CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206356Orig1s000

CHEMISTRY REVIEW(S)
Recommendation:
This 505(b)(2) application is not recommended for Approval as of this review, per 314.125(b)(6).

NDA 206356

Review # 1

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>Orfadin (nitisinone) Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant</td>
<td>Swedish Orphan Biovitrum AB</td>
</tr>
<tr>
<td>US agent, if applicable</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>SUBMISSION(S) REVIEWED</th>
<th>DOCUMENT DATE</th>
<th>DISCIPLINE(S) AFFECTED</th>
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<tr>
<td>NDA submission</td>
<td>22-Jun-2015</td>
<td>All</td>
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<tr>
<td>Amendment</td>
<td>05-Aug-2015</td>
<td>Biopharmaceutics</td>
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<td>Amendment</td>
<td>24-Aug-2015</td>
<td>Drug Substance</td>
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<td>Amendment</td>
<td>16-Oct-2015</td>
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<td>18-Dec-2015</td>
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<td>29-Jan-2016</td>
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<td>16-Feb-2016</td>
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<td>Amendment</td>
<td>29-Feb-2016</td>
<td>Drug Product</td>
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<td>REVIEWER</td>
<td>BRANCH/DIVISION</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Drug Substance</td>
<td>Debasis Ghosh</td>
<td>OMPT/CDER/OPQ/ONDP/DND API/NDBII</td>
</tr>
<tr>
<td>Drug Product Process</td>
<td>Hong Cai, Ph.D.</td>
<td>CDER/OPQ/ONDP/DNDPII</td>
</tr>
<tr>
<td>Microbiology Facility</td>
<td>David Bateman, Ph.D.</td>
<td>CDER/OPQ/OPF/DMA III</td>
</tr>
<tr>
<td>Biopharmaceutics Manager</td>
<td>Mei Ou, Ph.D.</td>
<td>CDER/OPQ/ONDP/DB II</td>
</tr>
<tr>
<td>Application Technical Lead</td>
<td>Truong Quach</td>
<td>OMPT/CDER/OPQ/OPRO/DRBP MI/RBPMBI</td>
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<tr>
<td>Laboratory (OTR)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>ORA Lead</td>
<td>Paul Perdue</td>
<td>OGROP/ORA/00/OMPTO/DMP TPO/MDTP</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td>Hong Cai, Ph.D.</td>
<td>CDER/OPQ/ONDP/DNDPII</td>
</tr>
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</table>
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# Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**

   A. **DMFs:**

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td>N/A</td>
<td>Type III</td>
<td>(3)(a)</td>
<td></td>
<td>N/A</td>
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<tr>
<td></td>
<td>Type IV</td>
<td></td>
<td></td>
<td>Adequate</td>
<td>March 18, 2008</td>
<td>Reviewed by Dr. Wendy Wilson</td>
</tr>
</tbody>
</table>

   N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

   B. **Other Documents:**

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>NDA 21-232</td>
<td>Orfadin Capsule</td>
</tr>
</tbody>
</table>

2. **CONSULTS:**

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>STATUS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biostatistics</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacology/Toxicology</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDRH</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Facility and Process has made a final overall manufacturing Inspection “Approval” recommendation for the facilities involved in this application.

However, issues on the label-labeling are still pending as of the date of this review.

Therefore, from the ONDP perspective, this NDA is not recommended for approval at this time in its present form per 21 CFR 314.125(b)(6), pending resolution of the labeling issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

Orfadin (nitisinone) is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase indicated for use as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1). Orfadin currently on the market is a hard white-opaque capsule. Orfadin capsules come in 2, 5, & 10-mg strengths of nitisinone.

Most of the HT-1 patients are infants and young children under age 10. Those young patients are likely to have difficulty to swallow the capsules. Most often the capsules are opened and the contents suspended in a small amount of water immediately before use. Therefore, Orfadin (nitisinone) Oral Suspension, a new formulation, was developed to provide ease of dose and the improvement of the dosing accuracy.

A. Drug Substance, nitisinone, Quality Summary

The drug substance information is referenced to NDA 21232 which was approved on 18-Jan-2002 for orfadin capsules.

Chemical Name (IUPAC): (2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclohexanediione)
Drug substance is manufactured by CMC information for the drug substance is referenced to NDA 21232 for orfadin capsules.

For the purpose of this suspension formulation, the drug substance is found to be suitable. Chemical and physical analysis of the experimental samples also supports the stability of the drug substance.

Drug substance is tested to the following specifications: appearance, identification (IR, melting point), assay, impurities (organic and inorganic), residual solvents, loss on drying and microbial contamination. The applicant included all critical quality attributes (CQAs), corresponding analytical methods and the acceptance criteria for each attribute.

The acceptance criterion for Total of Impurities is NMT $^{(0.4)}\%$, whereas each single impurity is controlled at the limit of NMT $^{(0.4)}\%$. The HPLC-MS method was used to characterize the impurities. Assay and impurities analytical method was validated for its intended use.

Residual solvents

The drug substance primary packaging material is made
QUALITY ASSESSMENT

Based on NDA 21232, the current retest period for nitisinone drug substance is

In conclusion, the nitisinone drug substance is acceptable for the proposed suspension formulation.

B. Drug Product, nitisinone, Quality Summary

Orfadin oral suspension, 4 mg/1mL, is a white, slightly viscous opaque suspension supplied in a 100 mL brown Type III medicinal glass bottle sealed with a child resistant cap. Each bottle contains 90 mL of the suspension. The composition of the orfadin oral suspension is based on drug substance nitisinone (NTBC) and the following inactive ingredients: hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dihydrate, strawberry aroma (artificial) and purified water. All these excipients are USP/NF/Ph. Eur. grade with the exception of strawberry aroma. Strawberry aroma, compositions only less than % (w/w) of total amount of the drug product, and is supplied by . Based on the assessment of the Drug Product reviewer, Dr. Hong Cai, orfadin suspension contains well established excipients that are considered safe from the CMC perspective.

The active ingredient nitisinone has a limited solubility in the proposed formulation (pH ). Therefore, the content of suspension is not uniform. On storage, this suspension settles (sedimentation is ) and forms a cake. Resuspendability of this formulation is one of the key parameters to ensure the dose accuracy. The applicant established the redispersion procedures using vigorous shaking for at least seconds prior to withdrawal of the first dose and another 5 seconds of shaking prior to withdrawal of each following dose.

Quality of orfadin suspension is controlled through a comprehensive release and stability specification that includes appearance, identification (by retention time and UV spectrum), related substances, pH, resuspendability, uniformity of maas, dissolution, and microbial testing.

