CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-232

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Swedish Orphan, AB
Drottninggatan 98
Stockholm, Sweden 111 60

2. TELEPHONE NUMBER *(Include Area Code)*

(858) 586-0751

3. PRODUCT NAME

ORFADIN, Nitisinone

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

Attached

5. USER FEE I.D. NUMBER

see Orphan Drug Letter (5/16/95)

6. LICENSE NUMBER / NDA NUMBER

Pending

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Ronald G. Leonardi, Ph.D.	R&R Registrations President	Dec. 27, 1995

FORM FDA 3397 (5/98)

Created by Electronic Document Services, DHHS (301) 443-2454 EF

01-1

Office of Drug Safety

MEMO

To: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

From: Carol Holquist
Deputy Director, Division of Medication Errors and Technical Support, HFD-400

Through: Jerry Phillips, RPh
Associate Director, Office of Drug Safety, HFD -400

CC: Su Yang, Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

Date: January 18, 2002

Re: ODS Consult 00-0307-1; **Orfadin** (Nitisinone Capsules), **NDA #: 21-232**

This memorandum is in response to a January 17, 2002, request from your Division for a re-review of the proprietary name, Orfadin. The Division of Medication Errors and Technical Support did not recommend the use of the proprietary name Orfadin upon our initial review in January 2001 (OPDRA consult 00-0307). The Division however, decided to permit the sponsor's proposed name based on the fact that this product is utilized for an extremely rare disease and the condition is such that it will be treated by a small number of specialists around the country. The care of these patients is likely to be intensive with frequent follow up because of the serious morbid and mortal risks associated with the disease that are unlikely to be completely eradicated by apparent effective therapy. DMETS was not aware at the time of review that the disease state was so rare and that the use of this product would be restricted to such a small patient population. Elements such as these are critical when determining the overall acceptability of a proprietary name. Therefore, based on the information that was not apparent at the time of our initial review DMETS reverses its decision on the acceptability of the proprietary name. DMETS has no objection to the use of the proprietary name "Orfadin".

Additionally, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Orfadin since we conducted our initial review that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

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

/s/

Carol Holquist
1/18/02 10:48:33 AM
PHARMACIST

Jerry Phillips
1/18/02 11:01:32 AM
DIRECTOR

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
November 8, 2000	January 26, 2001	00-0307

TO: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Su Yang, Project Manager
HFD-510

PRODUCT NAME:	MANUFACTURER: Swedish Orphan A
Orfadin (Nitisinone Capsule) 2 mg, 5 mg and 10 mg **NDA #: 21-232**	

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA conducted a review of the proposed proprietary name "Orfadin" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Orfadin". In addition, OPDRA recommends implementation of the enclosed labeling revisions in order to minimize the potential for medication errors.

APPEARS THIS WAY
ON ORIGINAL

/S/ 1/8/01

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 1/5/01

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **January 4, 2001**

NDA NUMBER: **21-232**

NAME OF DRUG: **Orfadin**
(Nitisinone Capsules) 2 mg, 5 mg and 10 mg

NDA HOLDER: **Orphan Pharmaceuticals USA**

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proposed proprietary drug name, Orfadin, regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION
Orfadin contains the active ingredient nitisinone and is indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) and has been granted Orphan Drug Designation. Hereditary tyrosinemia type 1 is a rare disease with poor prognosis. In patients with HT-1, toxic metabolites accumulate in liver and kidney because of a deficiency of fumarylacetoacetase, which is the final enzyme in the tyrosine catabolic pathway. Nitisinone inhibits the activity of 4-hydroxyphenylpyrubate dioxygenase, which is the second enzyme of the same pathway, and as a result the accumulation of toxic tyrosine metabolites in patients with HT-1 is reduced or prevented. An initial dose of 0.5 mg/kg/body weight twice daily is recommended. The product will be supplied as 2 mg, 5 mg and 10 mg capsules.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Orfadin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum. and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS. The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book

[v] WWW location http://www.uspto.gov/tmdb/index.html.

conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several products were identified in the Expert Panel Discussion that was thought to have potential for confusion with Orfadin. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns about the name with regard to promotional claims.

