CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206356Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 22, 2016
From	Dragos Roman, MD, Associate Director /Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
NLA #/Supplement #	NDA 206356
Applicant Name	Swedish Orphan Biovitrum
Date of Submission	June 22, 2015
PDUFA Goal Date	April 22, 2016
Proprietary Name / Established (USAN) Name	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
Action/Recommended	Approval

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer /CDTL Review	Laurie Muldowney, MD
Nonclinical Review	D. Gautam, PhD. S.Chakder, PhD
OPQ Review	D. Ghosh, D. Christner, PhD, H. Cai, PhD, M.J. Rhee, PhD, X Shen, CSO, E Kim, PhD, J Williams PhD, M. Ou, PhD, A. Chen, PhD, D Bateman, PhD, J Cole, PhD, D. Gromeck-Woods, PhD,
Clinical Pharmacology Review	S. Li, PhD/S. Lee, PhD
Labeling Review (OPDP, DMPP)	Adewale Adeleye, Pharm.D.,
Labeling Review (OSE/DMEPA)	Sherly Abraham, R.Ph.,Mishale Mistry, Pharm.D., MPH, Lubna Merchant, Pharm.D., M.S.
DPMH	Donna Snyder, MD, John Alexander, MD, MPH, Leyla Sahin, M.D., Tamara Johnson, M.D., M.S., Lynne P. Yao, M.D.

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
DPMH = Division of Pediatric and Maternal Health
OPDP= Office of Prescription Drug Promotion
DMPP: Division of Medical Policy Programs
OPQ: Office of Pharmaceutical Quality
DMEPA: Division of Medical Error Prevention and Analysis

1. Introduction

In this NDA supplement Swedish Orphan Biovitrum submits for approval a new formulation, an oral suspension of Orfadin (nitisinone). Currently, Orfadin is available as oral capsules in three dose strengths: 2 mg, 5 mg, and 10 mg. The indication sought for the oral formulation is the same as that approved for oral capsules under NDA 21,232 (initial approval, January 18, 2002): treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. A liquid formulation is desirable for children of younger ages (currently, capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce for use).

This supplemental NDA was submitted under Section 505(b)(1) of the Food, Drug, and Cosmetic Act. To support the approval of the oral suspension formulation, the applicant conducted a bioequivalence study in healthy adult volunteers comparing a single 30 mg dose of Orfadin suspension to 30 mg (3x 10 mg capsules) of the approved Orfadin formulation. The dosing regimen intended for the proposed suspension (b) (4) The review of this application was conducted as a Standard review.

2. Background

Hereditary tyrosinemia type 1 (HT-1) is a rare inborn error of metabolism with autosomal recessive pattern of inheritance. The biochemical defect in HT-1 is a deficiency of the final enzyme of the tyrosine catabolic pathway, fumarylacetoacetate hydrolase (FAH). FAH deficiency leads to the accumulation of toxic tyrosine metabolites, progressive liver dysfunction early in life (and an increased risk for hepatocellular carcinoma), impaired coagulation, renal Fanconi syndrome, renal failure, hypophosphatemic rickets, and painful neurological crises (porphyria-like). As with many other inborn errors of metabolism, the clinical phenotype is variable with acute (liver failure before age 6 months), sub-acute, and chronic forms being described. Disease incidence is estimated as one in 100,000 births.

Nitisinone is the only drug approved in the US for the treatment of HT-1. It is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme that converts 4-hydroxyphenylpyruvate to homogentisate; as such, nitisinone prevents the increase in maleylacetoacetate (MAA) and fumarylacetoacetate (FAA), two metabolic intermediates that are in excess in HT-1, and are converted into the toxic metabolites succinylacetone (SA) and succinylacetoacetate (SAA). Nitisinone treatment results in a normalization of urinary SA levels within weeks and plasma SA levels within months, and has favorable consequences on succinylacetone dependent porphyrin metabolism (normalizes erythrocyte porphobilinogen synthase activity and urine 5-ALA). Because it inhibits an enzyme in the tyrosine metabolic pathway, nitisinone may also cause am increase in blood concentration of tyrosine and its

precursors which, when in excess (>500 µmol/L for tyrosine), can lead to ocular pathology (corneal ulcers and opacities, keratitis, conjunctivitis, eye pain, and photophobia), mental retardation/developmental delay, and painful hyperkeratotic plaques on the soles and palms. Therefore nitisinone must be used in combination with a diet restrictive in phenylalanine and tyrosine.

Of note, the applicant had submitted an NDA for an oral suspension of nitisinone in 2013, but later withdrew it. At the time, the drug product was (b) (4) In the end, the applicant decided to withdraw the application.

Subsequently, the applicant decided to market the product simply as a bottle (b) (4) and sought agreement from the Agency regarding this simplified approach. In a Written Response Only communication issued on June 8, 2015, FDA confirmed that this approach is acceptable.

3. CMC/Device

I concur with the OPQ recommendation of approval. In making this recommendation, the OPQ reviewer notes that the applicant has provided "sufficient CMC information to assure the identity, strength, purity, and quality of the drug product." The facilities involved in this application were found to be acceptable by the Office of Facility and Process. There were no recommendations for any PMRs or PMCs.

The drug substance (nitisinone) for the Orfadin suspension is the same as for the approved Orfadin capsules (the applicant referenced CMC information from the original NDA). The drug substance (b) (4) formulated in hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dehydrate, strawberry aroma (artificial), and purified water at a concentration of 4 mg/mL. The excipients used in the suspension are well established that are considered safe from a CMC perspective. The proposed specifications were found to be acceptable. Impurities were in compliance with ICH Q3B (R2) guidelines. Stability data support an expiration period of 36 months; a categorical exclusion from the environmental assessment was granted.

