CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-232

CHEMISTRY REVIEW(S)

1-17-02

NDA 21-232

ORFADIN (nitisinone) Capsules 2, 5, 10 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Swedish Orphan, AB

Indication: Treatment of Hereditary Tyrosenemia Type I

Presentations: 60 count [redacted] HDPE bottles w/ [redacted] snap off caps

EER Status: Acceptable 9/13/2001

Consults: OPDRA – Not acceptable 1/9/01

Nitisidone Capsules 2, 5, 10 mg , was manufactured by Apoteket, AB Gothenburg Sweden for Swedish Orphan, AB. Drug substance was manufactured by [redacted], and [redacted] drug substance was produced and is expected to be sufficient for several years. The firm has agreed to qualify a new supplier and address attendant issues.

- Swedish Orphan, AB agrees to provide information regarding the characterization and proof of structure for the drug substance in a Prior Approval Supplement after a new manufacturer has finalized the drug substance manufacturing process.

[redacted]

The 5/3/01 AE letter has been adequately responded to. The dissolution specification was revised in accord with our request. The stability protocol has been revised and an expiry of 18 months for refrigerated product has been established.

FPL has been submitted and is acceptable.

Over-All Conclusion
From a CMC perspective the application is recommended for approval.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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

/s/

Eric Duffy
1/17/02 05:17:58 PM
CHEMIST

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ON ORIGINAL

CHEMISTRY REVIEW

NDA 21-232

Orfadin Capsules
(nitisinone)

Swedish Orphan, AB

Sheldon Markofsky
DIVISION OF Metabolism and Endocrine DRUG PRODUCTS

File: _____

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Table of Contents

Chemistry Review Data Sheet

1. NDA 21-232

2. REVIEW #3

3. REVIEW DATE: 12-26-01

4. REVIEWER: Sheldon Markofsky

5. PREVIOUS DOCUMENTS

Previous Documents	Document Date
NDA (Original)	07-Sep.-2000
Amendment	03-Nov-2000
Amendment	04-Dec.-2000
Amendment	25-Jan.-2001
Amendment	26-Jan.-2001
Discipline Review Letter	14-Feb.-2001
Action Letter	02-May-2001
IR Letter	09-Nov-2001

6. SUBMISSION(S) BEING REVIEWED

Submission(s) Reviewed	Document Date
Amendment[1]	30-Mar.-2001
Amendment[2]	19-Jul.-2001
Amendment[3]	24-Aug.-2001
Amendment[4]	21-Nov. 2001

1) The 3-30-01 amendment provided responses to our Discipline Review Letter, dated 2-14-01.
2) The 7-19-01 amendment provided responses to the Action Letter, dated 5-2-01.
3) The 8-24-01 amendment provided revised labeling.
4) The 11-21-01 amendment provided responses to the Information Request Letter, dated 11-9-01.

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7. NAME & ADDRESS OF APPLICANT:

Name:	Swedish Orphan, AB
Address:	Drottninggatan 98 S 111 60 Stockholm Sweden
Representative:	Dr. Ronald G. Leonardi R & R Registrations P.O. Box 262069 San Diego CA 92196-2069
Telephone:	(858) 586-0751

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Orfadin
b) Non-Proprietary Name: Nitisinone (INN name)
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type 1
- Submission Priority P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of hereditary tyrosinemia, Type I

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 2, 5, & 10 mg

13. ROUTE OF ADMINISTRATION: Oral [For infants and very young children, the contents of the capsules are mixed with drinkable liquids and the resulting solution or suspension is taken orally.]