Among the five identified NTBC organic impurities, are the impurities presented in the drug substance, nitisinone. are the newly identified impurities in the drug product. Impurity is projected to be readily to in-vivo in GI tract under low pH environment. Therefore, The specification is set as the sum amount of and . The absence of density and viscosity testing is discussed and is deemed acceptable.
Based on assessment of the Drug Products’s reviewer, the proposed drug product specification is satisfactory.

Drug product manufacturing process includes the following steps:

On the FDA request addressed by the Process reviewer, Dr. Xiaohui (Sherry) Shen, the applicant implemented testing for content uniformity on seven bottles for commercial manufacturing.

In conclusion, D. Shen states in her review that 1) formulation and process development information demonstrated the robustness of the proposed manufacturing process 2) description of manufacturing process is adequate and reflects that of process development, 3) controls for critical operation parameters and for in-process materials,

From the Biopharmaceutics perspective, the in-vitro dissolution method is well established, validated, and demonstrates adequate discriminating ability for the batches with different particle sizes. This NDA is recommended for approval from the Biopharmaceutics perspective.

The Division of Microbiology recommends approval of this NDA based on the micrology assessment.

The container closure system comprises a medicine glass bottle (100 mL) and a cap with sealing. The cap consists of high-density polyethylene (HDPE). The sealing is made by . The proposed container closure system is deemed satisfactory. To increase dosing accuracy, FDA discussed with the applicant including a Push-in Bottle Adaptor (PIBA) in the drug product package. In response, the applicant proposed that a single source pharmacy ( ) will provide a PIBA and an appropriate oral syringe to patients, and this arrangement is deemed acceptable from the clinical perspective.

Based on submitted stability data, a 36-month expiration dating period is granted when the drug product is stored under the following recommended storage conditions:
QUALITY ASSESSMENT

“Store refrigerated at 2° to 8°C (36° to 46°F) prior to first use. Do not freeze. Store upright. After first opening, store this product at room temperature (up to 25°C (77°F) for up to 60 days. The discard after date should be noted on the bottle.”

The inspectional assessment indicates that facilities are determined acceptable to support approval of this NDA 206 356.

However, the label/labeling issues are not finalized as of the date of this review.

C. Summary of Drug Product Intended Use

<table>
<thead>
<tr>
<th>Proprietary Name of the Drug Product</th>
<th>ORFADIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Proprietary Name of the Drug Product</td>
<td>nitisimone oral suspension</td>
</tr>
<tr>
<td>Non Proprietary Name of the Drug Substance</td>
<td>nitisimone</td>
</tr>
<tr>
<td>Proposed Indication(s) including Intended Patient Population</td>
<td>For use as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>N/A</td>
</tr>
<tr>
<td>Maximum Daily Dose</td>
<td>2 mg/kg/day</td>
</tr>
<tr>
<td>Alternative Methods of Administration</td>
<td>N/A</td>
</tr>
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</table>

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: (No BSC classification claim submitted)
   - Drug Product: (No BSC classification claim submitted)

2. Biowaivers/Biostudies
   - Biowaiver Requests: (No Biowaiver Request)
   - PK studies: (Will be reviewed by OCP review team)
   - IVIVC: (No IVIVC submitted)

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

From the ONDP perspective, this NDA is not recommended for approval at this time in its present form per 21 CFR 314.125(b)(6), pending resolution of the labeling issues.
OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer’s Assessment and Signature:

There appear to be no significant risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility’s inspection results, inspecional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 206356.

Sherry Xiaohui Shen, CSO
March 7, 2016

Digitally signed by Xiaohui S. Shen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
Q:924e2,1920000,100,1,1-20013468
SS: ci:Xiaohui S. Shen -S
Date: 2016.03.18 15:20:43 -04'00
Secondary Review Comments and Concurrence:

I concur with the overall recommendation.

Juandria Williams, PhD; DIA/B3
March 13, 2016
ASSESSMENT OF THE BIOPHARMACEUTICS

BACKGROUND

The Applicant, SOBI (Swedish Orphan Biovitrum), resubmitted this NDA 206356 on 06/22/2015 for their proposed drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL. This drug product is indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

This resubmitted NDA is a 505(b)(2) application. The Division of Biopharmaceutics focuses on the reviewing of in vitro dissolution of the proposed drug product. The two bioavailability/bioequivalence (BA/BE) studies (Sobi.NTBC-001 and Sobi.NTBC-002) are currently under review by the Office of Clinical Pharmacology.

BIOPHARMACEUTICS ASSESSMENT

1. The composition of proposed drug product

The composition and formulation of the proposed drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL, is in Table 1.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg)</th>
<th>Function</th>
<th>Reference to standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitisinone</td>
<td>4.0</td>
<td>Active substance</td>
<td>In-house specification</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (HPMC)</td>
<td></td>
<td></td>
<td>Ph. Eur./NF</td>
</tr>
<tr>
<td>Glycerol</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td></td>
<td></td>
<td>Ph. Eur./NF</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
<td>Ph. Eur./NF</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
<tr>
<td>Trisodium citrate dihydrate</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
<tr>
<td>Strawberry aroma</td>
<td></td>
<td></td>
<td>In-house specification</td>
</tr>
<tr>
<td>Water, purified</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
</tbody>
</table>

2. The proposed in vitro dissolution method and specification

The in vitro dissolution method development reports for drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL, are Report# L M721 (from M.3.2.P.5.2 of 06/22/2015 submission) and Report# DS-2015-020-2568 (from M. 1.11.1, IR response of 08/05/2015 submission), which are summarized in Table 2 for details:

1) Paddle, was selected.

2) Hydrochloric acid (pH 1.2, 1000 mL) was chosen as dissolution medium to obtain an acceptable and reproducible method with an optimal dissolution rate compared to...
that of pH 6.8 medium (see p.11/25 of response to IR#1, mean profile comparisons of in 08/05/2015 submission).