TABLE 1

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other****
Orfadin	Nitisinone Capsules, 2 mg, 5 mg, or 10 mg	0.5 mg/kg body weight twice daily.	
Rifadin	Rifampin Capsules, 150 mg and 300 mg Rifampin Injection, 600 mg/vial	For TB: 10 mg/kg, in a single daily administration. Meningococcal Carriers: 600 mg twice daily for 2 days	S/A, L/A per OPDRA
Coumadin	Warfarin Sodium Tablets, 1 mg, 2 mg, 2½ mg, 3 mg, 4 mg , 5 mg, 6 mg, 7½ mg and 10 mg. Warfarin Sodium Injection, 2 mg/mL	Dosage individualized according to the patient's PT/INR response to the drug.	S/A, L/A per OPDRA
Claritin	Loratadine Tablets, Syrup and Rapidly-Disintegrating tablets, 10 mg, 1 mg/mL	10 mg once daily.	S/A, L/A per OPDRA
Oraphen-PD	Acetaminophen Elixir 120 mg/5 mL	Dose dependent on age and weight.	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

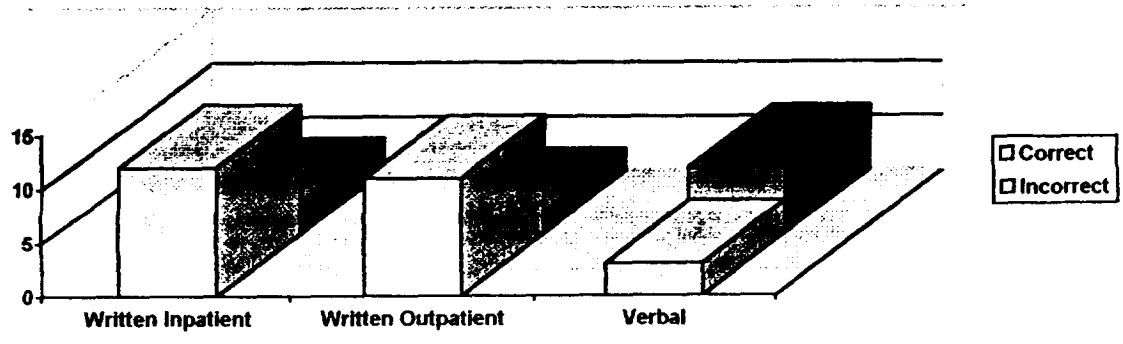
Three separate studies were conducted within FDA, to determine the degree of confusion of Orfadin with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 87 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Orfadin (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	**VERBAL PRESCRIPTION**
Outpatient: Orfadin 10 mg Sig: i po bid No refills	*Outpatient:* Orfadin 10 mg, Take one twice a day, with no refills
Inpatient: Orfadin 10 mg po bid	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Orfadin" response	Other response
Written: Outpatient	28	13 (46 %)	11 (85 %)	2 (15 %)
Inpatient	29	15 (52 %)	12 (80 %)	3 (20 %)
Verbal: Outpatient	30	9 (30 %)	3 (33 %)	6 (67 %)
Total:	87	37 (43 %)	26 (70 %)	11 (30 %)



Among participants in the written prescription studies for Orfadin, 23 of 28 respondents (82 %) interpreted the name correctly. *Three* respondents interpreted the name as *"Cefadin"*. The two remaining misinterpretations were: Crfadin and Gryadin.

Among participants in the verbal prescription study for Orfadin, 6 of 9 (67 %) participants interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Orfadin". Several respondents heard "fa" in "Orfadin" as a "p", "tho", "ph" or "fi". The misinterpretations were: Orpadin, orthoden, orfaden, orfedin, orphadin, and orfidin.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Orfadin", the primary concerns raised were related to several sound-alike, look-alike names that already exist in the U.S. marketplace. Rifadin and Coumadin were considered to be the most problematic in terms of their potential for medication errors.