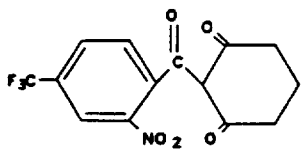
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical names
1. 2-(2-Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione
2. IUPAC name: 2-(2-Nitro-4-trifluoromethylbenzoyl)cyclohexane-1,3-dione
3. Other name: NTBC

Empirical formula: $C_{14}H_{10}NO_5F_3$
Mol Wt = 329.23

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	4	—	—	3	Adequate	5-6-99	----------
—	3	[ ]	Bottles & Caps	3	Adequate	8-9-01	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	—	IND for Nitisinone also called NTBC

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	9-13-01	
Pharm/Tox			
Biopharm	Acceptable	12-7-01	Hae-Young Ahn
LNC			
Methods Validation			
OPDRA			
EA	Consult not required		
Microbiology	Consult not required		

19. ORDER OF REVIEW OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

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ON ORIGINAL

The Chemistry Review for NDA 21-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry point of view, this NDA can be **approved.**

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

The applicant has made the following agreements:

- Swedish Orphan, AB agrees to provide information regarding the characterization and proof of structure for the drug substance in a Prior Approval Supplement after a new manufacturer has finalized the drug substance manufacturing process.
- Swedish Orphan, AB agrees to provide, in a Prior Approval Supplement for the qualification of a new manufacturer (for the drug substance)

[ ]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Product

Orfadin is a hard white-opaque capsule containing nitisinone, which is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate. The product is used in the treatment of hereditary tyrosinemia, Type I. Orfadin comes in 2, 5, & 10-mg strengths of nitisinone and is packaged in —-ml white-high-density-polyethylene bottles sealed with tamper-proof white-low-density polyethylene snap on caps.

This life-saving drug, for the treatment of 200-300 patients (worldwide) with hereditary tyrosinemia, Type I was given a high priority rating (1P).
The application is unusual in that, at present, ——— manufactures the drug substance. Due to a very small patient population, all of the CMC information was generated by a ——— of the drug substance, prepared by ——— Thus, the applicant has enough active ingredient on hand to manufacture the drug product, to be marketed after approval, but Swedish Orphan AB will have to qualify a new manufacturer of the drug substance in the future. In this connection, the applicant has made a number of agreements to assure the quality of any drug substance that will be produced by a new manufacturer.

The applicant has been granted an 18 month expiry for all strengths of Orfadin stored under refrigeration, 36-46 ^{0}F (2-8 ^{0}C).

All of the chemistry-related issues in the Discipline Review Letter, dated 14-Feb.-2001, the 02-May-2001Action Letter, and the Information request Letter of 09-Nov.-2001 have been satisfactorily addressed by the applicant.

2) Drug Substance

The chemistry, manufacturing, and controls information for Nitisinone, provided in NDA 21-232 is now considered satisfactory, after the application was revised based on reviewer's recommendations. All test method and acceptance criteria are considered to be **adequate** to assure the quality of the drug substance.

B. Description of How the Drug Product is Intended to be Used

In the treatment of hereditary tyrosinemia (type 1), the dose of nitisinone should be adjusted in each patient. The recommended initial dose is 1 mg/kg/day, divided for morning and evening administration. The total dose may be split unevenly as convenient in order to limit the total number of capsules given at each administration. For young children, the capsules may be opened and the contents suspended in a small amount of water immediately before use. In conjunction with the drug treatment, it is recommended that a nutritionist, skilled in managing children with inborn errors of metabolism, be employed to design a low-protein diet deficient in phenyalanine and tyrosine.

C. Basis for Approvability or Not-Approval Recommendation

Satisfactory CMC information has bee provided, and the cGMP compliance status is acceptable. Therefore the application is approvable from a Chemistry point of view.

