

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206356Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: April 19, 2016
From: Laurie Muldowney, MD
Subject: Addendum to April 1, 2016 Review

NDA 206356
Swedish Orphan Biovitrum
Orfadin® (nitisinone) oral suspension, 4 mg/mL
Adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of
hereditary tyrosinemia type 1

Summary:

This addendum confirms the Applicant's certification of financial interests and arrangements of clinical investigators. The applicant stated that no investigator or sub-investigator entered into any financial arrangement whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), nor did any investigator or sub-investigator disclose financial interests/arrangements. Therefore, there are no issues surrounding the approvability of the application or questions about the data integrity since there were no investigators with disclosed financial interests, nor did any investigator receive significant payments of other sorts as defined in 21 CFR 54.2(f).

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/s/

LAURIE B MULDOWNNEY
04/19/2016

Cross-Discipline Team Leader Review

Date	01April2016
From	Laurie Muldowney, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206356
Supplement#	
Applicant	Swedish Orphan Biovitrum
Date of Submission	22June2015
PDUFA Goal Date	22April2016
Proprietary Name / Established (USAN) names	Orfadin® (nitisinone)
Dosage forms / Strength	Oral suspension, 4 mg/mL
Proposed Indication(s)	Adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1
Recommended:	Approval

1. Introduction

On 22June2015 Swedish Orphan Biovitrum submitted a new drug application (NDA 206,356) to support marketing approval of a new formulation of nitisinone, Orfadin® (nitisinone) oral suspension. Orfadin is currently available in three dose strengths, 2 mg, 5 mg, and 10 mg, as Orfadin® (nitisinone) capsules, approved 18January2002 under NDA 21,232. The applicant proposes the same indication for nitisinone oral suspension as the reference product, Orfadin® capsules, based primarily on the results of a bioequivalence study. The currently labeled indication for Orfadin® capsules is:

- indicated for use as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1)

The recommended dosage is:

- The recommended (b) (4) dose is 1 mg/kg/day divided into two daily doses.
- Maximum dose is 2 mg/kg/day.

In support of this NDA, the applicant conducted 2 clinical studies: a bioequivalence study in healthy adult volunteers and a taste and palatability study in pediatric patients with HT-1. No additional clinical efficacy or safety trials evaluating the nitisinone oral suspension formulation were conducted.

The review of this application was conducted as a Standard review with the Prescription Drug User Fee Act (PDUFA) goal date of 22April2016. All of the review disciplines recommend in favor of approval of nitisinone oral suspension for the indication of treatment of hereditary tyrosinemia type 1 (HT-1) in combination with

dietary restriction of tyrosine and phenylalanine, with the exception of the Office of New Drug Products within the Office of Pharmaceutical Quality, who do not recommend approval in its present form, pending resolution of labeling issues. I recommend approval of NDA 206356, Orfadin® (nitisinone) oral suspension, 4 mg/mL for the indication listed, provided agreement can be reached regarding the final labeling language.

This memo summarizes the information contained in NDA 206356 and discusses the recommendations made by each review discipline.

2. Background

Clinical Background

Hereditary tyrosinemia type 1 (HT-1) is a rare, autosomal recessive, inborn error of metabolism which leads to the accumulation of toxic tyrosine metabolites. Clinical features include severe liver dysfunction with an increased risk for hepatocellular carcinoma (HCC) early in life, impaired coagulation, renal tubular dysfunction and failure, hypophosphatemic rickets, painful neurological crises, and porphyria. There is significant variability in disease course which can be divided into acute, sub-acute, and chronic forms. Patients with the acute form of HT-1 typically experience liver failure before 6 months of age. The biochemical defect in HT-1 is a deficiency of fumarylacetoacetate hydrolase (FAH), the final enzyme of the tyrosine catabolic pathway. Clinical manifestations of HT-1 are due to the formation of toxic metabolites.

Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme which precedes FAH in the tyrosine catabolic pathway. By inhibiting the catabolism of tyrosine, nitisinone prevents the formation of catabolic intermediates, maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate. Treatment with nitisinone leads to rapid normalization of plasma and urine succinylacetone, as well as normalization of succinylacetone dependent porphyrin metabolism, with normalized erythrocyte porphobilinogen (PBG) synthase activity and urine 5-ALA. As nitisinone is an inhibitor of an enzyme in the tyrosine metabolic pathway, treatment with nitisinone may also cause increase in blood tyrosine levels and must be used in combination with phenylalanine and tyrosine restricted diet.

Treatment of HT-1 with nitisinone may be initiated within weeks after birth and is expected to be life-long. The currently available Orfadin® capsules are available in 3 dosage strengths (2, 5, and 10 mg). The current dosage and administration for Orfadin® capsules includes a provision for patients who are unable to swallow a capsule that capsules may be opened and the contents suspended in a small amount of water or formula diet immediately before intake. The applicant has developed an oral suspension formulation to increase convenience for patients and caregivers and to allow for easier dose adjustments for individual patients.

Regulatory Background

16May1995: Nitisinone was granted Orphan Drug Designation for the treatment of HT-1 (Orphan Designation #95-890).

18January2002: Orfadin® (nitisinone) capsules, 2 mg, 5 mg, and 10 mg, were approved for use as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of HT-1 under NDA 21,232. Orfadin® was subsequently approved in a number of countries outside the US, including Europe, Russia, Australia, Chile, Israel, South Korea, and Mexico.

28October2013: Swedish Orphan Biovitrum submitted a new drug application (NDA 206,356) to support marketing approval of Orfadin® (nitisinone) oral suspension, 4 mg/mL. In this submission, a variety of plastic oral syringes were co-packaged with the drug product for dose administration, so the application was classified as a drug-device combination product.

20December2013: The application was withdrawn due to deficiencies in the file.

27January2014: FDA issued an Acknowledge Withdrawal - Pending Application letter which provided deficiency comments to the withdrawn NDA. These included primarily items related to the drug-device combination, specifically:

1. The submission does not include a systematic evaluation of use-related risk, a determination of the necessity of human factors validation and, if necessary, how you would undertake the human factors validation. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users.
2. There was no information pertaining to 21 CFR 820.50, purchasing controls. Specifically, there was no information about agreements with suppliers or controls over supplies. The description of the manufacturing activities of the finished combination product was inadequate and a proper review of the manufacturing, including packaging, of the finished product could not be conducted.
3. There was no information pertaining to 21 CFR 820.30, design controls. Specifically, there was no information regarding procedures to control the design of the finished product in order to ensure that specified design requirements are met. The description of the manufacturing activities of the finished combination product was inadequate and a proper review of the manufacturing, including packaging, of the finished product could not be conducted.
4. There was no information pertaining to 21 CFR 820.100, CAPA. Specifically, there was no information provided regarding the establishment of procedures for implementing corrective and preventive actions. The description of the manufacturing activities of the finished combination product was inadequate

and a proper review of the manufacturing, including packaging, of the finished product could not be conducted.

