Nexus analysis

Endpoint	Alert	Level of likelihood	Type of data in data set
Carcinogenicity	(b) (4) Nitisinone (b) (4)	**Plausible** in all mammalian species examined.	Carcinogenicity data
Chromosome damage *in vitro*	(b) (4) Nitisinone (b) (4)	Chromosome damage in vitro: **Equivocal** in all mammalian species examined.	*In vitro* chromosome aberration test data
Chromosome damage *in vivo*	(b) (4) Nitisinone (b) (4)	Chromosome damage *in vivo*: **Equivocal** in all mammalian species examined.	*In vivo* chromosome aberration test data, *in vivo* micronucleus test data
Mutagenicity *in vitro*	(b) (4) Nitisinone (b) (4)	Mutagenicity *in vitro*: **Plausible** in all bacterial species examined.	Ames test data
Skin sensitization	(b) (4) Nitisinone (b) (4) (b) (4)	**Plausible** in all mammalian species examined.	Guinea pig maximization test data, local lymph node assay data
Hepatotoxicity	(b) (4) Nitisinone (b) (4))	**Plausible** in all mammalian species examined	N/A

The results of the Derek Nexus analysis indicated that the nitisinone structure has the potential to be carcinogenic, hepatotoxic, and mutagenic. However, it was noted that nitisinone has already been shown to be negative in the Ames assay and in the in vivo mouse liver unscheduled DNA synthesis assay, and positive in the mouse lymphoma cell forward mutation test and the in vivo bone marrow micronucleus assay. Thus, the prediction of PLAUSIBLE for in vitro mutagenicity for nitisinone was demonstrated to be

a false positive. The Derek Nexus analysis indicated that [redacted] (b) (4) was unlikely to be genotoxic or mutagenic.

Leadscope: Analysis of the nitisinone structure resulted in three positive prediction calls, eight negative prediction calls, and two indeterminate prediction calls. A Positive Prediction Probability (PPP) under 0.4 was considered negative while a PPP of ≥ 0.6 was considered to be positive. If the PPP fell between these cutoffs, it was considered indeterminate. The structure of [redacted] (b) (4) was not in the domain of any of the selected models. The results of the Leadscope analysis are summarized in the Sponsor's table below.

Table 7: Leadscope analysis

Effect	Model	Prediction	Positive Prediction Probability
Genetic Toxicity Suite			
Clastogenicity In Vitro	In Vitro Chrom Ab CHL	Negative	0.355
	In Vitro Chrom Ab CHO	Negative	0.104
	In Vitro Chrom Ab Comp	Negative	0.206
	In Vitro Chrom Ab HL	Not in Domain	Not in Domain
	In Vitro Chrom Ab Other	Negative	0.00196
	In Vitro SCE CHO	Positive	0.617
	In Vitro SCE Comp	Indeterminate	0.479
	In Vitro SCE Other	Not in Domain	Not in Domain
Clastogenicity In Vivo	In Vivo Chrom Ab Comp	Negative Not	0.0377
	In Vivo Chrom Ab Other	in Domain Not	Not in Domain
	In Vivo Chrom Ab Rat	in Domain	Not in Domain
	In Vivo Micronuc Mouse	Not in Domain	Not in Domain
	In Vivo Micronuc Rodent	Negative	0.0254
Gene Mutation	HGPRT Mut	Not in Domain	Not in Domain
	Mouse Lymphoma	Negative	0.359
	In Vivo Rodent DL Mut	Positive	0.958
	In Vivo Rodent Mut	Positive	0.762
	E coli - Sal 102 A-T Mut	Negative	0.0289
	Salmonella Mut	Indeterminate	0.518

There was one negative and one indeterminate prediction call for bacterial mutagenicity for the nitisinone structure. Overall, the Leadscope results are consistent with the evidence that nitisinone is negative for bacterial mutagenicity.

Since [redacted] (b) (4) was out of the domain of applicability in all models in the Leadscope toxicity suite, additional QSAR analysis was performed using the open-source software Vega. A mutagenicity model (CAESAR) was used to determine the mutagenicity of nitisinone and [redacted] (b) (4) The results indicated that [redacted] (b) (4) was not predicted to be mutagenic while nitisinone was a suspected mutagen. The result for nitisinone was a false positive, [redacted] (b) (4) given that nitisinone is known to be Ames negative.

Conclusions:

(Q)SAR analysis of the nitisinone structure resulted in some false positive calls for bacterial mutagenicity due to the [redacted] (b) (4) The analysis also predicted that [redacted] (b) (4) is unlikely to be a bacterial mutagen.

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

N/A

9.2 Embryonic Fetal Development

N/A

9.3 Prenatal and Postnatal Development

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

Cycle Pharmaceuticals Ltd. seeks to market Nityr (nitisinone), a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), for the treatment of hereditary tyrosinemia type 1 (HT-1). At present, nitisinone is marketed as ORFADIN (capsules or suspension). These products are thermally unstable and require low temperature storage (2°C-8°C). To increase safety and convenience, Cycle Pharmaceuticals has developed a new thermal stable formulation that does not require low temperature storage and submitted this NDA for Nityr (Nitisinone tablets) under the 505(b)(2) pathway, using ORFADIN (nitisinone) capsules as the listed drug.

In the new thermal stable formulation, [redacted] (b) (4) were listed as potential and/or known impurities in the drug substance and/or drug product. A literature/database search performed for [redacted] (b) (4) determined that this impurity was non-mutagenic in the Ames test for bacterial mutagenicity. A computational toxicology assessment was performed using (Q)SAR methodologies to evaluate the mutagenic potential of nitisinone (structurally related to [redacted] (b) (4) Derek Nexus (rule-based expert system), Leadscope (statistical-based system), and Vega (open-source

rule-based and statistical-based system) were used to analyze the structures of nitisinone and [redacted].

Nitisinone received positive predictions for bacterial mutagenicity in the (Q)SAR analysis [redacted] However, since it has been previously shown to be negative in the Ames test for bacterial mutagenicity, these predictions were disregarded. The (Q)SAR analysis provided evidence that [redacted] is not likely to be a bacterial mutagen. Thus, [redacted] ere designated as carcinogenicity [redacted] (as per ICH M7), which indicates that there were no structural alerts or that there was an alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity.

Because of the carcinogenicity classification of [redacted] each of these can be managed as non-mutagenic impurities. Since the acceptance criteria for these impurities are compliant with the qualification thresholds stated in ICH guidances Q3A and Q3B, there are no safety concerns. However, it was noted that the acceptance criteria for total impurities in the drug product was set at ≤[redacted]%. This limit was considered too high since the total amount of unknown impurities is estimated to be ≤[redacted]%, and a range of only <[redacted]% was observed for total impurities in stability studies. Thus, it was recommended that the acceptance criteria for total impurities should be set at ≤[redacted]%.

12 Appendix/Attachments

N/A

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

/s/

FRESNIDA J RAMOS
06/15/2017

DAVID B JOSEPH
06/15/2017
I concur.