3) The rotation speed as 50 rpm showed no difference in dissolution profile (see the method development report, L M721)

4) The discriminatory ability of the method was investigated by performing dissolution tests of suspensions with various particle size distribution (PSD), The proposed dissolution is considered to have discriminating ability (see p.12/25 of response to IR#2, mean profile comparisons in 08/05/2015 submission)

**Table 2:** The summary of in vitro dissolution method (L M721) for drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL
(from M.3.2.P.5.2 of 06/22/2015 submission)

<table>
<thead>
<tr>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>The dissolution test is carried out using a paddle apparatus with hydrochloric acid buffer pH 1.2 as medium. The amount of nitisinone (NTBC) dissolved at 30 minutes in the medium is determined by HPLC with UV detection at 272 nm.</td>
</tr>
</tbody>
</table>

Reference standard, chemicals, solvents and equipment
Table 2: The summary of in vitro dissolution method (L M721) for drug product, Orifadin (mitisinone) Oral Suspension, 4 mg/mL (from M.3.2.P.5.2 of 06/22/2015 submission) (continued)

<table>
<thead>
<tr>
<th>Operating conditions for dissolution</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution apparatus</td>
<td>Paddle apparatus</td>
</tr>
<tr>
<td>Dissolution medium</td>
<td>Hydrochloric acid (HCl) buffer pH 1.2 (USP) degassed by sparging with helium for 30 minutes</td>
</tr>
<tr>
<td>Volume of medium</td>
<td>1000 mL</td>
</tr>
<tr>
<td>Number of suspension samples to be tested</td>
<td>6</td>
</tr>
<tr>
<td>Sinker devices</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Rotation speed</td>
<td>50 rpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>37 °C ± 0.5 °C</td>
</tr>
<tr>
<td>Sampling time</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

Preparation of sample, blank, standard and system suitability test (SST) solutions

- Sample preparation the day before analysis
- Sample preparation
- Sample application
- Standard calibration solutions
Table 2: The summary of in vitro dissolution method (L M721) for drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL (from M.3.2.P.5.2 of 06/22/2015 submission) (continued)
The proposed in vitro dissolution parameters and acceptance criterion for drug product are given in Table 3.

Table 3: Proposed in vitro dissolution parameters and specification for drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL (Dissolution Method: L M721) (from M.3.2.P.5.2 and M.3.2.P.5.1 of 06/22/2015 submission)

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>II (Paddle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>Hydrochloric acid (HCl) buffer pH 1.2 (USP) degassed by sparging with helium for 30 minutes</td>
</tr>
<tr>
<td>Volume</td>
<td>1000 mL</td>
</tr>
<tr>
<td>Rotation Speed</td>
<td>50 rpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>37°C ± 0.5°C</td>
</tr>
<tr>
<td>Sampling Time</td>
<td>5, 15, 30 and 45 minutes</td>
</tr>
<tr>
<td>Proposed Specification</td>
<td>Q = 80% of labeled amount at 40 minutes</td>
</tr>
</tbody>
</table>

The proposed dissolution acceptance criterion as Q = 80% at 40 minutes is considered too low, and a proposed acceptance criterion is needed and has been communicated to the Applicant.

3. The dissolution method validation

A summary of dissolution method validation report Report# A01868-01 is in M.3.2.P.5.3 of 06/22/2015 submission, which is given in Table 4, while the representative chromatograms are in Figure 1 and Figure 2.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS

Reviewer’s Assessment and Signature:

From the Biopharmaceutics perspective:

- In vitro dissolution method for the proposed drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL, is acceptable with adequate discriminating ability for the batches with different particle sizes;
- In vitro dissolution method validation for the proposed drug product is well established;
- In vitro dissolution acceptance criteria is well set as a good quality control specification for batch-to-batch uniformity for proposed drug product.
- The following in vitro dissolution method and specification are agreed and will be implemented for the proposed drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL.

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>II (Paddle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>Hydrochloric acid (HCl) buffer pH 1.2 (USP) degassed by sparging with helium for 30 minutes</td>
</tr>
<tr>
<td>Volume</td>
<td>1000 mL</td>
</tr>
<tr>
<td>Rotation Speed</td>
<td>50 rpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>37°C ± 0.5°C</td>
</tr>
<tr>
<td>Sampling Time</td>
<td>5, 15, 30 and 45 minutes</td>
</tr>
<tr>
<td>Specification</td>
<td>Q= η% of labeled amount at 15 minutes</td>
</tr>
</tbody>
</table>

This NDA 206356 for drug product, Orfadin (nitisinone) Oral Suspension, 4 mg/mL, is reviewed and found acceptable from the Biopharmaceutics perspective; therefore, this NDA 206356 is recommended for APPROVAL.

02/25/2016
Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Secondary Review Comments and Concurrence:

I concur 02/25/16

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

Digitally signed by Mei Ou -5
DN: c=US, o=U.S. Government, ou=HHS, ap=FDA, ou=People, cn=Mei Ou-5,
0-9714219200360.1001.1=2001622313
Date: 2016.03.18 12:47:35 -04'00'

Digitally signed by Tienmien Chen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tienmien Chen -S,
0-9234219200360.1001.1=1300073315
Date: 2016.03.18 13:46:06 -04'00'
7. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant’s Response:

P.1 Description of the Composition of the Drug Product

- Description of drug product –
  
  A non-soluble aqueous suspension of drug product white to yellowish white in color.

- Drug product composition –

  The applicant provided the following summary table (description-and-composition.pdf):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg)</th>
<th>Function</th>
<th>Reference to standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrominone</td>
<td>4.0</td>
<td>Active substance</td>
<td>In-house specification</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (HPMC)</td>
<td></td>
<td></td>
<td>Ph. Eur./NF</td>
</tr>
<tr>
<td>Glycerol</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td></td>
<td></td>
<td>Ph. Eur./NF</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td></td>
<td></td>
<td>Ph. Eur./NF</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
<tr>
<td>Tannic acid dihydrate</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
<tr>
<td>Strawberry aroma</td>
<td></td>
<td></td>
<td>In-house specification</td>
</tr>
<tr>
<td>Water, purified</td>
<td></td>
<td></td>
<td>Ph. Eur./USP</td>
</tr>
</tbody>
</table>

- Description of container closure system –
  (container-closure-system.pdf)

  A 100 mL medicine brown glass bottle with white high density polyethylene child resistance cap.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Antimicrobial Effectiveness Testing -
  (pharmaceutical-development.pdf, page 62)

  Antimicrobial effectiveness testing was performed according to USP <51>.

Results
Acceptable

Reviewer’s Assessment: ACCEPTABLE

The Division of Microbiology has no additional comments at this time.

2.3.P.7 Container/Closure System

8. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant’s Response:

See question 40 above.

Reviewer’s Assessment: ACCEPTABLE

The Division of Microbiolgy has no additional comments at this time.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

9. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?
Applicant’s Response: N/A

Reviewer’s Assessment: ACCEPTABLE
The Division of Microbiology has no additional comments at this time.

10. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant’s Response: N/A

Reviewer’s Assessment: ACCEPTABLE
The Division of Microbiology has no additional comments at this time.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer’s Assessment and Signature:
The Division of Microbiology recommends APPROVAL of NDA 206356, Orfadin Oral Suspension.

2/24/16

David Bateman, Ph.D.
Microbiology Reviewer
Division of Microbiology/OPF
Office of Pharmaceutical Quality

Digital signature of David A. Bateman - S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David A. Bateman - S
7ch- David A. Bateman - S
Date: 2016.03.18 13:28:35 -04'00'

Secondary Review Comments and Concurrence:
I concur with the above microbiology assessment.

2/24/2016
Jessica G. Cole, PhD
Quality Assessment Lead (Acting)
Division of Microbiology/OPF
Office of Pharmaceutical Quality

Digital signature of Jessica Cole - S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica Cole - S
7ch- Jessica Cole - S
Date: 2016.03.18 14:07:27 -04'00'
ASSESSMENT OF ENVIRONMENTAL ANALYSIS

11. Is the applicant’s claim for categorical exclusion acceptable?

12. Is the applicant’s Environmental Assessment adequate for approval of the application?

Applicant’s Response:

This application concerns a new dosage form for Orfadin; an (nitisinone) is approved for treatment of hereditary tyrosinemia type 1, which is a rare inborn error of metabolism, and is the only approved medicinal product for this orphan disease. The use of nitisinone, and consequently the concentration in the environment, will thus not increase due to the approval of the oral suspension. Approval of the oral suspension will merely replace use of the capsule for some patients having difficulty to swallow. In conclusion, we request a categorical exemption based on this rationale that the approval of this application will not increase the use of the active moiety and therefore will not significantly affect the quality of the human environment (21 CFR 25.5(c)).

Reviewer’s Assessment:
Acceptable.
(This is based on the recommendation from environmental assessment team reviewer Dr. James Laurenson (See APPENDIX A.)

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer’s Assessment and Signature:
Satisfactory.
Hong Cai, Ph.D.
Reviewer, Branch V
DNPD II/ONDNP

Secondary Review Comments and Concurrence:
I concur.
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert*

*The following “Labeling & Package Insert” review is limited to the content of Orfadin oral suspension (NDA206356).

1. Package Insert
(a) “Highlights” Section (21CFR 201.57(a))

These highlights do not include all the information needed to use ORFADIN safely and effectively. See full prescribing information for ORFADIN.

ORFADIN® (nitisinone) capsules, for oral use
ORFADIN® (nitisinone) oral suspension
Initial U.S. Approval: 2002

DOSAGE FORMS AND STRENGTHS
- Capsules: 2 mg, 5 mg, 10 mg. (3)
- Oral suspension: 4 mg/mL (3)

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
<th>Reviewer’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product title, Drug name (201.57(a)(2))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proprietary name and established name</td>
<td>ORFADIN® (nitisinone) oral suspension</td>
<td>Proprietary name and established name are provided.</td>
</tr>
<tr>
<td>Dosage form, route of administration</td>
<td>oral suspension</td>
<td>Dosage form and route of administration are provided.</td>
</tr>
<tr>
<td>Controlled drug substance symbol (if applicable)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Dosage Forms and Strengths (201.57(a)(8))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A concise summary of dosage forms and strengths</td>
<td>Oral suspension: 4 mg/mL</td>
<td>The dosage forms and strengths are described correctly.</td>
</tr>
</tbody>
</table>

**Conclusion:**

The highlights section of the PI is adequate.
(b) “Full Prescribing Information” Section

**# 3: Dosage Forms and Strengths (21 CFR 201.57(c)(4))**

Capsules: 2 mg, 5 mg, and 10 mg white capsules imprinted with “NTBC” followed by “2 mg”, “5 mg”, or “10 mg”, indicating the actual amount of nitisinone in each capsule. Oral suspension: 4 mg/mL [White, slightly viscous opaque suspension.]

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
<th>Reviewer’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available dosage forms</td>
<td>Oral suspension</td>
<td>Provided</td>
</tr>
</tbody>
</table>
| Strengths: in metric system                        | Oral suspension: 4 mg/mL [White, slightly viscous opaque suspension.]
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and im printing, when applicable. | Oral suspension: 4 mg/mL [White, slightly viscous opaque suspension.]

**Conclusion:**

- *Remove “[White, slightly viscous opaque suspension.”]*

**Unsatisfactory.**
ORFADIN contains nitisine, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

Nitisine occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol. Chemically, nitisine is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

![Structural formula of nitisine](image)

**Figure 1. The molecular formula is C_{13}H_{10}F_{3}NO_{5} with a relative mass of 329.23**

Capsules: Hard, white-opaque capsule, marked as 2 mg, 5 mg or 10 mg strengths of nitisine, intended for oral administration. Each capsule contains 2 mg, 5 mg or 10 mg nitisine, plus pre-gelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

Oral suspension: 4 mg/mL white, slightly viscous opaque suspension. The inactive ingredients are hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, sodium citrate, strawberry aroma (artificial) and purified water.

Glycerol: Each mL contains 500 mg.

Sodium: Each mL contains 0.7 mg (0.03 mmol).

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
<th>Reviewer’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name and established name</td>
<td>ORFADIN contains nitisine</td>
<td>Proprietary name and established name is described correctly. Satisfactory</td>
</tr>
<tr>
<td>Dosage form and route of administration</td>
<td>Oral suspension</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Active moiety expression of strength with equivalence statement for salt (if applicable)</td>
<td>Not applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Inactive ingredient information (quantitative, if injectables)</td>
<td>The inactive ingredients are</td>
<td>Revise `</td>
</tr>
</tbody>
</table>

135 OPQ-XOPQ-TEM-0001v02 Effective Date: 13 Mar 2015
| Statement of being sterile (if applicable) | Not applicable | Not applicable |
| Pharmacochemical/therapeutic class | ORFADIN contains nitisine, which is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1). | Satisfactory |
| Chemical name, structural formula, molecular weight | Chemical Name: 2-(2-nitro-4-trifluoromethylbenzoyl)cyclohexane-1,3-dione Structural formula: | All necessary information provided. |
Conclusion:

- Revise "..." to "trisodium citrate dihydrate".

- Remove the statement: "..." from this section. The clinical recommendations do not belong in this section. This section is intended only to relay CMC information.

- For sodium content, remove nmol and replace with mEq.

- Remove ...