Rifadin is a semisynthetic antibiotic derivative of rifampin SV. Rifampin is indicated for the treatment of all forms of tuberculosis and for the asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. Rifadin is available as 150 mg and 300 mg capsules for oral administration. Rifadin and Orfadin not only sound similar when spoken but look similar when scripted. Each name contains seven characters that are extremely similar to one another (see below). The two products will be available as capsules for oral administration. Furthermore, Orfadin is available as a capsule and is dosed on a mg/kg basis. Therefore, doses of 15 mg or 30 mg are possible. Rifadin is available as 150 mg and 300 mg capsule. Post-marketing experience has demonstrated errors confusing decimal point placement. If these products were inadvertently dispensed for one another it could result in a potentially fatal outcome. An interruption of Orfadin therapy could result in toxic effects caused by an increased plasma tyrosine level and death. Rifadin has also been shown to produce liver dysfunction and is only administered to patients with impaired liver function in cases of absolute necessity. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents.

rifadin 150 mg	Orfadin 15.0 mg

Coumadin is the proprietary name for warfarin sodium, which is an anticoagulant that acts by inhibiting vitamin K-dependent coagulation factors. Coumadin is available as a tablet with varying strengths. Orfadin and Coumadin look similar when scripted, share overlapping strengths (2 mg, 5 mg and 10 mg), and dosage forms (oral). As demonstrated in the written studies an "O" is often misinterpreted as a "C". Confusion between these two products could also result in hemorrhage and death.

coumadin 2mg	orfadin 2mg

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was *no* confirmation that *Orfadin* could be confused with *Rifadin* or *Coumadin*, however *negative* findings in these studies are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of incorrect responses were misspelled or phonetic variations of Orfadin, however, *three* respondents interpreted "Orfadin" as "Cefadin". Cefadin is a cephalosporin currently marketed in Europe.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the carton labeling, and draft package insert for Orfadin, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABELS

1. Relocate the strength so it does not appear as part of the established name.

2. The labels appear similar when compared side-by-side. Therefore, to minimize product confusion we recommend differentiating the product strengths with the use of boxing, contrasting colors or some other means.

3. Revise the "Caution: Federal Law..." statement to read "Rx only".

4. The manufactured by statement is not consistent with the statement that appears in the package insert labeling. Please revise accordingly.

B. INSERT LABELING

1. DOSAGE AND ADMINISTRATION

The insert states the dosage of orfadin should be adjusted individually and recommends an initial dose of 0.5 mg/kg/body weight twice daily.

[ ]

2. See comment 3 above.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name "Orfadin". OPDRA recommends implementation of the above labeling revisions in order to minimize the potential for medication errors.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph., at 301-827-3231.

/S/ 1-8-01

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

CC: NDA 21-232
HFD-510; Division Files/ Su Yang, Project Manager
HFD-510; David Orloff, M.D., Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA
Electronic only cc:
HFD-400; Peter Honig, Director, OPDRA
HFD-040; Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-440; Mary Dempsey, Project Manager, OPDRA
HFD-400; Sammie Beam, Project Manager, OPDRA

ITEM 14
Patent Certification:

Swedish Orphan, AB certifies that patent numbers 5,006,158; 4,695,673 and 5,550,165 will not be infringed by the manufacture, use, or sale of Orfadin™, nitisinone, for which this New Drug Application is submitted. Swedish Orphan, AB will comply with the requirements under 21CFR 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under 21CFR 314.52(c) with respect to the content of the notice.

ITEM 13
Patent Information:

Swedish Orphan, AB declares that the following patents cover the drug substance and drug product, Orfadine™, nitisinone, the subject of this New Drug Application.

Patent number 5,006,158: Composition of matter patent (Drug Substance).
Issued 9th April 1991, expiry date 9th April 2008.

Patent number 4, 695, 673: Process patent.
Issued 22nd September 1987, expiry date 20th December 2004.

