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RESEARCH**

APPLICATION NUMBER:

206356Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	206356 / SDN 11	<i>Submission Date(s)</i>	06/22/2015
<i>Brand Name</i>	Orfadin		
<i>Generic Name</i>	Nitisinone		
<i>Reviewer</i>	Shen Li, Ph.D.		
<i>Team Leader</i>	Sue-Chih Lee, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology 3		
<i>OND Division</i>	Division of Gastroenterology and Inborn Errors Products		
<i>Sponsor</i>	Swedish Orphan Biovitrum		
<i>Submission Type; Code</i>	New dosage form		
<i>Formulation; Strengths; Regimen</i>	<p><u>Proposed New Formulation:</u> Oral suspension (4 mg/mL).</p> <p><u>Approved Product:</u> 2 mg, 5 mg, 10 mg capsules.</p> <p>The (b) (4) dose is 1 mg/kg/day divided into two daily doses. The dose may be increased up to 2 mg/kg/day based on erythrocyte PBG-synthase activity and urine 5 ALA and urine succinylacetone.</p>		
<i>Indication</i>	(b) (4) treatment of hereditary tyrosinemia type 1 (HT-1).		

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1 Executive Summary

Nitisinone is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase. Orfadin capsules containing nitisinone 2 mg, 5 mg, and 10 mg were approved in 2002 under NDA 21232 for use as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1), a disease caused by the deficiency of an enzyme at the tailend of the tyrosine degradation pathway. This disorder is characterized by progressive liver failure, increased risk of hepatocellular carcinoma, coagulopathy, painful neurologic crises, and renal tubular dysfunction resulting in rickets.

This NDA submission (NDA 206356) provides for a new oral suspension formulation, which was developed to afford easier dosing in pediatric patients. To support the proposed suspension formulation, the sponsor conducted a bioequivalence and food effect study (Sobi.NTBC-001). In addition, a taste and palatability study (Sobi.NTBC-002) in pediatric patients was also submitted, which is being reviewed by DGIEP. 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. The dose may be increased up to 2 mg/kg/day based on erythrocyte PBG-synthase activity and urine 5 ALA and urine succinylacetone. Currently, Orfadin capsules are to be taken at least one hour before, or two hours after a meal, since food effect is unknown (see Clinical Pharmacology Review of NDA 21-232 for Orfadin capsules dated 02/02/2001). For the proposed suspension, the sponsor evaluated the food effect on nitisinone pharmacokinetics (PK).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this NDA submission and found it acceptable from a clinical pharmacology standpoint provided that a mutually satisfactory agreement can be reached between the sponsor and Agency regarding the labeling language.

1.2 Post-Marketing Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In Study Sobi.NTBC-001 (entitled “A study 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. An open-label, randomized, cross-over, single-dose study in healthy volunteers”), twelve male healthy subjects received single oral 30-mg doses of nitisinone as a suspension (under fasting and fed conditions) and as 3x10-mg capsules (fasting only) in a 3-way crossover fashion.

Nitisinone serum pharmacokinetic parameters following administration of the proposed suspension formulation (under fasting and fed conditions, respectively) and the approved capsules (under fasting conditions) are presented in Table 1. This study conducted in healthy male volunteers only was accepted for review as another BE study in both male and female subjects for the capsule formulation did not reveal a higher intersubject or intrasubject variability. Due to the very long half-life of nitisinone, the PK samples were collected for only 72 hours and truncated AUC_{72h} was used in the analysis.

Table 1: 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	3.50	403
		(8030 - 18000)	(0.75 - 8.00)	(315 - 500)
	suspension fasting	9741	0.38	346
		(7780 - 20300)	(0.25 - 4.00)	(264 - 456)
PPSFE (N=11)	suspension fasting	9807	0.50	347
		(7780 - 20300)	(0.25 - 4.00)	(264 - 456)
	suspension fed	7715	8.00	343
		(5300 - 12500)	(3.50 - 10.00)	(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.

Proposed Orfadin Suspension vs. Approved Orfadin Capsule: Bioequivalence under fasting conditions

Bioequivalence testing was conducted and the corresponding geometric mean ratios (and 90% CI) for C_{max} and AUC are presented in Table 2.

Table 2: Statistical analysis of bioequivalence.

Parameter	Geometric LS means		Ratio suspension/ capsule [90% CI] ^b		
	Capsule fasting	Suspension fasting	Estimate	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.

The 90% confidence intervals for the oral suspension/capsule ratios under fasting conditions were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max} and AUC_{72h}.

Orfadin Suspension: Food Effect on nitisinone PK

Statistical analysis of the food effect for the suspension formulation is presented in Table 3. The 90% confidence interval for AUC_{72h} of the fed/fasting ratio was within the bioequivalence range (0.80 to 1.25). However, 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. The sensitivity analysis results with the full analysis population (FAS) are consistent with those for the per-protocol set for food effect analysis, with a fed/fasting ratio for C_{max} of 0.80 and 90% CI of 0.71-0.90.