Unsatisfactory.
#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Capsules: White capsules marked in black with "NTBC" and identified as 2 mg, 5 mg or 10 mg strengths of nitisimone. The capsules are packed in a high density (HD) polyethylene container with a tamper-resistant low density (LD) polyethylene snap-on cap. Each bottle contains 60 capsules.

2 mg white capsules imprinted "NTBC 2 mg" in black ink, NDC 66658-102-60
5 mg white capsules imprinted "NTBC 5 mg" in black ink, NDC 66658-105-60
10 mg white capsules imprinted "NTBC 10 mg" in black ink, NDC 66658-110-60
Store refrigerated, 2-8°C (36-46°F).

Oral suspension: White, slightly viscous opaque suspension. 1 mL contains 4 mg of nitisimone. The suspension is provided in a 100 mL brown bottle (type III glass) with a white child resistant HDPE screw cap with sealing and tamper evidence. Each bottle contains 90 mL oral suspension. Oral suspension 4 mg/mL, NDC 66658-204-90
Store refrigerated, 2 to 8°C (36 to 46°F), prior to first use. Do not freeze. Store upright.

After first opening, should be noted on the bottle

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
<th>Reviewer’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of dosage form</td>
<td>Oral suspension 4 mg/mL</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Available units (e.g., bottles of 100 tablets)</td>
<td>Each bottle contains 90 mL oral suspension.</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td>
<td>Oral suspension: White, slightly viscous opaque suspension. NDC 66658-204-90</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Special handling (e.g., protect from light, do not freeze)</td>
<td>Do not freeze. Store upright</td>
<td>Unsatisfactory Revise the statement of See the notes in the Storage conditions.</td>
</tr>
<tr>
<td>Storage conditions</td>
<td>Store refrigerated, 2 to 8°C (36 to 46°F), prior to first use. Do not freeze. Store upright. After first opening, should be noted on the bottle.</td>
<td>Revise the storage statements to the following: Store refrigerated at 2°C to 8°C (36°C to 46°F) prior to first use. Do not freeze. should be noted on the bottle. Unsatisfactory</td>
</tr>
</tbody>
</table>
Manufacturer/distributor name listed at the end of PI, following Section #17

<table>
<thead>
<tr>
<th>Item</th>
<th>Information Provided in NDA</th>
<th>Reviewer’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer/distributor name (21 CFR 201.1)</td>
<td>Marketed by: Sobi, Inc 890 Winter Street Waltham, MA 02451</td>
<td>Satisfactory</td>
</tr>
<tr>
<td></td>
<td>Manufactured by: Apotek Produktion &amp; Laboratorier AB, Sweden</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:

Revise the storage statements to the following:

- Store refrigerated at 2° to 8°C (36° to 46°F) prior to first use. Do not freeze. Store upright. After first opening, store product at room temperature (up to 25°C (77°F)) for up to 60 days. The discard after date should be noted on the bottle.

Unsatisfactory.

2. Container and Carton Label

Reviewer’s Assessment:
<table>
<thead>
<tr>
<th>Item</th>
<th>Comments on the Information Provided in NDA</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | Proprietary name, established name are provided with appropriate font size, but the prominence does not satisfy 21 CFR 201.10(g) (2). | Revise the presentation so the established name is located after the proprietary name: *Orfadin®* *(nitisinone)*  
oral suspension  
4 mg/mL |
<p>| Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))                   | 4mg/mL                                                                                                     | Unsatisfactory                                                              |
| Route of administration 21.CFR 201.100(b)(3))                        | Oral                                                                                                       | Satisfactory                                                                |
| Net contents* (21 CFR 201.51(a))                                     | 90mL                                                                                                       | Satisfactory                                                                |
| Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21 CFR 201.100(b)(5)** | N/A                                                                                                        | Satisfactory                                                                |
| Lot number per 21 CFR 201.18                                          | The location on the immediate container label where the lot number will be displayed is provided. Satisfies 21 CFR 201.18. | Satisfactory                                                                |
| Expiration date per 21 CFR 201.17                                     | The location on the immediate container label where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17. | Satisfactory                                                                |
| “Rx only” statement per 21 CFR 201.100(b)(1)                          | “Rx only” is displayed. Satisfies 21 CFR 201.100(b) (1).                                                   | Satisfactory                                                                |
| Storage (not required)                                                 | Storage condition provided                                                                               | Satisfactory                                                                |
| NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3) | Provided.                                                                                                  | Satisfactory                                                                |</p>
<table>
<thead>
<tr>
<th>Bar Code per 21 CFR 201.25(c)(2)***</th>
<th>Provided.</th>
<th>Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of manufacturer/distributor (21 CFR 201.1)</td>
<td>Name of manufacturer/distributor is appropriately displayed.</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Others</td>
<td>Not applicable.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

**Conclusion:**

- Revise the presentation of tradename and the established name as follows:

  Orfadin®

  \((\text{nitisinone})\) oral suspension

  4 mg/mL

Unsatisfactory
2) Carton Label
<table>
<thead>
<tr>
<th>Item</th>
<th>Comments on the Information Provided in NDA</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name, established name (font size and prominence (FD&amp;C Act 502(e)(1)(A)(i), FD&amp;C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))</td>
<td><strong>Orfadin 4 mg/mL</strong> Oral Suspension (Nitisinone)</td>
<td>Unsatisfactory</td>
</tr>
<tr>
<td>Strength (21 CFR 201.10(d)(1); 21 CFR 201.100((d)(2))</td>
<td>4 mg/mL</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Net contents (21 CFR 201.51(a))</td>
<td>90mL</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Lot number per 21 CFR 201.18</td>
<td>Provided</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Expiration date per 21 CFR 201.17</td>
<td>Provided</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables) [201.10(a), 21 CFR 201.100(d)(2)]</td>
<td>Inactive ingredients: citric acid monohydrate, glycerol, hydroxypropyl methylcellulose, polysorbate 80, purified water, sodium benzoate, strawberry aroma (artificial).</td>
<td>Unsatisfactory</td>
</tr>
<tr>
<td>Sterility Information (if applicable)</td>
<td>N/A</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>“Rx only” statement per 21 CFR 201.100(d)(2), FD&amp;C Act 503(b)(4)</td>
<td>Provided</td>
<td>Satisfactory</td>
</tr>
</tbody>
</table>
### Storage Conditions

| (b)(4) | Revise the storage statements to the following:
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

**Unsatisfactory**

### NDC number

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th>Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>(per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)</td>
<td></td>
</tr>
</tbody>
</table>

**Satisfactory**

### Bar Code per 21 CFR 201.25(c)(2)**

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th>Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provided</td>
<td></td>
</tr>
</tbody>
</table>