Patent number 5, 550,165:Pharmaceutical composition/method of treatment patent.
Issued 27th August 1996, expiry date 27th August 2013.

Please also see the letter from AstraZenica, enclosed, noting that Swedish Orphan, AB has been granted a non-exclusive global sub-license and license to the product know as NTBC, chemical formula 2(2-nitro-4-trfluromethylbenzoyl)-1,3-cyclohex-anedione (Patent number 5,006,158).

AstraZeneca

TO WHOM IT MAY CONCERN

Your Ref	Our Ref	Direct Line	FAX Number	Date
	CRWP/vab/061	01625 512591	01625 585618	08 December 1999

Dear Sir

I confirm that Zeneca Limited has granted a non exclusive global sub-licence and licence to Swedish Orphan A.B. in respect of NTBC having the chemical formula 2 (2-nitro-4-trifluoromthylbenzoyl)-1,3-cyclohexanedione.

For and on behalf of
Zeneca Limited

C R W Petty
Authorised Signatory

AstraZeneca
Alderley House
Alderley Park
[illegible]
Cheshire SK10 4TF
England

Tel +44 (0)1625 582828
Fax +44 (0)1625 585022/582572

005

ITEM 16

DEBARMENT CERTIFICATION

Swedish Orphan, AB located at Drottninggatan 98, Stockholm, Sweden SE-111 60, certifies that we did not and will not use, in any capacity, the services of any person debarred under section 306(k)(1)(a) or (b) of the Act [21 U.S.C. 335 (a)(k)(1)] in connection with this New Drug application.

.....

Staffan Strömberg, Ph.D.
Swedish Orphan AB

.....

Ronald G. Leonardi, Ph.D
R&R Registrations
U.S. Agent for Swedish Orphan AB

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 18, 2002

To: Ronald G. Leonardi	From: Samuel Y. Wu
Company: R & R Registration	Division of Metabolic and Endocrine Drug Products
Fax number: 858-586-1108	Fax number: (301) 443-9282
Phone number: 858-586-0751	Phone number: 301-827-6416
Subject: Orfadin - Approval	
Total no. of pages including cover: 14	

Comments:

Document to be mailed: ☒ YES ☑ NO

APPEARS THIS WAY
ON ORIGINAL

SEP 21 2000

NDA 21-232

Swedish Orphan AB
R & R Registrations, agent
Attention: Ron Leonardi, PhD
President
P.O. Box 262069
San Diego, CA 92196-2069

Dear Dr. Leonardi:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our February 25, 2000, refusal to file letter for the following:

Name of Drug Product:	Orfadin (nitisinone) Capsules, 2, 5, 10 mg
Review Priority Classification:	To be determined at the filing meeting
Date of Application:	September 7, 2000
Date of Receipt:	September 8, 2000
Our Reference Number:	NDA 21-232

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 7, 2000, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA [redacted]
HFD-510/Div. Files
HFD-510/BLubas/DWu/JElHage/RShore/HAhn/TSahlroot
DISTRICT OFFICE

drafted by: MHess/9.15.00
initialed by: EGalliers/9.19.00
final: 9.20.00

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-232

5/3/01

Swedish Orphan, AB
R & R Registrations, U.S. Agent
Attention: Ronald G. Leonardi, Ph.D.
President
P.O. Box 262069
San Diego, CA 92196-2069

Dear Dr. Leonardi:

Please refer to your new drug application (NDA) dated September 7, 2000, received September 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orfadin Capsules (nitisinone) 2, 5, and 10 mg.

We acknowledge receipt of your submissions dated November 3 and December 4, 2000, and January 17, 18, 25, 26, and 29, 2001. We also acknowledge receipt of your submission dated March 30, 2001. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CHEMISTRY, MANUFACTURING, AND CONTROLS:

Drug Substance:

WITHHOLD 2 PAGE (S)

MANUFACTURING FACILITIES:

10. During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed by the inspector. Satisfactory inspections of all manufacturing facilities will be required before this application may be approved.