III. Administrative

A. Reviewer's Signature

Sheldon Markofsky (Acting Team Leader)

B. Endorsement Block (OGD only)

C. CC Block **(OGD only)**

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ON ORIGINAL

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

/s/

Sheldon Markofsky
12/26/01 08:58:10 AM
CHEMIST

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ON ORIGINAL

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-232 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 4-4-01

SUBMISSION TYPE	DOCUMENT DATE	CDER Date	ASSIGNED DATE
NDA (Original)	9-7-00	9-8-00	10-20-00
Amendment	11-3-00	11-6-00	11-8-00
Amendment	12-4-00	12-6-00	12-12-00
Amendment	1-25-01	1-26-01	1-31-01
Amendment	1-26-01	1-29-01	1-31-01

NAME & ADDRESS OF APPLICANT:
Swedish Orphan, AB
Drottninggatan 98
Stockholm
Sweden 111 60

USA Authorized Representative:
Dr. Ronald G. Leonardi
R & R Registrations
P.O. Box 262069
San Diego CA 92196-2069
Tel: (858) 586-0751

DRUG PRODUCT NAME:
Proprietary: Orfadin
Nonproprietary: Nitisinone (proposed INN name)
Chem. type/Ther. Class: 1P

PHARMACOL.CATEGORY/INDICATION:
Treatment of hereditary tyrosinemia, Type I

DOSAGE FORMS:
Capsules

STRENGTHS: 2, 5, & 10 mg

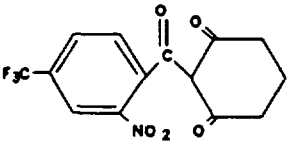
ROUTE OF ADMINISTRATION: Oral [For infants and very young children, the contents of the capsules are dissolved and the resulting solution taken orally]

DISPENSED: _X_ Rx __ OTC

SPECIAL PRODUCTS: _X_ Yes __ No
The capsules are made from gelatin, but we do not yet have conformation that the gelatin is in compliance with the (Sept. 1997) guidance on "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use".

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

2-(2-Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione
IUPAC name: 2-(2-Nitro-4-trifluoromethylbenzoyl)cyclohexane-1,3-dione
Other name: NTBC
$C_{14}H_{10}NO_5F_3$ Mol Wt = 329.23



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date
DMF —	———	———	Adequate	5-6-99

RELATED DOCUMENTS: IND —

CONSULTS: Office of Post-Marketing Drug Risk Assessment

REMARKS/COMMENTS:

This review is an addendum to Chemistry Review # 1, dated 2-5-01; and this latest review identifies additional deficiencies that the applicant should address. [The deficiencies noted in Review # 1 were forwarded to the applicant in a 2-14-01 Discipline (Information Request) Review Letter.]

As noted in Chemistry Review #1, this life-saving drug, for the treatment of 200-300 patients (worldwide) with hereditary tyrosinemia, Type I was given a high priority rating (1P).

The application is unusual in that, at present — manufactures the drug substance. Due to a very small patient population, all of the CMC information was generated by a ——— of the drug substance, prepared by ——— Thus, the applicant has enough active ingredient on hand to manufacture the drug product, to be marketed after approval, but Swedish Orphan AB will have to qualify a new manufacturer of the drug substance in the future.

The deficiencies listed in Chemistry Reviews # 1 and # 2 are numerous, but the applicant should readily be able to remedy these deficiencies so as to produce satisfactory drug product from the ——— of drug substance. However, time consuming development and documentation will be needed to qualify drug substance from a new manufacturer.

CONCLUSIONS & RECOMMENDATIONS:

From a Chemistry point of view, this submission is approvable pending an acceptable cGMP status for the relevant manufacturing and testing facilities and satisfactory responses to the chemistry deficiencies. Issue an Information Request Letter.

cc:
Orig. NDA 21-232
HFD-510/Division File
HFD-510/Sheldon Markofsky (Review Chemist)
HFD-510/S.Yang (CSO)
HFD-510/D-G. Wu (Team Leader)
HFD-820/ S.Koepke/C. Hoiberg

Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader filename: _____

APPEARS THIS WAY
ON ORIGINAL

/s/

Sheldon Markofsky
4/5/01 08:52:14 AM
CHEMIST

You signed the hard copy [Shelly]