**Satisfactory**

### Name of manufacturer/distributor

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th>Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provided</td>
<td></td>
</tr>
</tbody>
</table>

**Satisfactory**

### “See package insert for dosage information” (21 CFR 201.55)

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th>Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provided</td>
<td></td>
</tr>
</tbody>
</table>

**Satisfactory**

### “Keep out of reach of children” (optional for Rx, required for OTC)

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th>Not Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Provided</td>
<td></td>
</tr>
</tbody>
</table>

**Satisfactory**

### Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th>Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provided</td>
<td></td>
</tr>
</tbody>
</table>

**Satisfactory**

---

**Conclusion:**
The carton label needs to be changes as follows:

- Revise the drug name presentation as follows:
  
  *Orfadin® (nitisinone) oral suspension 4 mg/mL*

- Revise (b)(4) to “trisodium citrate dihydrate” in the inactive ingredients.
QUALITY ASSESSMENT

- Revise the storage statements to the following:

  Must be refrigerated, store at 2°C 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.

Unsatisfactory

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer’s Assessment and Signature:
Unsatisfactory.

The following comments should be conveyed to the applicant:

1) #3: Dosage Forms and Strengths
   Remove

2) #11 Description:
   - Revise to “trisodium citrate dihydrate” in the inactive ingredients.
   - Remove the following statement from this section:

3) #16 How Supplied/Storage and Handling:
   - Revise the storage condition:

   Store refrigerated at 2° to 8°C (36° to 46°F) prior to first use. Do not freeze. Store upright. After first opening, store this product at room temperature (up to 25°C (77°F)) for up to 60 days. The discard after date should be noted on the bottle.

4) Container/carton Labels
   - Revise the drug name presentation as follows:
     Orfadin®
     (nitisinone) oral suspension
II. List of Deficiencies To Be Communicated

Label/Labeling

The following deficiencies only limited to Orfadin oral suspension.

a. Remove ______ from the entire Label/Labeling documents.

b. Container and Carton Labeling:
Revise the presentation so the established name is located after the proprietary name:

Orfadin®
(nitisinone) oral suspension
4 mg/mL

#11: Description (21CFR 201.57(c)(12))

Revise ______ to “trisodium citrate dihydrate”

Remove the statement: ______
For sodium content, remove the mmol and replace with mEq.

d. #16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Revise the storage statements to the following:

“Store refrigerated at 2° to 8°C (36° to 46°F) prior to first use. Do not freeze. Store upright. After first opening, store this product at room temperature (up to 25°C (77°F)) for up to 60 days. The discard after date should be noted on the bottle.”

c. Carton Labeling

Revise the presentation so the established name is located after the proprietary name:

Orfadin®

(nitisinone) oral suspension

4 mg/mL

Revise to “trisodium citrate dihydrate” in the inactive ingredients.

Revise the storage statements to the following:

“Must be refrigerated, store at 2°C 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.”

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

<table>
<thead>
<tr>
<th>Attribute/CQA</th>
<th>Factors that can impact the CQA</th>
<th>Initial Risk Ranking</th>
<th>Risk Evaluation</th>
<th>Risk Mitigation</th>
<th>Final Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low content of active ingredient NTBC in the formulation</td>
<td>Manufacturing process; Storage condition</td>
<td>H</td>
<td>Considering the manufacturing process controls in place as well as drug product testing on release and stability, and proper instructions for use, (IFU), risk to the drug product quality is</td>
<td>Adequate in-process control, testing of inter content uniformity and resuspendability at drug release and/or shelf life</td>
<td>L</td>
</tr>
<tr>
<td>Attribute/CQA</td>
<td>Factors that can impact the CQA</td>
<td>Initial Risk Ranking</td>
<td>Risk Evaluation</td>
<td>Risk Mitigation</td>
<td>Final Risk</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------</td>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Dosing accuracy</td>
<td>Caking of the formulation during long term storage; Shaking time of the formulation</td>
<td>M</td>
<td>Resuspendability testing at drug release and shelf life is found adequate. Clear instructions of use are provided in IFU.</td>
<td>Resuspendability testing at drug release and shelf life, IFU</td>
<td>L</td>
</tr>
</tbody>
</table>
| Assay, stability | • Formulation  
• Container closure  
• Raw materials  
• Process parameters  
• Scale/equipment  
• Site | L                   | Considering the drug substance and drug product physico-chemical properties and proper controls in place, including validated analytical methodology, the risk to the drug product (suspension) is considered to be low. | Adequate physical and chemical testing in place, and clear IFU.                                       | L          |
| Physical stability (solid state) | • Formulation  
• Raw materials  
• Process parameters  
• Scale/equipment  
• Site | L                   | The active ingredient nitisinone has a limited solubility in the proposed formulation (pH 9). Therefore, the content of suspension is not uniform. On storage, this suspension settles (sedimentation is 6%/60 sec/min) and forms a cake. | Resuspendability of this formulation is one of the key parameters to ensure the dose accuracy. The applicant established the re-dispersion procedures using vigorous shaking. The drug substance is | L          |
| Impurities/related substances/residual solvents | • Formulation  
• Excipient change  
• Process parameters  
• Scale/equipment  
• Site | M                   | Controlled at the level of the drug substance and the drug product via adequate analytical methodology and proper storage conditions.                                                              | Through proper drug substance and drug product process controls as well as adequate testing on release and stability using validated regulatory methods. | L          |
| Microbial limits | • Formulation  
• Container closure  
• Raw materials  
• Process parameters  
• Scale/equipment  
• Site | L                   | As per the microbiology review, the applicant implemented proper microbial testing for the drug product.                                                                                                        | Proper microbial testing at release and stability as well as proper container/closure and handling.    | L          |
| Palatability | • Formulation  
• Excipient change  
• Site | M                   | The acceptability of the final formulation was confirmed by children up to 18 years in the taste and                                                                                                         | To improve the taste characteristics, the suspension formulation                                      | L          |
<table>
<thead>
<tr>
<th>Attribute/CQA</th>
<th>Factors that can impact the CQA</th>
<th>Initial Risk Ranking</th>
<th>Risk Evaluation</th>
<th>Risk Mitigation</th>
<th>Final Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>palatability study Sobi.NTBC-002.</td>
<td></td>
<td>(0)</td>
</tr>
</tbody>
</table>
APPENDIX A.

Cai, Hong

From: Laurenson, James
Sent: Thursday, March 10, 2016 11:21 AM
To: Cai, Hong
Subject: RE: Consultation request for EA (NDA206356)

This is a basic “no increased use”, which the chemists almost always address. All that is needed is adding the following to your review. This doesn’t rise to the level of a separate EA section.