5. Your labeling states

(b) (4)

08June2015: Written response only meeting. The sponsor asked if the agency agreed with an approach

(b) (4)

Submission and Review

The NDA was received electronically on 22June2015 and granted a Standard Review status with a goal date of 22April2016. The review disciplines have written review documents. The primary review documents relied upon in my CDTL memo are listed below in a table of review team assignments:

Table 1: Review Team Assignments

Review Team – Disciplines	Name(s) of discipline reviewers
Medical Officer review/CDTL	L. Muldowney, MD
Nonclinical (DGIEP)	D. Gautam, PhD/S. Chakder, PhD, dated 09Mar2016
OPQ Review Drug Substance (OPQ/ONDP/DNDAPI/ Branch II)	D. Ghosh, D. Christner, PhD, dated 17Mar2016
OPQ Review Drug Product (OPQ/ONDP/DNDP II)	H. Cai, PhD, M.J. Rhee, PhD, dated 17Mar2016
OPQ Process Review (OPF/Division of Process Assessment II/Branch V)	X Shen, CSO, E Kim, PhD, dated 10Mar2016
OPQ Review Facility (OPQ/OPF/DIA/Branch III)	X Shen, CSO, J Williams PhD, dated 13Mar2016
OPQ Biopharmaceutics (OPQ/ONDP/DB II)	M. Ou, PhD, A. Chen, PhD, dated 25Feb2016
OPQ Microbiology (OPQ/OPF/DM)	D Bateman, PhD, J Cole, PhD, dated 24Feb2016
Application Technical Lead (OPQ/OPRO/DNDPII)	D. Gromeck-Woods, dated 17Mar2016
Clinical Pharmacology Review (OCP/DCP3)	S. Li, PhD/S. Lee, PhD, dated 25Mar2016
Labeling Review (OPDP, DMPP)	K Dowdy, RN, BSN, M Williams, PhD, dated 09Mar2016
Labeling Review (OSE/DMEPA)	S. Abraham, RPh, M Mistry, MPH, dated 09Mar2016
Other: Consultation review (DPMH)	D. Snyder, MD/email correspondence Mar2016

DGIEP: Division of Gastroenterology and Inborn Errors Product, OPQ: Office of Pharmaceutical Quality, ONDP: Office of new Drug Products, DNDP: Division of New Drug Products, OCP: Office of Clinical Pharmacology, DCP3: Division of Clinical Pharmacology 3, OPDP: Office of Prescription Drug Promotion, DMPP: Division of Medical Policy Programs, OSE: Office of Surveillance and Epidemiology, DMEPA: Division of Medical Error Prevention and Analysis, DPMH: Division of Pediatric and Maternal Health

The reader is referred to the primary review documents for more specific details of the application and review conclusions. This memo summarizes selected information from the primary review documents.

3. CMC/Device

The quality reviewers concluded that the applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Facility and Process recommends approval for the manufacturing facilities involved in this application based on the results of their manufacturing inspection. However, there remained outstanding labeling issues at the time of the OPQ Integrated Quality Assessment, thus the application technical lead, D Gromeck-Woods, recommended the NDA not be approved in her review dated 17Mar2016, pending resolution of the labeling issues. I have summarized the key review findings

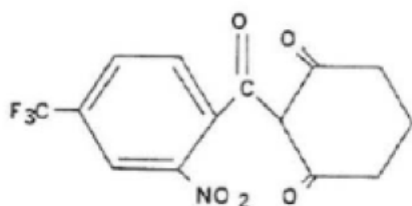
below. The reader is referred to the OPQ Integrated Quality Assessment review, dated 17Mar2016, for the complete information.

CMC/Drug Substance Quality Review

The drug substance (nitisinone) is the same for Orfadin® (nitisinone) capsules, NDA 21232, approved 18January2002, and the current NDA 206356, thus the applicant referenced CMC information for the drug substance in ND 21232. Any changes to CMC drug substance information were previously submitted to NDA 21232. All those post approval supplements or annual reports were reviewed and approved, thus referencing drug substance information from NDA 21232 was found to be acceptable.

The chemical name (IUPAC) is (2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclohexanedione). The chemical structure is shown in Figure 1 below.

Figure 1: Chemical Structure of Nitisinone



Source: OPQ Integrated Quality Assessment, dated 17March2016, page 6/151.

The drug substance is manufactured by (b) (4). For the purposes of the suspension formulation, the drug substance is (b) (4)

The proposed process was found to be acceptable to the CMC reviewers and chemical and physical analysis of samples support the stability of the (b) (4) drug substance. The reviewers state that the stability data provided in the referenced product, Orfadin® (nitisinone) capsules, (NDA 21232) support the proposed retest period of (b) (4) for nitisinone drug substance when stored at (b) (4) in the proposed container/closure system. The quality reviewers concluded that the (b) (4) nitisinone drug substance is acceptable for the proposed suspension formulation.

CMC/Drug Product Quality Review

Orfadin oral suspension is provided a white, slightly viscous, opaque suspension supplied in a 100 mL brown Type III medicinal glass bottle with child resistant cap. Each bottle contains 90 mL of the 4 mg/1 mL suspension. The composition of the oral suspension:

- (b) (4) drug substance nitisinone (NTBC), hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dehydrate, strawberry aroma (artificial), and purified water.

All excipients are USP/NF/Ph. Eur. Grade with the exception of the strawberry aroma which composes less than (b) (4) (w/w) of total amount of the drug product. The DMF of the strawberry flavor (b) (4) has been reviewed previously by Dr. Wendy Wilson on 18March2008 and found to be adequate. The Drug Product reviewer concluded that the nitisinone suspension contains well established excipients that are safe from a CMC perspective.

The pH of Orfadin oral suspension is (b) (4) and the active ingredient nitisinone (NTBC) has limited solubility in this formulation; thus the content of the dosage form is not uniform. The suspension settles and forms a cake during storage, and vigorous shaking is required to achieve content uniformity prior to dosing the drug product. As such, consistent resuspension is a key parameter to ensuring dose accuracy of the drug product. The applicant recommends shaking the drug product for at least (b) (4) seconds prior to withdrawal of the first dose and for a minimum of 5 seconds prior to withdrawal of all subsequent doses. The applicant assessed dose accuracy and content uniformity covering volume ranges from (b) (4) oral syringes. As per the Drug Product reviewer, the applicant demonstrated acceptable dose accuracy and content uniformity of the drug product by following USP<905> for the content uniformity and Ph. Eur. 2.9.27 for the uniformity of mass of delivered doses from multidose containers.

The proposed acceptance criteria in the drug product specification were found to be acceptable. Five NTBC related drug product organic impurities were identified, (b) (4) are the impurities presented in the drug substance nitisinone (NTBC). The newly identified drug product impurities were (b) (4)

Therefore, the specification was set as the sum amount of (b) (4). The proposed specification for individual impurity: (b) (4) and the sum of (b) (4), and the specification limit for any unspecified individual impurity is set at (b) (4). The Drug Product reviewer reports that this is in compliance of ICH Q3B (R2) guideline and is acceptable.

NTBC is relatively stable in pH (b) (4) formulation. A shelf life of 36 months is granted under the storage condition of refrigeration at +2°C to +8°C. Within this period the drug product may be used for 2 months at a temperature not exceeding +25 °C after first opening, after which the product must be discarded. The proposed pH range (b) (4). The Drug Product reviewer found the results from long-term and accelerated stability studies with the proposed marketing container and closure system to be acceptable. No significant changes in the nitisinone drug substance and (b) (4) sodium benzoate contents were observed under tested conditions; however, there is a (b) (4). The reviewer agrees with immediate administration after withdrawal from the bottle and finds the proposed formulation acceptable from a CMC perspective.