Table 3: Statistical analysis of the food effects.

Population ^a	Parameter	Geometric LS means		Estimate	Ratio fed/fasting [90 % CI] ^b	
		Suspension fasting	Suspension fed		Lower	Upper
FAS	AUC _{72h} (μM·h)	346	350	1.013	0.96	1.07
	C _{max} (nM)	9741	7808	0.802	0.71	0.90
PPSFE	AUC _{72h} (μM·h)	342	346	1.012	0.93	1.09
	C _{max} (nM)	9627	7844	0.815	0.74	0.90

CI = confidence interval; LS = least squares.

FAS = Full analysis set (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.

Administration of a single 30 mg dose of nitisinone as an oral suspension (7.5 mL; 4 mg/mL) under fasting and fed conditions provided equivalent AUC_{72h}, but failed the BE criteria for C_{max}. Because of the long half-life of nitisinone and the BID dosing, the accumulation ratio is estimated to be 7.0 and 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.

Inspection of the BE study by OSIS:

A request to conduct an inspection of the clinical and bioanalytical sites for the BE study was submitted to the Office of Study Integrity and Surveillance (OSIS). Based on the recent inspection results unrelated to this study, OSIS considers the conduct of the clinical and bioanalytical sites for this study acceptable without an on-site inspection (see Appendix II).

Formulation of the proposed Orfadin suspension:

The composition of the suspension for the proposed drug product is shown in the table below:

Ingredient	Quantity (mg)	Function
Nitisinone	4.0	Active substance
Hydroxypropyl methylcellulose (HPMC)		(b) (4)
Glycerol		
Polysorbate 80		
Sodium benzoate		
Citric acid monohydrate		
Trisodium citrate dihydrate		
Strawberry aroma		
Water, purified		

2 Individual Study Review: Sobi.NTBC-001

Title: A study 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. An open-label, randomized, cross-over, single-dose study in healthy volunteers

Sponsor: Swedish Orphan Biovitrum AB
 Clinical Site: PRA, Stationsweg 163, 9471 GP Zuidlaren, The Netherlands
 Bioanalytical Site: (b) (4)
 Pharmacogenomic: Not applicable
 Study Date: 08/29/2012 – 10/25/2012

Study Objectives:

- To show bioequivalence between nitisinone oral suspension and nitisinone capsules.
- To assess the effect of food on the bioavailability of nitisinone oral suspension.
- To assess selected PK variables for nitisinone capsules and suspension, the latter given with and without food, at a single oral dose of 30 mg.
- To assess the tolerability and safety of nitisinone capsules and suspension, the latter given with and without food, after single oral doses of 30 mg.

Study Design:

This was an open, randomized 3-way crossover study in 12 healthy volunteers. Subjects received single oral 30-mg doses of nitisinone as a suspension (under fasting and fed conditions) and as capsules (fasting only). There was a 2-week washout period between the doses.

Treatment	Investigational medicinal product	Route and mode of administration	Dosing regimen
A	Orfadin capsules, 10 mg	Oral, fasting	Single dose, 30 mg (3 capsules)
B	Orfadin suspension, 4 mg/mL	Oral, fasting	Single dose, 30 mg (7.5 mL)
C	Orfadin suspension, 4 mg/mL	Oral, with food	Single dose, 30 mg (7.5 mL)

Excluded Medications and Dietary Products

All regular use of non-topical medications was prohibited from 1 month before the first admission. All other medication (including over-the-counter medication, health supplements, and herbal remedies) had to be stopped at least 14 days prior to the first admission.

None of the subjects used concomitant medication during this study.

Study Population: The study included healthy male volunteers aged 18-55 years, inclusive, with a BMI between 18.5-30.0 kg/m². 12 volunteers were enrolled and all 12 volunteers received study medication and completed the study as per protocol, except for Subject 003 who did not complete his breakfast when the suspension was administered after food intake. Subject 003 was included in the full analysis set and per protocol set for bioequivalence, but excluded from per protocol set for food effect analysis.

Three analysis populations were used to assess the PK by the sponsor:

- The full analysis set (FAS) was used in the analysis of variance (ANOVA). subjects with available AUC_{72h} and C_{max} data for at least one of the treatments.
- Per-protocol set (bioequivalence) (PPSBE) was used for descriptive statistics: subjects with available PK data for capsule fasting and suspension fasting treatments.
- Per-protocol set (food effect) (PPSFE) was used for descriptive statistics: subjects with available PK data for suspension fasting and suspension fed treatments.

Pharmacokinetic Measurements:

Blood PK samples were collected at predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours postdose in each period to determine serum nitisinone concentrations.