Duu-gong Wu
4/6/01 10:04:18 AM
CHEMIST

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-232 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 2-5-01

SUBMISSION TYPE	DOCUMENT DATE	CDER Date	ASSIGNED DATE
NDA (Original)	9-7-00	9-8-00	10-20-00
Amendment	11-3-00	11-6-00	11-8-00
Amendment	12-4-00	12-6-00	12-12-00
Amendment	1-25-01	1-26-01	1-31-01
Amendment	1-26-01	1-29-01	1-31-01

NAME & ADDRESS OF APPLICANT:
Swedish Orphan, AB
Drottninggatan 98
Stockholm
Sweden 111 60

USA Authorized Representative:
Dr. Ronald G. Leonardi
R & R Registrations
P.O. Box 262069
San Diego CA 92196-2069
Tel: (858) 586-0751

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Chem. type/Ther. Class: 1P

PHARMACOL.CATEGORY/INDICATION:
Treatment of hereditary tyrosinemia, Type I

DOSAGE FORMS:
Capsules

STRENGTHS: 2, 5, & 10 mg

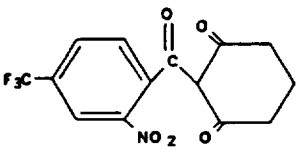
ROUTE OF ADMINISTRATION: Oral [For infants and very young children, the contents of the capsules are dissolved and the resulting solution taken orally]

DISPENSED: _X_ Rx ___ OTC

SPECIAL PRODUCTS: ____Yes _X_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

2-(2-Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione
IUPAC name: 2-(2-Nitro-4-trifluoromethylbenzoyl)cyclohexane-1,3-dione
Other name: NTBC
$C_{14}H_{10}NO_5F_3$ Mol Wt = 329.23



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date
DMF —	—	—	Adequate	5-6-99

RELATED DOCUMENTS: IND —

CONSULTS: Office of Post-Marketing Drug Risk Assessment

REMARKS/COMMENTS:

This life-saving drug, for the treatment of 200-300 patients (worldwide) with hereditary tyrosinemia, Type I was given a high priority rating (1P). Accordingly, the review process has been put on a "fast track".

The application is also unusual in that, at present, — manufactures the drug substance. Due to a very small patient population, all of the CMC information was generated by a — of the drug substance, prepared by — Thus, the applicant has enough active ingredient on hand to manufacture the drug product, to be marketed after approval, but Swedish Orphan AB will have to qualify a new manufacturer of the drug substance in the future.

The amendment, dated 11-3-00, provided details on the purification of the drug substance, the 12-4-00 amendment contained up-dated specifications for the drug substance, and the 1-25-01 amendment revised the labeling. The 1-26-01 amendment provided responses to a number of questions, posed in telephone conversations, with the applicant's USA representative. (See the **Telephone Memoranda** at the end of this review.)

The NDA is deficient for both the drug substance and the drug product in many ways (see **DRAFT LIST OF DEFICIENCIES** and **SUMMARY OF CHEMISTRY REVIEW**), but the applicant should readily be able to remedy these deficiencies. The cGMP inspections are still pending.

CONCLUSIONS & RECOMMENDATIONS:

From a Chemistry point of view, this submission is approvable pending acceptable cGMP inspections and satisfactory responses to the chemistry deficiencies. Issue an Information Request Letter. —

cc:
Orig. NDA 21-232
HFD-510/Division File
HFD-510/Sheldon Markofsky (Review Chemist)
HFD-510/S.Yang (CSO)
HFD-510/D-G. Wu (Team Leader)
HFD-820/ S.Koepke/C. Hoiberg

Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader filename: [redacted]

APPEARS THIS WAY
ON ORIGINAL

/s/

Sheldon Markofsky
2/6/01 11:21:10 AM
CHEMIST

Duu-Gong: You have already signed the hard copy

Duu-gong Wu
2/6/01 11:27:11 AM
CHEMIST