Nitisinone oral suspension will be administered orally to patients, preferably using an oral syringe. Re-dispersing of the suspension is required before each use by vigorous shaking which results in some foaming of the suspension. As such, a Push-in Bottle Adaptor (PIBA) is used to allow patients or parents/caregivers to turn the bottle upside down to withdraw the appropriate dose (the oral syringe is intended to fit firmly into the hole at the top of the PIBA). The applicant does not intend to package the drug product with the relevant syringe or PIBA, rather they intend to rely on the single source pharmacy to distribute appropriate administration materials to patients.

As an accurate fit of the PIBA is necessary to allow accurate dosing, the Agency held a teleconference with the applicant on 08February2016 to discuss how they would ensure that patients received a PIBA that would accurately fit their bottle. The applicant explained that they would be using a single source pharmacy and will thus have control over the PIBA dispensed to patients. They stated that they could use the same PIBA that is co-packaged with nitisinone oral suspension in Europe. The Agency's recommendation to the applicant during the meeting was that they consider co-packaging a PIBA with the drug product, to minimize potential issues if the pharmacy source were to change, for example. If the same PIBA that is currently co-packaged in Europe with nitisinone oral suspension is used, the applicant should have available data on the PIBA to streamline the process (data to assure the safety, strength, quality, and purity of the suspension while using PIBA). No agreements were made at that meeting.

In a subsequent information request/advice letter to the applicant dated 11February2016, the Agency provided the following recommendations:

FDA agrees that you can use a single source pharmacy with a commitment to supply the Push-in Bottle Adaptor (PIBA) currently marketed in Europe. However, please confirm that the sample adaptor sent to FDA is the same type/material as the one packaged with the drug product in Europe. Otherwise, the same type/material of PIBA marketed in Europe needs to be sent in for evaluation before Feb.19, 2016.

In addition, we would like you to make the following post-marketing commitment (PMC): Submit a Prior Approval Supplement (PAS) to update the packaging contents to include a Push-in Bottle Adaptor (PIBA) within six months after the approval of the application.

The applicant subsequently informed the Agency by email on 11February2016 that this would not be possible due to insurance restrictions on the amount of drug product that can be supplied with a single pharmacy dispensing. As insurance providers will only cover a 30 day supply, the pharmacy will need to dispense in increments outside of 90 mL (the size of the stock manufacturer bottle which will be provided to the pharmacy). The pharmacy will be required to suspend the drug product in the manufacturer stock bottle and dispense the appropriate 30-day supply into a

pharmacy bottle to be dispensed to the patient. The PIBA co-packaged with the European Orfadin oral suspension is designed to fit the manufacturer stock bottle and would not be appropriate for the pharmacy bottles.

A teleconference was held with the applicant on 12February2016 to discuss options to ensure dosing accuracy for nitisinone oral suspension. The applicant assured the Agency, that the single source pharmacy has the capability to include a PIBA for the pharmacy bottle, at the time of dispensing. The Agency thought this approach might be acceptable and asked the applicant to provide their rationale for this approach in writing to the NDA. No agreements were made during the teleconference.

The sponsor provided their written response on 16February2016. Specifically,

- Orfadin oral suspension will be sourced through a single source specialty pharmacy, (b) (4)
- (b) (4) has the capability to include a PIBA at the time of dispensing, that will fit the pharmacy bottle
- Standard pharmacy procedures will be followed to dispense the product.

(b) (4)

The applicant's response provided reassurance that an appropriate PIBA and oral syringe will be provided to all patients at the time of dispensing. This was found to be acceptable for this rare disease and given the use of a single source pharmacy. The Drug Product Reviewer recommends approval with an expiration dating period of 36 months.

CMC/Manufacturing Process Review

The quality reviewers concluded that the formulation and process development information are based on the attributes/properties of critical materials and demonstrated the robustness of the proposed manufacturing process. The applicant has provided sufficient description of the manufacturing process and controls for critical operation parameters and for-in-process materials are adequate. Therefore, from the manufacturing process perspective, the reviewers have recommended approval.

CMC/Biopharmaceutics Review

The biopharmaceutics reviewers recommend approval of this application. The reviewers concluded that the in vitro dissolution method and specification are acceptable and will be implemented for the drug product, Orfadin Oral Suspension, 4 mg/mL.

CMC/Microbiology Review

The Division of Microbiology found the applicants application to be acceptable and recommends approval of NDA 206356, Orfadin Oral Suspension.

CMC/Environmental Assessment

The quality reviewers granted the applicant's request for the categorical exclusion from the environmental assessment.

Carton and Container Labeling

The Drug Product reviewer finds the current carton and container labeling to be unsatisfactory and requires the following revisions in order to find the labeling acceptable:

- Remove (b) (4) from the label/labeling documents
- Revise the drug name presentation

Orfadin®
Nitisinone oral suspension
4 mg/mL

5 Revise “(b) (4)” to “trisodium citrate dehydrate” in the inactive ingredients

- Revise the storage statements to the following: *Must be refrigerated, store at 2° to 8°C (36° to 46°F) prior to first use. After first opening, store this product at room temperature (up to 25°C (77°F)) for up to 60 days. If not used within 60 days, discard the unused portion.*

The CMC/quality reviewers have not recommended PMCs or PMRs. The final labeling includes the recommended changes by the quality reviewers.

Facilities review/inspection

The facilities reviewer found no significant risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities were determined acceptable to support approval of Orfadin suspension under ND 206356.

Summary

The quality primary reviewers concluded that there are sufficient CMC information to assure the identity, purity, strength, and quality of the drug product. The quality primary reviewers have recommended approval of NDA 206356 with a drug product expiration dating period of 36 months. The technical lead does NOT recommend this NDA for approval, as not all labeling issues were resolved at the time the OPQ Integrated Quality Assessment was finalized, however, she agrees with all assessments from the primary reviewers. Labeling negotiations are ongoing at the time of this CDTL memo; I therefore recommend approval, provided agreement can be reached regarding the final labeling language.

The drug quality reviewers have not recommended PMCs or PMRs.

4. Nonclinical Pharmacology/Toxicology

The nonclinical team has recommended approval, and I agree with the recommendation. For complete information, the reader is referred to the Pharmacology/Toxicology review by Dr. D. Gautam, Ph.D. (primary review) and Dr. S. Chakder, Ph.D. (secondary review), dated 09Mar2016. I have summarized the key review findings below.

The applicant relied on the Agency's previous assessment of safety of nitisinone. In the current suspension formulation, the Applicant identified three degradation products, (b) (4) is a known impurity/degradation product in the drug substance as well as in the current solid oral dosage form. (b) (4) are novel degradation products noted during storage of the oral suspension.