Because the drug product settles and forms a cake during storage, it requires vigorous

shaking to achieve uniform suspension and ensure dosing accuracy. Specifically, such shaking needs to be done for at least (b) (4) seconds prior to removal of the first dose from the bottle, and for a minimum of 5 seconds prior to withdrawal of each subsequent dose (i.e., subsequent resuspensions are facilitated by the original vigorous suspension). The Drug Product reviewer concludes that the applicant demonstrated acceptable dose accuracy and content uniformity of the drug product (b) (4)

Of note, proper dose withdrawal requires the use of a push-in bottle adaptor (PIBA) which allows patients or parents/caregivers to turn the bottle upside down, and withdraw the appropriate dose with a syringe that fits tightly in the PIBA. (b) (4) the applicant intends to rely on a single source pharmacy to ensure that the appropriate materials (syringe and push-in bottle adapter) are provided to patients. Given the rarity of the disease, and the use of a single source pharmacy, the proposal was found to be acceptable by the CMC and clinical teams, as long as the labeling provides adequate instructions. It is worth noting that during the review of the application, several other options were discussed, (refer to Dr. Muldowney's CDTL review, CMC section for details).

4. Nonclinical Pharmacology/Toxicology

I am in agreement with the nonclinical team's recommendation for approval without additional PMCs or PMRs. The applicant did not submit any new nonclinical studies of nitisinone in this application. Three new degradation products have been identified for this new formulation. The applicant assessed the genotoxic potential of these impurities through a computational toxicology based assessment and through *in vitro* and *in vivo* genotoxicity assays. The nonclinical reviewer concludes that "there are no safety concerns for the impurities/degradants in the drug product, and no pharm-tox related safety issues were identified for ORFADIN (nitisinone) oral suspension." Of note, some of these degradants showed a potential genotoxic profile; nitisinone itself is also predicted to be mutagenic in the mouse lymphoma cell (L5178Y/TK+/-). The reviewer notes that "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 impurities are all qualified per ICH Q3A.

5. Clinical Pharmacology/Biopharmaceutics

I agree with the recommendation for approval made by the clinical pharmacology team.

In support of the new oral suspension formulation of nitisinone, the applicant conducted Study Sobi.NTBC-001, a bioequivalence and food-effect study. Study Sobi.NTBC-001 was designed as an open-label, randomized, cross-over, single-dose study conducted in healthy volunteers. It compared a single 30 mg dose of Orfadin suspension to

Orfadin capsules (3x 10 mg capsules); in addition, it evaluated the effect of food on the bioavailability of the suspension by evaluating bioequivalence under fasting and fed conditions. The study was conducted in twelve healthy subjects, ages 18 to 55 years.

The study demonstrated bioequivalence between the oral capsule and liquid suspension formulations: the 90% confidence intervals for the ratio of Orfadin oral suspension/capsule was contained entirely within the bioequivalence range of 0.80 to 1.25 with respect to Cmax and AUC_{72h}, as shown in Table 2 below, reproduced from page 3 of the clinical pharmacology review. The comparison was done under fasting conditions.

Table 2: Statistical analysis of bioequivalence.

	Geometric LS means		Ratio suspension/ capsule [90% CI] [b]		
Parameter	**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.

With respect to the food effect, bioequivalence criteria were met only for AUC_{72h} (90% confidence interval for AUC_{72h} of the fed/fasting ratio was within the bioequivalence range of 0.80 to 1.25), but failed the BE criteria for C_{max} (the 90 % CI was 0.74-0.90 for the per-protocol analysis; similar results were observed for the full analysis population, with a 90% CI of 0.71-0.90). The clinical pharmacology reviewer considers that the difference in C_{max} under fed and fasting conditions is not significant (refer to page 13 of the clinical pharmacology review), and recommends that the suspension be taken without regard to meal. Given that the effect of Orfadin in the treatment of hereditary tyrosinemia type 1 is likely to be due to the overall exposure rather than the peak exposure, I agree with this recommendation.

6. Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This NDA application did not include any efficacy studies.

The applicant submitted a taste and palatability study (Study Sobi-NTBC-002), conducted as an open-label, single-arm, multiple-dose study of nitisinone oral suspension in 18 pediatric patients with HT-1. The study, summarized in the CDTL review, indicates that the nitisinone oral suspension has an acceptable taste and palatability.

8. Safety

There were no safety findings of relevance in the bioequivalence study Sobi.NTBC-001 (12 patients, all healthy volunteers) or in the taste and palatability study Sobi.NTBC-003 (18 pediatric patients with HT-1). Specifically, there were no deaths, serious adverse events, or discontinuations, and no new safety signals were identified for the oral suspension formulation in the above-mentioned studies.

9. Advisory Committee Meeting

There were no issues in this application that required advice from experts outside the Agency. Therefore there was no Advisory Committee meeting for this application.

10. Pediatrics

Because nitisinone was granted orphan product designation (May 16, 1995; Orphan Designation #95-890) this application is exempted from the Pediatric Equity and Research Act (PREA) requirements.

11. Other Relevant Regulatory Issues

None.

12. Labeling

Labeling negotiations have been completed at the time of this memorandum. I agree with the changes made to the label. Recommendations made by DPMH and labeling consultants have been reviewed, discussed and incorporated into the label.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I agree with the recommendation made by the cross-discipline team leader (Dr. Muldowney) that nitisinone oral suspension, 4 mg/mL, be approved for the treatment of hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine.

- Risk Benefit Assessment

The data submitted in this NDA supplement do not change the risk and benefit assessment of nitisinone in general, and do not raise any additional risks specific for the oral formulation relative to the already approved capsule formulation. The risk benefit analysis remains favorable for oral nitisinone.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

DRAGOS G ROMAN
04/22/2016