PK Parameters Analysis:

Pharmacokinetic parameter estimates for nitisinone, were calculated using WinNonlin Professional Version 5.0.1 with non-compartmental methods.

Statistical analysis was performed using a pre-defined ANOVA model to compare the log-transformed PK parameters AUC_{72h} and C_{max} of nitisinone. The ANOVA model included sequence, treatment and period as fixed effects and subject nested in sequence as a random effect. Bioequivalence (BE) between the regimens was concluded if the 90% CIs would fall within 0.80 to 1.25 for both AUC_{72h} and C_{max}.

Due to a period effect observed for both AUC72h and Cmax, the sponsor also conducted post-hoc sensitivity analyses by including a treatment by period interaction in the statistical model, in addition to the effects described above.

Bioanalytical Method:

Bioanalytical analysis of nitisinone in the serum samples was performed at (b) (4) Serum samples were stored frozen at -20°C or colder until analysis.

Serum nitisinone concentrations were measured using a protein precipitation liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with electrospray detection in negative mode and using [¹³C₆] nitisinone as an internal standard. The assay method had a lower quantification limit of 60 nM for nitisinone using 20 µL of serum. Dilution integrity was demonstrated for a 10-fold dilution.

Assay validation calibration standard curve consisted of 9 levels ranged from 60 to 50000 nM in human serum, and was calculated using least squares quadratic regression with the reciprocal of the concentration (1/x) as weighting. The R² ranged between 0.9972 and 0.9998. Precision (% CV) for the calibration standards ranged from 1.3% to 7.8%, while accuracy (% Bias) ranged from -5.1% to 6.6%. Overall mean recovery of nitisinone at 60, 1500, and 40000 nM was 100.9%, 100.7%, and 97.9%, respectively. Stability of nitisinone in human serum was demonstrated to be 28 hours at room temperature and 122 days at -20 °C. Stability was shown up to four freeze-thaw cycles. No matrix interference was noted.

Calibration standard curve for this study consisted of 9 levels ranged from 60 to 50000 nM in human serum, and the R² ranged between 0.9973 and 1.0000. Quality control samples at 3 different concentrations (180, 2750, and 40000 nM) of nitisinone were prepared. Precision (%CV) for the calibration standards for this study ranged from 1.2% to 5.0%, while precision for the quality controls ranged from 3.5% to 3.9%. Accuracy (%Bias) ranged from -2.5% to 2.5% for calibration standards, and from -1.5% to 2.0% for quality controls. No interfering peaks (>20% of the LLOQ) were detected at the expected retention time of the analyte or internal standard. There were 72 samples (10.5% of a total of 684 analyzed samples) reanalyzed to test the reproducibility of the method. Acceptance criteria were met for incurred sample reanalysis as 75% (54 out of 72) of the repeat results and original results were within 20% of their mean value.

There were 4 samples reanalyzed for analytical reasons (0.58% of the total). All 4 samples contained a high internal standard response upon initial analysis. The repeat results confirmed the original results therefore the original result was reported.

Reviewer's Note: The largest percent difference between the repeated result and the original value was 10.4%.

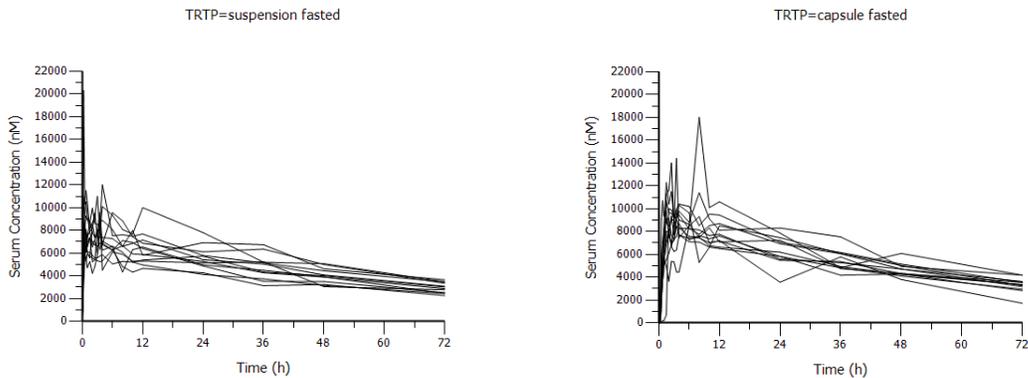
Pharmacokinetics Results:

Concentration-time profiles for suspension and capsule under fasting conditions:

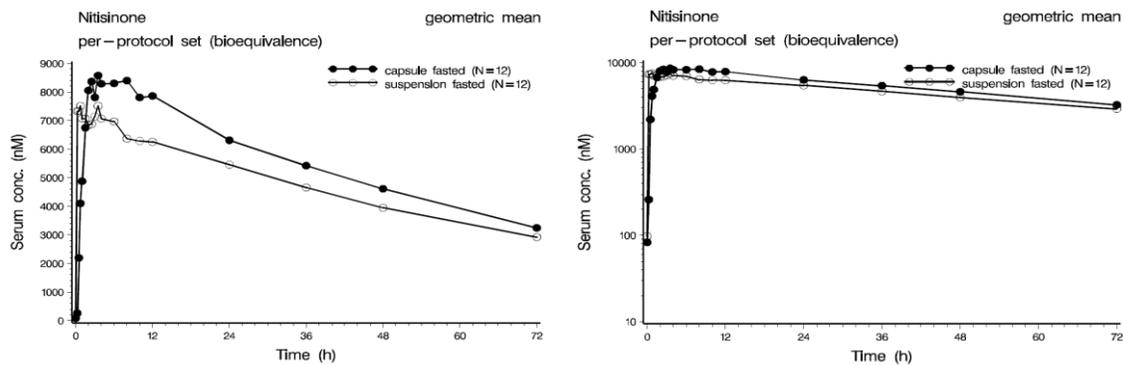
After administration of the capsule under fasting conditions, individual profiles had multiple peaks up to several hours after dosing.

After administration of the suspension under fasting conditions, the pattern was similar with multiple peaks occurring during the absorption phase. The mean profile showed 2 almost equally high maxima; one at 45 minutes and the other at 3.5 hours postdose. During the first 1.5 hours postdose, the mean concentrations for the suspension exceeded those of the capsule, but from 2 hours onward the concentrations for the suspension were lower than for the capsule.

Combined individual plots of serum concentration profiles for the suspension (left) and capsules (right) under fasting conditions (N=12).



Geometric mean nitisinone serum concentration-time profiles for suspension and capsule under fasting conditions

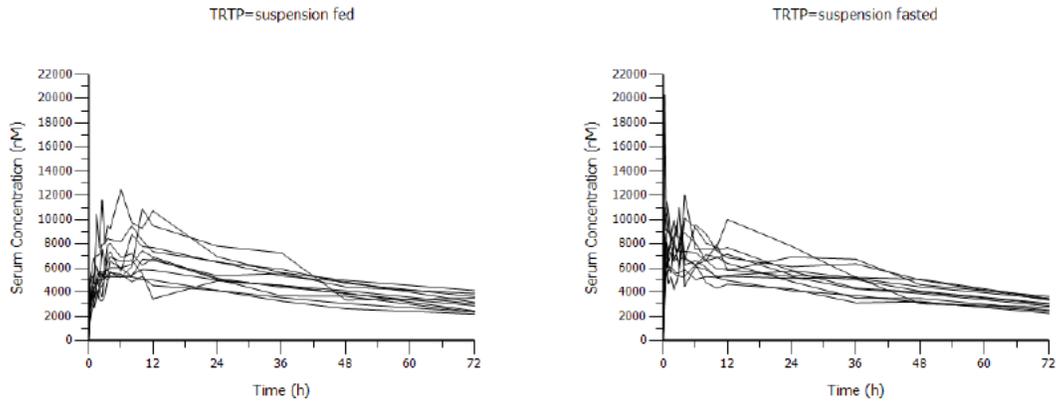


Concentration-time profiles for suspension under fed and fasting conditions

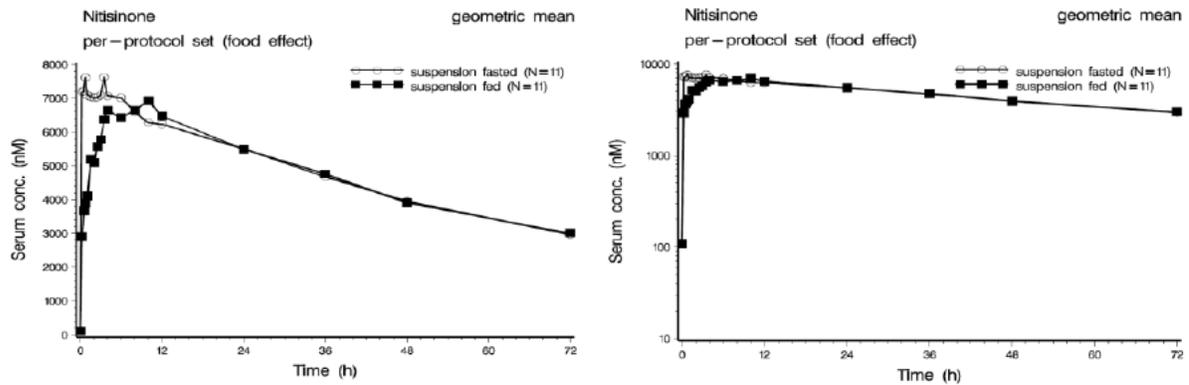
Administration of the nitisinone suspension under fed conditions resulted in a slower absorption than for the 2 fasting administrations described above. Multiple peaks were also seen here during the absorption phase, with the maximum concentrations usually appearing either at 3.5 to 4 hours (5 subjects) or 8-10 hours (6 subjects). One subject

showed a maximum at 6 hours. This was reflected in the mean serum concentration profile which showed one peak at 4 hours and another one at 10 hours.