PRECLINICAL:

11. Your application does not contain an adequate reproductive toxicity evaluation. Submit data to address this deficiency or an argument to justify why the data are not needed prior to approval.

BIOPHARMACEUTICS:

12. To elucidate the effect of food on the bioavailability of nitisinone, submit data that indicate how the drug product was actually administered during the clinical trial in relationship to food. These data can include dosing diaries from patients or verbal recommendations made from

clinical study staff. In addition, provide information on the palatability of the drug product in water.

MISCELLANEOUS:

13. Submit a Form FDA 356h signed by the applicant and countersigned by you, as agent.

14. Submit a debarment certification signed by a responsible officer of the applicant and countersigned by you.

15. Provide a Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators signed by the applicant and countersigned by you.

16. It will be necessary for you to submit revised draft labeling.

    a. Our comments are included in the enclosed underline/strikeout version of your proposed package insert.

    b. Regarding container labels:

        i) Relocate the strength so it does not appear as part of the established name. The name of drug should be "Orfadin capsule (nitisinone) 10 mg. The trade name, the established name, and the strength should appear on separate lines.

        ii) The labels for the 2, 5, 10 mg capsule containers appear similar when compared side-by-side. Therefore, to minimize product confusion we recommend differentiating the product strengths with the use of boxing, contrasting colors, or some other means.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

17. Amend your application to state the following using identical or similar wording.

    a. Swedish Orphan AB will complete the ongoing stability studies (through the expiration period) on the three production (validation) batches of each strength of the drug product capsules, manufactured at the Apoteket AB production site, according to the approved, updated version of the Stability Protocol found in Vol. 1.3, page 196, of the initial submission.

    b. The approved Stability protocol may be used to extend the expiration date of the drug product based on real-time, long-term data under the approved storage conditions. Any post-approval extension will be reported in the annual report.

    c. One batch will be placed on stability annually under the approved storage conditions and tested until the end of shelf life.

d. The stability data will be submitted at the appropriate time intervals in the annual experience report or in a format specified by the FDA.

e. Any batch stored under label conditions that falls outside the approved specifications for the drug product will be withdrawn from the market or the deviation will be discussed with the FDA if Swedish Orphan AB believes that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product. A justification for the continued distribution of the batch will be included in the discussion.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   b. Present tabulations of the new safety data combined with the original NDA data.

   d. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   e. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final

print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Su Yang, MSN, RN, Regulatory Project Manager, at (301) 827-6385.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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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/

John Jenkins
5/3/01 01:24:16 PM

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NDA 21-232

Swedish Orphan, AB
R & R Registrations, agent
Attention: Ronald G. Leonardi, Ph.D.
President
P.O. Box 262096
San Diego, CA 92196

2/25/00

Dear Dr. Leonardi:

Please refer to your December 27, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Orfadin (nitisinone) Capsules, 2, 5, and 10 mg.

We have given your NDA a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this NDA under 21 CFR 314.101(d) for the following reasons:

1. No data were provided in the NDA to adequately link the bioavailability and/or clinical activity of the to-be-marketed formulation of nitisinone to the formulation that was used in the clinical trials that were submitted in support of the safety and effectiveness of the drug. The necessary linkage may be provided by submitting data from a comparative bioavailability study of the to-be-marketed formulation and the formulation used in the clinical trials. Alternatively, it may be possible to establish an adequate linkage between the two formulations by providing a complete report of the clinical data from those patients who received the formulation used in the clinical trials and those patients who received the to-be-marketed formulation. The complete report of the clinical data should include an intra-patient analysis; i.e., an analysis of data for each patient who received the clinical trials formulation and who was subsequently treated with the to-be-marketed formulation, and an inter-patient analysis; i.e., an analysis of data from patients who received the clinical trials formulation compared to patients who received the to-be-marketed formulation. The clinical study report should include laboratory data (e.g., plasma succinylacetone, urine succinylacetone, and urine 5-aminolevulinic acid,) and NTBC (nitisinone) serum concentrations. You are encouraged to consult the Division of Metabolic and Endocrine Drug Products (the Division) for guidance regarding the collection, analysis, and format for submission of the clinical data if you decide to pursue this

option to link the two formulations. You are also encouraged to consult the Division for guidance regarding the design of a comparative bioavailability study of the two formulations if you decide to pursue this option and such data are not currently available.