Additional nonclinical studies submitted in support of this NDA were:

- Nitisinone: Potential Genotoxic Degradants Risk Assessment Report evaluated by the QSAR analysis, using Derek Nexus 2.0 and Leadscape models
- (b) (4) Bacterial Reverse Mutation Assay
- (b) (4): Bacterial Reverse Mutation Assay
- (b) (4): Mouse micronucleus and alkaline comet assay

The potential genotoxicity profiles of these compounds were determined by QSAR analysis and AMES tests. (b) (4) was negative in QSAR and Ames test. (b) (4), however, was found to be positive in QSAR analysis, AMES test and bone marrow micronucleus assay. (b) (4) was further investigated in vivo in mice using bone marrow micronucleus assay and the alkaline comet assay. (b) (4) was negative in the nitro-reductase deficient TA100NR strain in Ames test, and no DNA damage could be detected with the Comet assay in duodenum, liver or blood cell tissue. Importantly, (b) (4) contains the same functional group as the parent compound (nitisinone), which is also predicted to be mutagenic in the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test and in an in vivo mouse bone marrow micronucleus test. As per the nonclinical reviewer, according to ICH M7 guidance (2015), if the drug substance itself is mutagenic, exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. The Guidance also recommends that these "impurities could be controlled at acceptable levels for non-mutagenic impurities". Thus, the nonclinical team concluded that there are no safety concerns for the impurities/degradants in the drug product, and no pharm-tox related safety issues were identified for the oral suspension formulation.

There were no carcinogenicity studies, reproductive and developmental toxicology studies, or special toxicology studies submitted in support of this NDA.

The reviewers have not recommended PMCs or PMRs. The draft labeling of Orfadin® (nitisinone) generally conforms to the format specified under 21CFR 201.57(c)(9)(i) through (c)(9)(iii) Requirements for PLLR (Pregnancy and Lactation Labeling Rule) Prescription Drug Labeling.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team has recommended approval, and I agree with the recommendation. For complete information, the reader is referred to the Office of Clinical Pharmacology review by Dr. S Li, Ph.D. (primary review) and Dr. S. Lee, Ph.D. (secondary review), dated 25Mar2016. I have summarized the key review findings below.

NDA 206356 provides for a new oral suspension formulation of nitisinone for HT-1, (b) (4) The dosing regimen for the proposed suspension (b) (4) for the approved capsule product, i.e., 1 mg/kg/day divided into two daily doses with allowance for dose increase up to 2 mg/kg/day (b) (4)

(b) (4) The current label indicates that Orfadin capsules are to be taken at least one hour before, or two hours after a meal. To support the proposed oral suspension formulation, the applicant conducted a bioequivalence and food effect study (Sobi.NTBC-001), which were reviewed by the Office of Clinical Pharmacology.

Sobi.NTBC-001

Sobi.NTBC-001 was an open-label, randomized, cross-over, single-dose study in healthy volunteers to evaluate the bioequivalence of Orfadin suspension 4 mg/mL compared to Orfadin capsules 10 mg, and the effect of food on the bioavailability of the suspension. Twelve healthy male subjects age 18 to 55 years received single oral 30 mg doses of nitisinone as a suspension (under fasting and fed conditions) and as 3 x 10mg capsules (fasting only) in a 3-way crossover fashion. As a previously completed BE study for the Orfadin capsule formulation included both male and female subjects and did not reveal a higher intersubject or intrasubject variability in females, the clinical pharmacology reviewer found this study in male subjects only to be acceptable. The serum PK parameters following administration of the approved capsule formulation and the proposed suspension formulation is shown in Table 2 below.

Table 2: Summary of serum pharmacokinetic parameters of nitisinone

Population	Treatment	C _{max} (nM)	t _{max} (h)	AUC _{72h} (μM·h)
PPSBE (N=12)	capsule fasting	10213 (8030 - 18000)	3.50 (0.75 - 8.00)	403 (315 - 500)
	suspension fasting	9741 (7780 - 20300)	0.38 (0.25 - 4.00)	346 (264 - 456)
PPSFE (N=11)	suspension fasting	9807 (7780 - 20300)	0.50 (0.25 - 4.00)	347 (264 - 456)
	suspension fed	7715 (5300 - 12500)	8.00 (3.50 - 10.00)	343 (251 - 467)

Geometric mean (min-max) is presented, except for t_{max}: median (min-max).

PPSBE = Per-protocol set (bioequivalence): subjects with available PK data for capsule fasting and suspension fasting treatments (n=12).

PPSFE = Per-protocol set (food effect): subjects with available PK data for suspension fasting and suspension fed treatments (n=11). One subject did not complete the breakfast when the suspension was administered after food intake and thus was excluded from per-protocol set for food effect analysis.

Source: Clinical pharmacology review by Dr. S. Li, dated 25March2016, Table 1, page 3/26.

Bioequivalence testing was conducted, and as per the clinical pharmacology reviewer, the 90% confidence intervals for the oral suspension/capsule ratios under fasting conditions were entirely contained within the 0.80 to 1.25 bioequivalence range for both C_{max} and AUC_{72h}, as is shown in Table 3 below.

Table 3: Statistical Analysis of Bioequivalence

Parameter	Geometric LS means		Ratio suspension/ capsule [90% CI] ^b	Estimate	
	Capsule fasting	Suspension fasting		Lower	Upper
AUC _{72h} (μM·h)	403	346	0.858	0.81	0.91
C _{max} (nM)	10213	9741	0.954	0.85	1.07

CI = confidence interval; LS = least squares.

Source: Clinical pharmacology review by Dr. S. Li, dated 25March2016, Table 2, page 3/26.

The applicant also analyzed the food effect for the suspension formulation and found the 90% confidence interval for AUC_{72h} of the fed/fasting ratio was within the bioequivalence range. The fed/fasting ratio for C_{max} was 0.82 with a 90% CI of 0.74-0.90 for the per-protocol set of analysis. While this is outside the bioequivalence range, nitisinone is dosed twice daily and has a long half-life. As such, the clinical

pharmacology reviewer stated that “the C_{max} differences (suspension/fed vs suspension/fasting) at steady state will be diminished because of similar AUC under both fed and fasting conditions. As such, we recommend that the suspension can be taken without regard to meal.”

The clinical pharmacology reviewers have not recommended PMCs or PMRs. The most recent labeling recommendations to the applicant includes all recommended changes to the label by the clinical pharmacology reviewers, and the clinical pharmacology team recommends approval, provided a mutually satisfactory agreement can be reached regarding the labeling language.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application. Nitisinone oral suspension is not intended as an antimicrobial product.

7. Clinical/Statistical- Efficacy

No clinical efficacy studies were conducted as part of this NDA application. The application for Orfadin suspension is supported by a bioequivalence study (See Section 5) and a taste and palatability study. Study Sobi-NTBC-002 was an open-label, single-arm, multiple-dose study of nitisinone oral suspension in 18 pediatric patients with HT-1, in order to assess the taste and palatability of the suspension formulation. The study supports that the nitisinone oral suspension is an acceptable alternative to the capsule formulation, as it pertains to taste and palatability. Study Sobi-NTBC-002 is briefly summarized below.