Combined individual plots of serum concentration profiles for the suspension administered under fed (left) and fasting (right) conditions (N=11).



Geometric mean nitisinone serum concentration-time profiles for the suspension administered under fed and fasting conditions



Summary of PK parameters

Summary of the PK parameters C_{max}, t_{max}, AUC_{72h} 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); PPSFE = Per-protocol set (food effect).

Analysis of bioequivalence between Orfadin oral suspension and capsules

The 90 % CI of the ratio suspension/capsule of C_{max} (0.85 - 1.07) and AUC_{72h} (0.81 - 0.91) were within the 0.80 - 1.25 acceptance range for bioequivalence. The point estimate for C_{max} was 0.954 and for AUC_{72h} was 0.858.

Parameter	Geometric LS means		Ratio suspension/ capsule [90% CI] ^b		
	Capsule fasting	Suspension fasting	Estimate	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.

Analysis of food effect on the bioavailability of Orfadin oral suspension

The comparison of AUC_{72h} resulted in a 90 % CI of 0.93 – 1.09 for the food effect analysis set, indicating that food did not influence the bioavailability of nitisinone. The fed/fasting ratio for C_{max} was 0.815, with a 90 % CI of 0.74-0.90 in the per-protocol set for food effect analysis. The sensitivity analysis results with the full analysis population are consistent with those for the per-protocol set for food effect analysis, with a fed/fasting ratio for C_{max} of 0.802 and 90% CI of 0.71-0.90.

Population ^a	Parameter	Geometric LS means		Ratio fed/fasting [90 % CI] ^b		
		Suspension fasting	Suspension fed	Estimate	Lower	Upper
FAS	AUC _{72h} (μM·h)	346	350	1.013	0.96	1.07
	C _{max} (nM)	9741	7808	0.802	0.71	0.90
PPSFE	AUC _{72h} (μM·h)	342	346	1.012	0.93	1.09
	C _{max} (nM)	9627	7844	0.815	0.74	0.90

CI = confidence interval; FAS = Full analysis set (n=12); LS = least squares; PPSFE = Per-protocol set for food effect analysis (n=11).

Reviewer's Comments:

- *This study was conducted in 12 healthy male volunteers only. No female volunteers were included. This approach is being allowed because another BE study in both male and female subjects for the capsule formulation revealed a low variability in the study.*
- *In this BE/food-effect study, the sponsor evaluated AUC72h instead of AUCinf in this BE study, citing the long half-life of nitisinone (54 hours). This approach is acceptable. Per the current FDA guidance, an AUC truncated at 72 hours (AUC0-72 hr) can be used in place of AUC0-t or AUC0-inf for drugs that demonstrate low intrasubject variability in distribution and clearance. Intrasubject variability for nitisinone is not reported by the sponsor. Reviewer's analysis results indicate that intrasubject variability on Cmax and AUC72h of nitisinone is less than 30%.*
- *The bioanalytical method used to determine serum nitisinone concentrations is acceptable. A request to conduct a thorough inspection of the clinical and bioanalytical sites to determine acceptability of the data has been submitted to the Office of Study Integrity and Surveillance (OSIS). OSIS recommends accepting data without an on-site inspection of the clinical site or bioanalytical site.*
- *A washout period of 2 weeks is reasonable as the mean t1/2 of nitisinone in healthy male volunteers was reported as 54 hours previously (Orfadin label approved on 05/21/2014). At the start of Periods 2 and 3, predose concentrations for nitisinone were quantifiable in all subjects, but were all less than 5 % of the corresponding Cmax value.*
- *The sponsor's PK analysis and PK bioequivalence have been repeated by the reviewer. The results confirmed the sponsor's conclusion that the oral suspension (7.5 mL; 4 mg/mL) is bioequivalent to the three 10-mg capsules under fasting conditions. The 90 % CI for both AUC72h and Cmax were contained entirely*

within the 0.80 - 1.25 range for bioequivalence. The reviewer's analysis results are presented below.