The cited categorical exclusion at 21 CFR 25.31(a) is appropriate for the submitted application because no increase in use of the active moiety is expected. A statement of no significant impact was provided, which suffices for the statement of no extraordinary circumstances for this type of categorical exclusion. The claim of categorical exclusion is acceptable.

From: Cai, Hong
Sent: Wednesday, March 09, 2016 5:58 PM
To: Laurenson, James
Subject: RE: Consultation request for EA (NDA206356)

James,
I was just informed that the review of EA part of NDA206356 need to be done by you. or. Sorry for the confusion since this is my first time doing this. Below is the link for IQA template for your convenient. Thanks. Hong
NDA 206356 Share Point Folder

From: Laurenson, James
Sent: Wednesday, March 09, 2016 2:33 PM
To: Cai, Hong
Subject: RE: Consultation request for EA (NDA206356)

Here’s the draft template guidance we put together for all options hopefully. Section C2 is what you want, though modify to say that while the exact statement was not provided, a sufficiently similar statement was provided for purposes of this particular exclusion.
Jim

CMC Reviewer’s Assessment:
A. Assess whether the EA Team needs to be contacted.
   Does the product meet any of the following criteria?
   1. New Molecular Entity (NME).
   2. API or API precursor derived from plants or animals.
   3. Efficacy supplement with a claim of categorical exclusion under 21 CFR 25.31(b) for API with estrogenic, androgenic, or thyroid activity. See
      for more detail.
   If any of the above responses are “Yes” or “Unsure”, contact the EA team at CDER.EA.Team@fda.hhs.gov.
   If all the above responses are “No”, proceed to B.

B. Assess whether the claim of categorical exclusion is acceptable.
   Background: To claim a categorical exclusion the applicant must provide: (1) a statement that the action requested qualifies for a specific categorical exclusion, citing the particular categorical exclusion that is claimed; and (2) a statement that, to the applicant’s knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)).
   1. Has the applicant submitted a claim of categorical exclusion?
QUALITY ASSESSMENT

2. Does the applicant cite the specific categorical exclusion that is claimed (21 CFR 25.31(a)-(c))?  
3. Is sufficient information available to determine if the following criteria for the claimed categorical exclusion is met?  
   ii. 25.31(b): < 1 part per billion (ppb) for the expected introduction concentration (EIC) of the API for this application plus the quantity used in an applicant's related applications based on the highest quantity expected to be produced for direct use in any of the 5 years post-approval (or < approx. 40,000 kg/yr API). Many submissions include the estimated EIC and a supporting calculation for this exclusion, while others do not (and are not required to). The EIC can be verified, if needed (e.g., if the drug is widely used), by accessing manufacturing and/or dose and patient data. Accept the exclusion if the estimate is below 1 ppb.  
   iii. 25.31(c): This exclusion is used primarily for Biological License Applications (BLAs). The exclusion is for drug substances (or metabolites) that occur naturally in the environment and it is reasonable that approval of the application would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.  
4. Does the submission provide a statement that "to the applicant's knowledge no extraordinary circumstances exist" (21 CFR 25.21)?  
   If all the above responses are "Yes", the claim of categorical exclusion should be accepted. See language in C, below.  
   If any of the above responses are "No" or "Unsure", request the applicant to submit the missing information and/or consult with the EA Team.  

C. Language for accepting categorical exclusion. If additional information was requested and reviewed or missing information or statements had to be requested, go to 3 below.  
1. For an acceptable claim of categorical exclusion at 25.31(b): The cited categorical exclusion at 21 CFR 25.31(b) is appropriate for the anticipated amount of drug to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.  
2. For an acceptable claim of categorical exclusion at 25.31(a) or (c): The cited categorical exclusion at 21 CFR 25.31(a) or (c)--select exclusion is appropriate for the submitted application, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.  
3. Examples for when additional information or statements were needed:  
   i. Missing statement of no extraordinary circumstances: The applicant submitted a claim of categorical exclusion but did not provide an explicit statement that, to their knowledge, no extraordinary circumstances exist, as required by 21 CFR 25.15 (a) and (d). The applicant was notified and an adequate statement was provided. The cited categorical exclusion at 21 CFR 25.31(c) is appropriate for the submitted application. The claim of categorical exclusion is acceptable.  
   ii. Additional detail needed: The applicant submitted a claim of categorical exclusion under 21 CFR 25.31(b), but the amount of API was potentially greater than 40,000 kg/year (equivalent to about 1 ppb) based on patient and dose information. Quantity information was requested from the applicant. An adequate calculation was provided. [Provide additional details as needed.] The cited categorical exclusion at 21 CFR 25.31(b) is appropriate for the anticipated amount of drug to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

From: Cai, Hong  
Sent: Wednesday, March 09, 2016 12:58 PM  
To: Laurensen, James  
Subject: Consultation request for EA (NDA206356)  

James,  
I am the drug product reviewer for NDA 208356 which has PDUFA goal date April 22.  
I would like to consult you regarding the EA statement by the applicant. Is it acceptable or not? This is for a new dosage, Orfadin Oral suspension for the treatment of a form of rare disease.  
If not, what kind of statements I should request from the applicant?  
Thank you in advance,  
Best regards,  
Hong
Memorandum

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

Date: April 11, 2016
From: Hong Cai, Ph.D.
Drug Product Reviewer, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 206356

Subject: Finalized Label/labeling of CMC Sections

At the time when drug product review #1 was completed (03/18/2016), this NDA was not recommended for approval from the ONDP perspective due to unresolved CMC label/labeling issue. To resolve the outstanding label/labeling issues, the applicant submitted the amendments to the NDA on 03/24/2016 and 04/11/2016, those provide the revised container labels and package insert. The revised container labels and package insert adequately address all CMC labeling issues. The relevant sections of revised label/labeling are provided in Attachment 1. Therefore, this application is now recommended for approval from the ONDP perspective.

CMC Label/Labeling Issues Conveyed to the Applicant:*
(*Minor adaptions may occur with the considerations of the review comments from DMEPA to maintain the consistency.)

1) Remove [REDACTED] from the entire document of package insert.

2) #11 Description:
   - Revise [REDACTED] to “trisodium citrate dihydrate” in the inactive Ingredients.
   - Remove the following statement from this section: [REDACTED]
   - Remove mmol and replace with mEq.