Taste and palatability study protocol summary:

Study Design and Objective:

The applicant completed Study Sobi.NTBC-002, an open, non-controlled, multiple-dose, multi-center study in 18 pediatric patients with hereditary tyrosinemia type 1 treated with Orfadin capsules, in order to assess the taste and palatability of the proposed liquid formulation of nitisinone in these patients. The objective of this study was to demonstrate that the taste and palatability of the oral suspension are acceptable to patients, not to compare the taste of the suspension to the approval oral capsule formulation. The applicant thus selected an open-label, non-randomized design.

Eligibility:

The study included 18 pediatric patients, age 1 month to < 18 years, with hereditary tyrosinemia type 1 treated with Orfadin capsules. Patients could be excluded if they had any medical condition which, in the opinion of the investigator, made the subject unsuitable for inclusion, or if they were enrolled in concurrent clinical study or currently taking an investigational medical product.

Six patients in each of the following age subsets were included:

- 1 month to < 2 years
- 2 years to < 12 years
- 12 to < 18 years

Study Visits and Procedures:

The treatment period was 3 days with twice daily dosing. Administration of the first dose occurred in the clinic, and subsequent doses were given at home. The daily dose of Orfadin suspension was the same as that prescribed for the capsule, for each individual patient. If the investigator found that an adjustment of the capsule dose was necessary, for example, due to weight gain since the last check up, the dose adjustment was made after completion of the 3-day treatment period. A visit to the clinic was scheduled for screening/Day 1, and there was a subsequent follow-up telephone visit 1 week after administration of the last dose on Day 3. A schedule of events is shown in Figure 2 below:

Figure 2: Schedule of Events

Event	Screening within 3 weeks before, or on, Day 1	Day 1	Day 2	Day 3	1 week after last dose Follow up ^a
Informed consent/assent	X				
Medical history	X				
Demography	X				
Physical examination (weight and height)	X				
Inclusion / exclusion criteria	X	X			
Dispensing of IMP		X			
Administration of IMP		X	X	X	
Instructions to subjects/parents regarding dosing of the suspension and how to fill out the questionnaire		X			
Rating of taste and palatability		X ^b	X ^c	X ^c	
AEs ^d		X	X	X	X
Concomitant medication		X	X	X	X

^a By telephone.

^b First dose of the day, at clinic.

^c Last dose of the day.

^d Serious adverse events (SAEs) were collected from signing of the informed consent until 28 days after last dose of IMP.

Source: Sobi.NTBC-002 Clinical Study Report, Table 4

Assessments of taste and palatability were made at the clinic after the first dose on Day 1 and after the evening doses at home on Days 2 and 3. Patients age 5 to <18 years of age completed a questionnaire to rate taste and palatability as shown in Figure 3.

Figure 3: Taste and Palatability Questionnaire for patients age 5 to < 18 years

1. "What did you think of the taste of the new medicine that you just took?" The scale had the following 5 response options:

5. Very good taste	☐	
4. Good taste	☐	
3. Neither good nor bad taste	☐	
2. Bad taste	☐	
1. Very bad taste	☐	

2. "How did the new medicine feel in your mouth?" The scale had the following 5 response options:

5. Very good	☐	
4. Good	☐	
3. Neither good nor bad	☐	
2. Bad	☐	
1. Very bad	☐	

Source: Sobi.NTBC-002 Clinical Study Report page 19

For patients less than 5 years of age, one of the parents rated the child's acceptability of the suspension on a verbal/numerical scale at the clinic after the first dose and at home after the evening doses on Days 2 and 3. Figure 4 below shows the question asked to assess acceptability:

Figure 4: Acceptability Questionnaire for parents/caregivers of patients < 5 years of age

The question asked was “How did your child accept taking the suspension?”

The 5 response alternatives were:

5. Very well

4. Well

3. Neither well nor badly

2. Badly

1. Very badly

Source: Sobi.NTBC-002 Clinical Study Report, page 20

Primary endpoints:

- Taste score at the last dose of the suspension on Day 3 for patients 5 - < 18 years
- Acceptability score at the last dose of the suspension on Day 3 for subjects < 5 years

Secondary endpoints:

- The taste scores on Days 1 and 2 (subjects 5 - < 18 years).
- The acceptability scores on Days 1 and 2 (subjects < 5 years).
- The palatability scores on Days 1, 2 and 3 (subjects 5 - < 18 years).
- The overall acceptability response (subjects 1 month - < 18).
- Adverse events (AEs).

Statistical Information:

This study was a descriptive study only, without formal hypothesis testing. No sample size calculation was performed and results were summarized by standard descriptive statistics. This study was conducted in compliance with the ICH Guideline for Good Clinical Practice, including the archiving of essential documents.

Taste and palatability study results summary:

Demographics and Disposition:

A total of 18 subjects were enrolled in this study at 7 centers in Germany, France, and the United Kingdom. There were an equal number of male and female patients enrolled, and the majority of subjects were caucasian. All patients had been diagnosed with HT-1 before the age of 1.3 years, and treatment with Orfadin capsules was initiated immediately at the time of diagnosis. All enrolled subjects completed the study. Table 4 below shows the analysis data sets by age group; < 5 years, 5 to < 12, and 12 to < 18 years.

Table 4: Analysis data sets by age groups

Analysis set	Age group			Total N = 18
	< 5 years N = 6	5 - < 12 years N = 6	12 - < 18 years N = 6	
Safety Analysis set	6 (100%)	6 (100%)	6 (100%)	18 (100%)
Full analysis set (FAS)	6 (100%)	6 (100%)	6 (100%)	18 (100%)
Per protocol analysis set (PPAS)	6 (100%)	6 (100%)	6 (100%)	18 (100%)

Source: Sobi.NTBC-002 Clinical Study Report, Table 10.1.5

Primary Endpoint:**Taste on Day 3**

The primary endpoint for patients age 5 to < 18 years of age was taste score at the last dose of the suspension on Day 3, where taste was assessed on a scale of 1 to 5 with 1 being very bad taste and 5 being very good taste (see figure xx for the actual questionnaire). The median taste score for subjects 5 to < 18 years of age was 4.0 in the full analysis set following the last dose of the suspension on Day 3. None of the subjects rated the taste as very bad, and two-thirds of subjects rated the taste as good or very good. Table 5 below summarizes the taste scores from Day 3.

Table 5: Taste score for the last dose on Day 3; age group 5 to < 18 years (FAS)

Taste Score	5 - < 18 years N = 12
N	12
Very bad taste (1)	0
Bad taste (2)	1 (8.3%)
Neither good nor bad taste (3)	3 (25%)
Good taste (4)	4 (33.3%)
Very good taste (5)	5 (33.3%)
Median (min, max)	4.0 (2, 5)

Source: Sobi.NTBC-002 Clinical Study Report, Table 10.2.1

Note: there were no missing observations

For patients less than 5, parents assessed the acceptability of the suspension. Six of 6 subjects accepted the suspension very well or well, as assessed by the parents. This is shown in Table 6 below:

Table 6: Acceptability score for the last dose on Day 3; age group < 5 years (FAS)

Acceptability Score	< 5 years N = 6
N	6
Very badly (1)	0
Badly (2)	0
Neither well nor badly (3)	0
Well (4)	2 (33.3%)
Very well (5)	4 (66.7%)
Median (min, max)	5.0 (4, 5)

Source: Sobi.NTBC-002 Clinical Study Report, Table 10.2.2

Note: there were no missing observations

Secondary Endpoints:

Secondary endpoints included:

- The taste scores on Days 1 and 2 (subjects 5 - < 18 years).
- The acceptability scores on Days 1 and 2 (subjects < 5 years).
- The palatability scores on Days 1, 2 and 3 (subjects 5 - < 18 years).
- The overall acceptability response (subjects 1 month - < 18).