Reviewer's bioequivalence analysis for suspension formulation and capsule formulation under fasting conditions:

Population	Parameter	Geometric LS Means		Ratio (Suspension fasting/Capsule fasting)		
		Capsule fasting (reference)	Suspension fasting (test)	Estimate (%)	Lower 90% CI	Upper 90% CI
FAS	AUC72h (µM*h)	403	346	85.84	81.03	90.93
	Cmax (nM)	10213	9741	95.38	84.99	107.04
PPSBE	AUC72h (µM*h)	403	346	85.84	81.58	90.32
	Cmax (nM)	10213	9741	95.38	83.22	109.31

- *The sponsor's food effect analyses have been repeated by the reviewer. The results confirmed the sponsor's conclusion that an oral suspension (7.5 mL; 4 mg/mL) under fasting and fed conditions provided equivalent AUC72h, but failed the BE for Cmax.*

Reviewer's food effect analysis for suspension formulation:

Population	Parameter	Geometric LS Means		Ratio (Suspension fed/Suspension fasting)		
		Suspension fasting (reference)	Suspension fed (test)	Estimate (%)	Lower 90% CI	Upper 90% CI
FAS	AUC72h (µM*h)	346	350	101.3	95.62	107.3
	Cmax (nM)	9741	7808	80.16	71.43	89.96
PPSFE	AUC72h (µM*h)	342	346	101.16	93.46	109.49
	Cmax (nM)	9627	7844	81.48	73.86	89.89

In addition, the reviewer also performed the food-effect analysis comparing the bioavailability between the suspension formulation (fed) vs capsules (fasting). The results indicate that AUC72h is also similar between the suspension formulation (fed) and capsules (fasting), but failed the BE for Cmax.

Reviewer's food effect analysis for suspension formulation (fed) vs capsules (fasting):

Population	Parameter	Geometric LS Means		Ratio (Suspension fed/Capsule fasting)		
		Capsule fasting (reference)	Suspension fed (test)	Estimate (%)	Lower 90% CI	Upper 90% CI
FAS	AUC72h (µM*h)	403	350	86.95	82.08	92.11
	Cmax (nM)	10213	7808	76.45	68.12	85.8

PPSFE	AUC72h ($\mu\text{M}\cdot\text{h}$)	396	345	87.08	81.78	92.72
	C _{max} (nM)	9965	7871	78.99	70.06	89.06

Based on the half-life of nitisinone, the accumulation ratio is estimated to be 7 following BID dosing. At steady state the C_{max} ratio (suspension/fed vs suspension/fasting) will be greatly influenced by the AUC ratio for the single dose administration. This is due to the long half-life and BID dosing. As such, the difference in C_{max} observed following single dose administration will be diminished at steady state.

- ***The ADME characteristics and DDI potential information from the package insert of approved Orfadin Capsules is noted below:***

Per the approved label for Orfadin capsules, the median t_{max} of nitisinone was 3 hours following a single-dose of nitisinone. The effect of food on the pharmacokinetics of nitisinone following administration of Orfadin capsules has not been studied. In vitro binding of nitisinone to human plasma proteins is greater than 95% at 50 μM concentration. In vitro studies have shown that nitisinone is relatively stable in human liver microsomes with minor metabolism possibly mediated by CYP3A4 enzyme. The mean terminal plasma half-life of nitisinone was 54 hours.

Based on in vitro studies, there is a potential for nitisinone to inhibit CYP2C9 at clinical dose. Nitisinone is not expected to inhibit CYP 1A2, 2C19, or 3A4 based on in vitro studies. Nitisinone's potential to inhibit CYP2D6 and CYP2E1 at the clinical dose is unknown due to limited data.

Appendix I: OCP Filing Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206356

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	206356	Brand Name	Orfadin	
OCP Division (I, II, III, IV, V)	DCPIII	Generic Name	Nitisinone	
Medical Division	DGIEP	Drug Class	hydroxyphenyl-pyruvate dioxxygenase inhibitor	
OCP Reviewer	Sandhya Apparaju, Ph.D.	Indication(s)	(b) (4) Hereditary Tyrosinemia Type 1 (HT- I)	
OCP Team Leader	Sue Chih Lee, Ph.D.	Dosage Form	4 mg/mL Oral suspension	
Pharmacometrics Reviewer	N/A	Dosing Regimen	1- 2 mg/kg/day (b) (4)	
Date of Submission	06/22/2015	Route of Administration	Oral	
Estimated Due Date of OCP Review	02/22/2016	Sponsor	Swedish Orphan Biovitrum	
Medical Division Due Date		Priority Classification	Standard	
PDUFA Due Date	April 22, 2016 (tentative)			
<i>Clinical Pharmacology and Biopharmaceutics Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	2		BE study Sobi.NTBC-001; Taste and palatability study Sobi.NTBC-002
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Method validation report Bioanalytical report
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA 206356**

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X			Conducted as part of the pivotal BE study
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	2	1	The 2 nd study is a taste and palatability study;

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information? (RTF only if information is completely absent)	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			

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5	Has a rationale for dose selection been submitted?	X			BE study used 30 mg in all groups; Nitisinone dose is individualized by BW and response (1-2 mg/kg/day)
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Dosing recommendations are per approved labeling for Orfadin capsules, assuming a bioequivalent formulation.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and	X			

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	biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Submit *in vitro* study reports for review, in order to support your proposed labeling language related to drug metabolism and drug-drug interaction potential for nitisinone.