3) #16 How Supplied/Storage and Handling:
   - Revise the storage condition:
Store refrigerated at 2°C to 8°C (36°F to 46°F) prior to first use. Do not freeze. Store upright. After first opening, store the product at room temperature (up to 25°C (77°F)) for up to 60 days. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle.

4) Container/carton Labels
   - Revise the drug name presentation as follows:
     Orfadin®
     (nitisinone) oral suspension
     4 mg/mL
   - Revise “☐” to “trisodium citrate dihydrate” in the inactive ingredients.
   - Revise the storage statements to the following:
     Must be refrigerated, store at 2°C to 8°C (36°F 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.

Recommendation:
The outstanding CMC label/labeling issues have been resolved. This application is now recommended for approval from the ONDP perspective.
Attachment - 1 (CMC Sections of the Revised Labeling and Container Labels)

1. Selected Sections of Revised Package Insert:

3. DOSAGE FORMS AND STRENGTHS
   - Capsules: 2 mg, 5 mg, and 10 mg white capsules imprinted with "NTBC" followed by "2 mg", "5 mg", or "10 mg", indicating the actual amount of nitisinone in each capsule.
   - Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension.

11. DESCRIPTION

ORI'ADIN contains nitisinone, which is a hydroxyphenylpyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

Nitisinone occurs as a white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

![Structural formula of nitisinone]

Figure 1. The molecular formula is C_{14}H_{13}F_{3}NO_{5} with a relative mass of 329.23

Capsules: Hard, white-opaque capsule, marked as 2 mg, 5 mg or 10 mg strengths of nitisinone, intended for oral administration. Each capsule contains 2 mg, 5 mg or 10 mg nitisinone, plus pregelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension. The inactive ingredients are hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzoate, citric acid monohydrate, trisodium citrate dihydrate, strawberry aroma (artificial) and purified water.

Glycerol: Each mL contains 500 mg.

Sodium: Each mL contains 0.7 mg (0.03 mEq).

16. HOW SUPPLIED/STORAGE AND HANDLING

Capsules: White capsules marked in black with "NTBC" and identified as 2 mg, 5 mg or 10 mg strengths of nitisinone. The capsules are packed in a high density (HD) polyethylene container with a tamper-resistant low density (LD) polyethylene snap-on cap. Each bottle contains 66 capsules.

2 mg white capsules imprinted "NTBC 2 mg" in black ink, NDC 66658-102-60

5 mg white capsules imprinted "NTBC 5 mg" in black ink, NDC 66658-105-60

10 mg white capsules imprinted "NTBC 10 mg" in black ink, NDC 66658-110-60

Store refrigerated, 2-8°C (36-46°F).

Oral suspension: White, slightly viscous opaque suspension. 1 mL contains 4 mg of nitisinone. The suspension is provided in a 100 mL brown bottle (type III glass) with a white child resistant HDPE screw cap with scaling and tamper evidence. Each bottle contains 90 mL oral suspension.

Oral suspension 4 mg/mL, NDC 66658-204-90

Store refrigerated at 2°C to 8°C (36°F to 46°F) prior to first use. Do not freeze. Store upright.
After first opening, store the product at room temperature (up to 25°C (77°F)) for up to 60 days. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle.

2. **Container labels (Final)**
Memorandum

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

Date: April 12, 2016
From: Danuta Gromek-Woods, Ph.D.
CMC Lead/ATL, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 206 356

Subject: Final Approval Recommendation

At the time when drug product review #1 was completed (03/18/2016), this NDA was not recommended for approval from the OPQ perspective due to unresolved CMC label/labeling issue.

Now the labeling issues are satisfactorily resolved via Amendments dated 03/24/2016 and 04/11/2016 with revised container labels and package insert. The revised container labels and package insert adequately addressed all CMC labeling issues (see the Addendum dated 4/12/16 prepared by Dr. Hong Cai).

The revised label/labeling are provided in the Attachment 1.

Recommendation:

This application is now recommended for Approval from the OPQ perspective.
Attachment – 1: Revised Labeling and Labels

1. Selected Sections of Revised Package Insert:

3. DOSAGE FORMS AND STRENGTHS
   - Capsules: 2 mg, 5 mg, and 10 mg white capsules imprinted with "NTBC" followed by "2 mg", "5 mg", or "10 mg", indicating the actual amount of nitisinone in each capsule.
   - Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension.

11. DESCRIPTION

ORFADIN contains nitisinone, which is a hydroxypyrophyl-pyruvate dioxygenase inhibitor indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

![Molecular structure of nitisinone]

Figure 1. The molecular formula is C_{12}H_{10}F_{3}NO_{4} with a relative mass of 329.23

Capsules: Hard, white-opaque capsule, marked as 2 mg, 5 mg or 10 mg strengths of nitisinone, intended for oral administration. Each capsule contains 2 mg, 5 mg or 10 mg nitisinone, plus pre-gelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

Oral suspension: 4 mg/mL, a white, slightly viscous opaque suspension. The inactive ingredients are hydroxypropyl methylcellulose, glycerol, polysorbate 80, sodium benzolate, citric acid monohydrate, trisodium citrate dihydrate, strawberry aroma (artificial) and purified water.

Glycerol: Each mL contains 500 mg.
Sodium: Each mL contains 0.7 mg (0.03 mEq).

16. HOW SUPPLIED/STORAGE AND HANDLING

Capsules: White capsules marked in black with "NTBC" and identified as 2 mg, 5 mg or 10 mg strengths of nitisinone. The capsules are packed in a high density (HD) polyethylene container with a tamper-resistant low density (LD) polyethylene snap-on cap. Each bottle contains 60 capsules.

2 mg white capsules imprinted "NTBC 2 mg" in black ink, NDC 66658-102-60

5 mg white capsules imprinted "NTBC 5 mg" in black ink, NDC 66658-105-60

10 mg white capsules imprinted "NTBC 10 mg" in black ink, NDC 66658-110-60

Store refrigerated, 2-8°C (36-46°F).

Oral suspension: White, slightly viscous opaque suspension. 1 mL contains 4 mg of nitisinone. The suspension is provided in a 100 mL brown bottle (type III glass) with a white child resistant HDPE screw cap with sealing and tamper evidence. Each bottle contains 90 mL oral suspension.
Oral suspension 4 mg/mL, NDC 66658-204-90

Store refrigerated at 2°C to 8°C (36°F to 46°F) prior to first use. Do not freeze. Store upright. After first opening, store the product at room temperature (up to 25°C (77°F)) for up to 60 days. If not used within 60 days, discard unused portion. The discard after date should be noted on the bottle.

2. Container labels (Final)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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ROBYN S JORDON
05/02/2016