For patients 5 to < 18 years of age, the taste results on Days 1 and 2 were comparable to the results shown in **Error! Reference source not found.** for Day 3. Palatability was also assessed on Days 1 through 3 in patients 5 to < 18 years of age, using a 1 to 5 scale where 1 is very bad and 5 is very good. The majority of the 12 patients assessed the palatability as good or very good on all 3 days, and no patients assessed the palatability as very bad. A single patient assessed the palatability as bad on Days 2 and 3. The palatability scores are summarized in Table 7 below.

Table 7: Palatability score on Days 1, 2, and 3; age group 5 to < 18 years (FAS)

Palatability score	Age group 5 to < 18 years N = 12		
	Day 1	Day 2	Day 3
N	12	12	12
Very bad (1)	0	0	0
Bad (2)	0	1 (8.3%)	1 (8.3%)
Neither good nor bad (3)	3 (25.0%)	4 (33.3%)	2 (16.7%)
Good (4)	4 (33.3%)	3 (25.0%)	4 (33.3%)
Very good (5)	5 (41.7%)	4 (33.3%)	5 (41.7%)
Median (min, max)	4 (3, 5)	4 (2, 5)	4 (2, 5)

Source: Sobi.NTBC-002 Clinical Study Report, Table 10.2.5

Note: there were no missing observations

For patients less than 5 years of age, the parental perception of how well the children accepted the oral suspension was rated well or very well for all children on Days 1 and 2, similar to the results for Day 3 shown in Table 6. Finally, at the end of the treatment period (second dose on Day 3), patients or parents/caregivers were asked

about overall acceptability of the oral solution formulation. Specifically, “Would you/your child accept taking the new medicine again?”. The response options were “Yes” or “No”. A majority of patients would accept taking the medication again, including 100% of those < 5 years of age.

Overall, study Sobi-NTBC-002, a taste and palatability of nitisinone suspension study, supports that the nitisinone oral suspension is an acceptable alternative to the capsule formulation.

8. Safety

Nitisinone oral suspension contains the same active moiety as Orfadin® capsules, approved 18 January 2002 under NDA 21,232. As the overall safety of Orfadin® capsules has already been established in the initial application for Orfadin® NDA 21232, it was not presented in the safety summary for nitisinone oral suspension. This application included 2 clinical studies on which the submission is based, a bioequivalence study in 12 healthy volunteers (Sobi.NTBC-001) and a taste and palatability study in 18 pediatric patients with HT-1 (Sobi.NTBC-003). As one study was conducted in healthy adults and the other in pediatric patients with HT-1, the applicant did not pool the safety results from these studies and they are shown separately below. Both studies were conducted in accordance with the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and are summarized in Table 8 below.

Overall, there were no deaths, serious adverse events, or discontinuations, and no new safety signals were identified for nitisinone oral suspension during the clinical studies.

Table 8: Summary of Clinical Studies conducted in support of NDA 206356

	Study Design	Study Population	Study Enrollment and Treatment Arms	Primary Objective
Sobi.NTBC-001	open-label, randomized, single-dose, 3-way, cross-over study	Healthy adult volunteers	12 subjects, all receive single dose, 30 mg nitisinone, provided as Orfadin (nitisinone) capsules and nitisinone suspension	To show bioequivalence between nitisinone oral suspension and nitisinone capsules
Sobi.NTBC-002	Open label, uncontrolled, 3-day taste and palatability study	Pediatric patients with HT-1 treated with Orfadin	18 pediatric patients receive Orfadin suspension at the same dose they are receiving Orfadin capsules - 6, < 5 years of age - 6, 5 to < 12 years - 6, 12 to < 18 years	Taste (ages 5 to < 18) and acceptability (age < 5) of suspension formulation

Source: CDTL Table Summarized from Applicant's Submission

Exposure and Demographics

The 2 clinical studies performed included healthy adult volunteers and pediatric patients with HT-1. Neither study was designed to assess the safety of nitisinone, as the safety profile has already been established. Study Sobi.NTBC-001 was a bioequivalence study in which 12 healthy adult volunteer received 30 mg of nitisinone, provided as either capsules or suspension formulation, on 3 separate occasions xx weeks apart. The dose, duration, and demographics of the subjects do not reflect the use of nitisinone in the target population. Study Sobi.NTBC-002 was a taste and palatability study of 18 pediatric patients with HT-1. The study represented all pediatric subsets (< 5 years, 5 years to < 12 years, and 12 years to < 18 years) who would be expected to be the target population for a liquid formulation, and patients were maintained on their clinical dose of nitisinone from prior to study enrollment. However, the duration of dosing (3 days) does not reflect the expected chronic use of the product in the clinical setting. The exposure and demographics of these two studies are summarized below.

Sobi.NTBC-001 included 12 healthy adults who received 3 separate single doses of nitisinone 30mg, each given 2 weeks apart. The recommended dosing of Orfadin® is between 1 and 2 mg/kg/day, and the product is dosed chronically for patients with HT-1. The average weight of subjects in this study was 80.7 kg, so a 30 mg dose of nitisinone is substantially less than would be expected in clinical practice. Thus, the dose, duration, and demographics of the subjects in this study do not reflect the use of nitisinone in the target population. Table 9 below provides a summary of overall exposure to nitisinone in study Sobi.NTBC-001.

Table 9: Summary of Exposure, Study NTBC-001

Treatments	Total nitisinone exposure per subject	Number of subjects exposed
A Orfadin capsule, 3 x 10 mg nitisinone (oral, fasting)	30 mg	N = 12
B Orfadin suspension, 30 mg (7.5 mL) nitisinone (oral, fasting)	30 mg	N = 12
C Orfadin suspension, 30 mg (7.5 mL) nitisinone (oral, fasting)	30 mg	N = 12
Total administered over a period of 4 weeks	90 mg	N = 12

Source: Sobi.NTBC-001 study report, Appendix 2.5.2

Table 10 below provides a summary of demographics and baseline characteristics for the subjects in study Sobi.NTBC-001. The mean age of subjects was 35 years of age, and 100% of subjects were men. The majority (92%) of subjects were white.

Table 10: Demographics, Study NTBC-001

Characteristic		All Subjects, N = 12
Age (year)	Mean (SD)	35 (12)
	Median	31
	Range	19 - 53
Weight (kg)	Mean (SD)	80.7 (12.1)
	Median	82.3
	Range	60.3 – 99.0
Gender	Male (n[%])	12 (100%)
	Female (n[%])	0 (0%)
Race	White	11 (92%)
	Other (Asian)	1 (8%)

Source: Sobi.NTBC-001 Study Report, Table 10.1.1

Sobi.NTBC-002 was a short-term (3 day) study in 18 pediatric patients who had been diagnosed with HT-1 and were treated with Orfadin capsules and diet restrictions, according to standard of care, before entering the study. Nitisinone suspension administered twice daily, replaced the regular administration of Orfadin capsules during the 3-day study treatment period. Thus, the dosing of the subjects in this study reflect the use of nitisinone in the target population, however, the duration of use in the study (3 days) does not reflect the chronic use recommended for patients with HT-1. The mean total daily dose of the nitisinone suspension was 0.86 mg/kg, which was equal to the mean dose of the Orfadin capsule prescribed prior to the study. Table 11

below summarizes the total daily dose of Orfadin capsules and suspension by age group.