Sandhya Apparaju, Ph.D.	Date
Reviewing Clinical Pharmacologist	
Sue Chih Lee, Ph.D.	Date
Team Leader/Supervisor	

Clinical Pharmacology Filing memo

This eCTD application, NDA 206356, concerns a new dosage form, an oral suspension, of the product Orfadin (nitisinone) 2 mg, 5 mg and 10 mg hard capsules, NDA 21-232, approved by the FDA 18th of January 2002 for the treatment of an inborn error of metabolism disease ‘hereditary tyrosinemia’ (HT-1), in combination with dietary restrictions of tyrosine and phenylalanine. This application is a re-submission of an application that was originally submitted in October 2013 and was withdrawn in December 2013 (b) (4)

Orfadin is approved for HT-1 in the form of hard capsules (2 mg, 5 mg and 10 mg). According to sponsor, presently, approximately (b) (4) patients are treated with Orfadin capsules worldwide. The majority of patients currently treated with Orfadin are infants and children. Treatment should, if possible, be initiated as early as a couple of weeks after birth, and is life-long. The (b) (4) dose is 1 mg/kg/day divided in 2 doses, and the maximum dose is 2 mg/kg/day

For ease of pediatric patient use, sponsor has developed a suspension formulation of nitisinone (4 mg/mL) and has conducted a pivotal BE/food-effect study in healthy adult volunteers and a taste & palatability study in pediatric patients in support of this application. Labeling has been provided with the various sections populated, subject to review. The inactive ingredients of the new suspension are hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dehydrate, strawberry aroma (artificial) and purified water.

A tabular list of the two studies submitted in the NDA is provided below; there is no additional clinical trial data; the pivotal bioequivalence aspects of study Sobi.NTBC-001 (including analytical methodology review, request of OSI inspection & review of findings) will be conducted by OCP. Study Sobi.NTBC.002 (taste and palatability trial) doesn’t appear to include PK or efficacy information. However, the dosing was done in pediatric patients with HT-1 and may provide some safety information

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206356

in the target pediatric population, along with the BE trial in healthy volunteers. Review of this study will not be an OCP responsibility.

Study nr	Study objectives	Study design	Treatments	Subjects	Main variables
Sobi.NTBC-001 (Netherlands)	To assess bioequivalence between nitisinone oral suspension and nitisinone capsules; effect of food on the bioavailability of nitisinone oral suspension; safety	Open, randomized, 3-way crossover study, single-center study	Orfadin suspension containing 4 mg/mL nitisinone: Dose: 30 mg (7.5 mL), oral. Batch number: 3014653 Orfadin capsule, containing 10 mg nitisinone: Dose 30 mg (3 capsules), oral. Batch number: 3012535	Healthy male volunteers, aged 18-55 years (inclusive). n=12	AUC _{72h} and C _{max} (suspension and capsules under fasting conditions, suspension with food), t _{max} , safety assessments
Sobi.NTBC-002 (UK, Germany, France)	To assess acceptability of the oral suspension in the pediatric population; safety	Open, non-randomized, non-controlled, multi-center study	Orfadin suspension containing 4 mg/mL nitisinone. Dose as determined by the investigator based on each patient's current prescribed dose, oral. Batch number: 3015416	Pediatric patients diagnosed with HT-1, aged 1 month to <18 years. n=18	Patient questionnaire data on taste, palatability and acceptability, safety assessments

AUC_{72h} = the area under the serum concentration vs. time profile curve during 72 hours after dose; C_{max} = the maximum serum concentration; HT-1 = hereditary tyrosinemia type 1; t_{max} = time to reach C_{max}; UK = United Kingdom

Per sponsor, bioequivalence of the two formulations was demonstrated. The 90 % confidence interval (CI) for the ratio of means of suspension and capsule fasting treatments for C_{max} (0.85 - 1.07) and AUC_{72h} (0.81 - 0.91) were within the predefined 0.80 - 1.25 acceptance range for bioequivalence. The point estimate for C_{max} was 0.954 and for AUC_{72h} 0.858. Sponsor evaluated AUC_{72h} instead of AUC_{inf}, citing the long half-life of nitisinone (54 hours) in this BE study. This will be a review issue.

According to the sponsor, food did not affect the bioavailability of Orfadin suspension (pending review). The comparison of AUC_{72h} resulted in a 90% CI of 0.96 – 1.07 for the fed/fasting ratio. When the suspension was administered with food, the fed/fasting ratio for C_{max} was 0.802, with a 90 % CI of 0.71-0.90, reflecting a slower absorption of nitisinone under fed conditions. There were differences in median T_{max} for the capsule vs. suspension under fasted conditions (faster absorption from suspension), as well as for the new suspension under fed vs. fasted conditions (slower absorption of the suspension under fed conditions). The relevance of this finding will be a review issue; Sponsor notes the following in the draft labeling regarding dosing and food intake: “Food does not influence the bioavailability of nitisinone, but intake together with food decreases the absorption rate and consequently leads to lower fluctuations in serum concentrations within a dosage interval”.