Table 11: Orfadin (nitisinone) daily dose, Study NTBC-002

	Age group		Total N = 18
	< 5 years N = 6	5 - < 18 years N = 12	
Total daily dose of Orfadin capsule (mg/kg bodyweight) before entering study			
Mean (SD)	0.84 (0.40)	0.87 (0.19)	0.86 (0.27)
Median (Min, Max)	0.84 (0.4, 1.5)	0.95 (0.5, 1.2)	0.92 (0.4, 1.5)
Total daily dose of nitisinone suspension (mg/kg bodyweight) during study			
Mean (SD)	0.84 (0.40)	0.87 (0.19)	0.86 (0.27)
Median (Min, Max)	0.85 (0.4, 1.5)	0.95 (0.5, 1.2)	0.93 (0.4, 1.5)

Source: Sobi.NTBC-002 study report, Table 10.1.9 and Table 10.1.11

Patients in Sobi.NTBC-002 ranged in age from 0.7 to 15.7 years. This includes relevant age groups likely to receive an oral suspension. Fourteen of 18 (78%) were white which and there was an equal number of male and female patients. All patients had been diagnosed before 1.3 years of age and treatment with Orfadin capsules was initiated immediately. This is consistent with current standard of care. Overall, while the sample size was small, it accurately reflects the patients who would receive nitisinone oral suspension in clinical care. Table 12 below summarizes baseline demographics and disease factors from the study.

Table 12: Baseline demographics and treatment characteristics, Study Sobi.NTBC-002

	Age group		Total N = 18
	< 5 years N = 6	5 - < 18 years N = 12	
Select Demographics			
Baseline age (years)			
Mean (SD)	1.22 (0.35)	11.44 (3.24)	8.03 (5.60)
Median (Min, Max)	1.29 (0.7, 1.6)	11.46 (6.2, 15.7)	9.25 (0.7, 15.7)
Sex			
Male	3 (50%)	6 (50%)	9 (50%)
Female	3 (50%)	6 (50%)	9 (50%)
Race			
Asian	0	4 (33.3%)	4 (22.2%)
White	6 (100%)	8 (66.7%)	14 (77.8%)
Select Patient and Treatment Characteristics			
Age at diagnosis (years)			
Mean (SD)	0.10 (0.24)	0.25 (0.46)	0.20 (0.40)
Median (Min, Max)	0.00 (0.0, 0.6)	0.04 (0.0, 1.3)	0.00 (0.0, 1.3)
Age at Orfadin treatment start (years)			
Mean (SD)	0.10 (0.24)	0.26 (0.46)	0.20 (0.40)
Median (Min, Max)	0.00 (0.0, 0.6)	0.04 (0.0, 1.3)	0.00 (0.0, 1.3)
Duration of Orfadin treatment (months)			
Mean (SD)	13.7 (3.9)	134.3 (36.2)	94.1 (65.4)
Median (Min, Max)	13.0 (8, 18)	136.5 (72, 185)	110.5 (8, 185)

Source: Sobi.NTBC-002 Clinical Study Report, Tables 10.1.7 and 10.1.9

Deaths, Discontinuations, and Serious Adverse Events

There were no deaths, discontinuations, or serious adverse events reported during the studies.

Treatment-Emergent Adverse Events (TEAEs)

Sobi.NTBC-001: There were 8 treatment emergent adverse events (TEAEs) reported in 5 (42%) of subjects. No single adverse event was reported more than once, and the number of subjects reporting AEs was similar for the oral suspension and capsule formulations. All AEs were of mild intensity. Table 13 below summarizes the TEAEs in study Sobi.NTBC-001.

Table 13: Treatment-emergent Adverse Events by Preferred Term, Study Sobi.NTBC-001

Preferred term	Capsule fasting (N = 12)		Suspension fasting (N = 12)		Suspension fed (N = 12)		Total (N = 12)	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Total	1 (%)	1	2 (17%)	3	2 (17%)	4	5 (42%)	8
Dyspepsia	0	0	0	0	1 (8%)	1	1 (8%)	1
Catheter site	0	0	1 (8%)	1	0	0	1 (8%)	1

related reactions								
Nasopharyngitis	1 (8%)	1	0	0	0	0	1 (8%)	1
Musculoskeletal pain	0	0	0	0	1 (8%)	1	1 (8%)	1
Dizziness	0	0	0	0	1 (8%)*	1	1 (8%)	1
Headache	0	0	1 (8%)	1	0	0	1 (8%)	1
Epistaxis	0	0	0	0	1 (8%)	1	1 (8%)	1
Nasal congestion	0	0	1 (8%)	1	0	0	1 (8%)	1

Source: Sobi.NTBC-001 Clinical Study Report, Table 10.3.1.1.

Adverse events were classified according to MedDRA version 15.0

* This event was considered related to Orfadin by the investigator

N = number of subjects exposed per treatment, n = number of subjects that experienced the adverse event per treatment, e = number of adverse events per treatment

Sobi.NTBC-002: There were 5 total treatment emergent adverse events reported by 4 (22%) of patients. No single adverse event was reported more than once. Four AEs were considered mild intensity and 1 was assessed as moderate. Table 14 below summarizes the TEAEs in study Sobi.NTBC-002.

Table 14: Adverse Events by Preferred Term by Age Group < 5 years and 5 to < 18 years, Sobi.NTBC-002

Preferred term	Age < 5 years N = 6		Age 5 to < 18 years N = 12		Total N = 18	
	n (%)	e	n (%)	e	n (%)	e
Total	2 (33.3%)	3	2 (16.7%)	2	4 (22.2%)	5
Diarrhea	0	0	1 (8.3%)	1	1 (5.6%)	1
Mouth Hemorrhage	0	0	1 (8.3%)	1	1 (5.6%)	1
Regurgitation	1 (16.7%)	1	0	0	1 (5.6%)	1
Pyrexia	1 (16.7%)	1	0	0	1 (5.6%)	1
Nasopharyngitis	1 (16.7%)	1	0	0	1 (5.6%)	1

Source: Sobi.NTBC-002 Clinical Study Report, Tables 10.3.1 and 10.3.2

Adverse events were classified according to MedDRA version 15.1

N = number of subjects exposed per treatment, n = number of subjects that experienced the adverse event per treatment, e = number of adverse events per treatment

9. Advisory Committee Meeting

No advisory committee was held for review of this application.

10. Pediatrics

Nitisinone was granted Orphan Drug Designation on May 16, 1995 (Orphan Designation #95-890). As such and in accordance with Section 505B(g) of the Food,

Drug, and Cosmetic Act and Title 21 CFR 314.55(d), the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to nitisinone. The submission was not presented to the Pediatric Review Committee (PeRC).