Approved nitisinone oral capsule is labeled for dosing at least one hour before or at least two hours after a meal (i.e. fasted), since food-effect on PK from the capsule is unknown. The proposed labeling which includes both capsules and the new suspension recommends (b) (4)

This dosing proposal will be evaluated as a review issue.

Analytical methods: Serum nitisinone concentrations were determined using validated LC-MS/MS methodology. Analytical method validation and bioanalytical report for the pivotal study were located:

For the BE study, the details of the bioanalytical investigator and principal investigator are provided below (also available in the report):

NDA Sponsor: Tommy Andersson
Swedish Orphan Biovitrum AB
SE-112 76
Stockholm
Sweden

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Study title: Validation of an Analytical Procedure for the Determination of Nitisinone concentrations in Human Serum using Protein Precipitation followed by Liquid Chromatography with Tandem Mass Spectrometric Detection (LC-MS/MS) [Validated method HB-12-102; (b) (4) Report number 8267467]

Location: 5.3.1.2. Sobi-NTBC-001- Study Report Body- Validation of nitisinone concentration in human serum; [Application 206356 - Sequence 0003 - Sobi.NTBC-001 - Validation of Nitisinone concentration in human serum](#)

Study title: Sobi.NTBC-001- Determination of Nitisinone in Human Serum Samples from a Study 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. An Open-Label, Randomized, Cross-Over, Single-Dose Study in Healthy Volunteers

Location: 5.3.1.2. Sobi-NTBC-001- Study Report Body- CSR Appendix 1- Study Information- Section 1.10 Bioanalytical Report; [Application 206356 - Sequence 0000 - Sobi.NTBC-001 CSR Appendix 1](#)

Bioanalytical investigator

(b) (4)

(b) (4)

Clinical study number Sobi.NTBC-001- A study 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 - an open-label, randomized, cross-over, single-dose study in healthy volunteers.
PRA code: SOB042EC-120421

Principal investigator

Nada Al Kotbi, MD
alkotbinada@praintl.com
Telephone +31 (0)50 402 2326

Pharmaceutical Research Associates Group
B.V. (PRA), Early Development Services
Zuidlaren, The Netherlands

Sponsor's Medical Officer

Maarten de Chateau, MD, PhD
Swedish Orphan Biovitrum AB
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E-mail maarten.dechateau@sobi.com

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206356

Study design: Sponsor utilized C_{max} and AUC_{0-72 h} as the primary endpoints for BE assessment. The following is an excerpt from the BA/BE guidance for evaluation of drugs with long half-life (defined by guidance as > 24 h); nitisinone has a T_{1/2} of ~ 54 h.

D. Long-Half-Life Drugs

In a BA or PK study involving an IR oral product with a long half-life (≥ 24 hours), adequate characterization of the half-life should include blood sampling over a long period of time. For BA or BE determination of a drug product containing a drug with a long half-life, a nonreplicate, single-dose, crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a study with a parallel design can be used. For either a crossover or parallel study, we recommend that the sample collection time be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. C_{max} and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, a truncated AUC (e.g., AUC_{0-72 hr}) can be used in place of AUC_{0-t} or AUC_{0-∞}. For drugs that demonstrate high intrasubject variability in distribution and clearance, AUC truncation should not be used. In such cases, we recommend that sponsors and/or applicants consult the appropriate review division.

Label: Labeling that incorporates both the approved capsule and suspension formulation has been provided in PLR format.

7 DRUG INTERACTIONS

(b) (4)

12.3. Pharmacokinetics

No pharmacokinetic studies of nitisinone have been conducted in children or HT-1 patients.

The single-dose pharmacokinetics of nitisinone have been studied in ten healthy

(b) (4)

(b) (4)

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/s/

SANDHYA K APPARAJU
07/17/2015

SUE CHIH H LEE
07/17/2015

Reviewed for fileability determination only. A thorough review will be conducted later.

Appendix II: OSIS Inspection Reports

A. Clinical Study Site

MEMORANDUM

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

DATE: 12/2/2015

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 206356

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the nature of the findings from the last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	PRA Health Sciences Zuidlaren	Stationweg 163, 9471 GP Zuidlaren, The Netherlands

Reference ID: 3855034

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/s/

SHILA S NKAH
12/02/2015

Reference ID: 3855034

B. Analytical Site

MEMORANDUM

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

DATE: 10/12/2015

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 206356

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

Reference ID: 3832116

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/s/

SHILA S NKAH
10/12/2015

Reference ID: 3832116

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/s/

SHEN LI
03/25/2016

SUE CHIH H LEE
03/25/2016