The Division consulted the Division of Pediatric and Maternal Health (DPMH) to aid in the review of the labeling. Specifically, the applicant proposed including language in

(b) (4)



11. Other Relevant Regulatory Issues

There are no additional regulatory issues with this application.

12. Labeling

Proprietary Name:

The Office of Medication Error Prevention and Risk Management determined that the proposed proprietary name Orfadin is acceptable. The reader is referred to the Proprietary Name review by Drs. S. Abraham, K. Worthy, and L. Merchant, dated 25September2015.

Labeling Consults and Reviews:

The Division consulted the Division of Pediatric and Maternal Health (DPMH) during the review cycle to seek guidance for the Warning and Precautions section of the product labeling,

(b) (4)



(b) (4)

Specific Labeling Issues:

Information on nitisinone oral suspension is proposed to be added to the approved label for Orfadin® capsules. Labeling negotiations were ongoing at the time of this document. For final labeling agreements, the reader is referred to the approved product label. The key changes and recommended changes to the labeling at the time of this review are summarized below.

Highlights

- The indication was modified to: indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine, from [REDACTED] (b) (4). The applicant felt the revised indication was clearer and did not change the meaning. The review team agreed with this rationale.
- Information was added to include dosage and administration instructions for nitisinone oral suspension and the addition of the oral suspension dosage form and strength
- A potential for risk of adverse reactions due to glycerol content of Orfadin oral suspension was added to the highlights with a recommendation to consider switching patients to Orfadin capsules should such ARs occur.

Section 2 Dosage and Administration

- Language added to indicate that the oral suspension will be dispensed with an oral syringe of appropriate size and a bottle adaptor provided by a pharmacist or healthcare provider.

- Specific information was added to inform prescribers of the administration procedures for Orfadin oral suspension, which must be re-dispersed through vigorous shaking before each use and then withdrawn and administered immediately, preferably with an oral syringe.

(b) (4)

Section 3: Dosage Forms and Strengths

- The oral suspension dosage form and strength was added

Section 5: Warnings and Precautions

(b) (4)

[Redacted] (b) (4)

- The oral suspension formulation contains 500 mg/mL glycerol.

(b) (4)

[Redacted]

Section 6: Adverse Reactions

- [Redacted] (b) (4)
- [Redacted] (b) (4)

. Therefore, the applicant was advised to reinsert porphyria and epistaxis adverse events. In the listing of less common adverse reactions, it was recommended that the applicant retain serious adverse events as adverse reactions, but remove those terms that are non-serious or non-specific (e.g., tooth discoloration, hepatic function disorder, thirst, infection, otitis, infection (not otherwise specified), pathologic fracture).

- [Redacted] (b) (4)
- [Redacted]

Section 8: Use in Special Populations

- Updates were made to the pregnancy section as recommended by DPMH, specifically, language was updated to be consistent with PLLR labeling. A statement was added regarding the background risk of miscarriages and birth defects (new template language from DPMH).
- Updates were made to the lactation section to clearly state there are no data on the presence of nitisinone in human milk, the effects on the breastfed infant,

or the effects on milk production. In addition, a statement was added: the development and health benefits of breastfeeding should be considered along with the mother's clinical need for Orfadin and any potential adverse effects on the breastfed infant from Orfadin or from the underlying maternal condition.

Section 11: Description

- A description of the oral suspension dosage form was added
- The applicant proposed the addition of language related to potential risks from glycerol in the oral suspension formulation (headache, stomach upset, and diarrhea). The Division recommends this language be removed from Section 11 and asked that the applicant provide data to support the oral dosage range for glycerol that may result in clinically relevant adverse reactions. If clinically important, this information should be moved to the Warnings and Precautions section. These changes were still being negotiated at the time of this review.

Section 12: Clinical Pharmacology

- The applicant provided revised language that Orfadin suspension or capsule can be taken without regards to meals. The clinical pharmacology reviewers agree on this language for the oral suspension formulation, based on data regarding the impact of food on the bioavailability of nitisinone oral suspension. However, as no food effect study was performed with the Orfadin capsules, the administration of the capsules should remain unchanged (i.e., capsules should be taken at least one hour before, or two hours after a meal). These changes were still being negotiated at the time of this review.

Section 16: How Supplied/Storage and Handling

- Storage and handling information was added for the oral suspension dosage form. Specifically, the oral suspension should be stored refrigerated prior to first use. After first opening, the product should be stored at room temperature for up to 60 days. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle

Patient Labeling/Instructions for Use:

The proposed Orfadin oral suspension requires that patients or parents/caregivers re-dispersed the drug product through vigorous shaking before each use and then withdrawn and administered immediately. In addition, accurate dosing requires the use of a Push-in Bottle Adaptor and oral syringe, which will be dispensed to the patients with the drug product from a single source pharmacy. Instructions for use were determined to be necessary to ensure accurate understanding by the patient or parent/caregiver of the proper handling, dosing and administration of Orfadin oral suspension.



Labeling Conclusions:

In addition to the review team and DPMH consultant, the labeling was also reviewed by the Division of Medical Policy Programs (patient labeling) and the Division of Medication Error Prevention and Analysis. Their comments and recommendations have been incorporated into the labeling recommendations to the applicant. At the time of this review, labeling negotiations are still ongoing, so the reader is referred to the approved product label for the final agreed upon label.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:

I recommend that nitisinone oral suspension, 4 mg/mL be approved for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Risk Benefit Assessment

In support of this NDA, the applicant conducted a bioequivalence study in healthy adult volunteers and a taste and acceptability study in pediatric patients with HT-1. No additional clinical efficacy or safety trials were conducted and submitted in this NDA.

The quality reviewers concluded that the applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

I agree with the reviewers that the data submitted in this NDA establish bioequivalence between Orfadin suspension 4 mg/mL and Orfadin capsules 10 mg. The 90% confidence intervals for the oral suspension/capsule ratios under fasting conditions were entirely contained within the 0.80 to 1.25 bioequivalence range for both C_{max} and AUC_{72h} , and the 90% confidence interval for AUC_{72h} of the fed/fasting ratio was within the bioequivalence range. The fed/fasting ratio for C_{max} was 0.82 with a 90 % CI of 0.74-0.90 for the per-protocol set of analysis. While this is outside the bioequivalence range, nitisinone is dosed twice daily and has a long half-life. As such, the clinical pharmacology reviewer concluded that the C_{max} differences between fed and fasting at steady state will be diminished because of similar AUC and the suspension can be taken without regard to meal.

An open-label, taste and palatability study in pediatric patients with HT-1 supports that the nitisinone oral suspension is an acceptable alternative to the capsule formulation, as it pertains to taste and palatability.

No new safety signals were identified for nitisinone oral suspension during the clinical studies.

Based on the data provided, I agree that Orfadin oral suspension should be approved for HT-1 and that the benefits of the oral suspension formulation outweigh the risks associated with the use of this product.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments

There are no postmarketing requirements (PMRs) or commitments (PMCs) recommended for this NDA.

Recommended Comments to Applicant

There are no recommended comments to the applicant at this time.

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

/s/

LAURIE B MULDOWNNEY
04/01/2016