2. No data were provided in the NDA to adequately validate the assays for plasma concentrations of NTBC and tyrosine. Without adequate data to validate these assays it is not possible to review and evaluate the pharmacokinetic data included in the NDA. Such data should consist of a complete assay description and assay validation report including information of sensitivity, specificity, recovery, linearity, percent accuracy, and precision (within and between runs) for the assay. Representative standard curves covering the range of concentrations found in the studies and chromatograms should be included in the report. In addition, drug stability data during collection, processing, and storage of samples, and during assay procedures should be provided.

We also offer the following comments and recommendations unrelated to our refusal to file your application that should be considered upon resubmission:

1. Please refer to the Agency's minutes of the December 17, 1998, pre-NDA meeting with representatives of your company. At that time it was agreed that plasma concentrations of NTBC were to be collected from study subjects and that similar data in children would be submitted. This information was not included in the NDA submission. Also, at the same pre-NDA meeting, solubility profiles at different pHs as well as dissolution data were requested. This information, along with justification of the proposed dissolution method and specification, should also be provided in the NDA.

2. Please submit pharmacokinetic data from study CCT/96/001 (capsule and liquid bioavailability study) in electronic format, (preferably in Excel on a 3.5" diskette).

3. Please submit any information available (e.g., published literature) that pertains to the metabolism and excretion of NTBC in humans.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions, please call Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely yours,

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
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Concurrences:
RShore/2.24.00/HAhn/2.24.00/DOrloff/2.24.00/EGalliers/2.24.00/JJenkins/2.24.00

cc:
NDA 21-232
HFD-510/Div. File
HFD-510/WLubas/DOrloff/DWu/RSteigerwalt//DHertig/RShore/HAhn/Galliers
HFD-715/TSahlroot
HFD-094/DDMS
HF-35/MHaffner
DISTRICT OFFICE

drafted by: MHess/2.23.00/n21232 refuse to file.doc
final: 2.24.00

REFUSAL TO FILE (RF)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: February 17, 2001

FROM: David G. Orloff, M.D. /S/ 2-20-01
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-232
Orfadin (nitisinone) capsules
Swedish Orphan, AB

SUBJECT: NDA review issues and action

Background

Hereditary tyrosinemia Type 1 is an autosomal recessive inherited disease resulting from a deficiency in fumarylacetoacetase (FAH), the terminal step in tyrosine catabolism. The resultant block leads to toxic accumulation of tyrosine leading to ocular and dermatologic lesions and to renal phosphate wasting and rickets. In addition, and of greatest clinical significance in this disease, the site of the enzymatic block leads to shunting of tyrosine metabolism through succinylacetone and succinylacetate, metabolites apparently responsible for the attendant hepatic injury leading to liver failure and frequent hepatocellular carcinoma (HCC). In addition, the intermediates act as inhibitors of porphobilinogen synthase, leading to elevated plasma levels of 5-aminolevulinic acid and frequent porphyria-like crises.

Homozygotes exhibit a range of clinical presentations, likely related to the specific mutation(s) within the FAH gene carried by the patients. The variable natural history directs three categories of severity of HT-1 based upon age at presentation: those presenting before 6 months of age (the majority of cases), those presenting between 6 and 12 months of age, and those presenting after 1 year of age. All are prone to the same complications, with the later presenters exhibiting a more chronic progression to liver failure and possible hepatocellular carcinoma.

Conventional therapy involves dietary restriction of tyrosine and phenylalanine and liver transplantation in the event of hepatic failure or HCC. Liver transplantation does not result in resolution of the renal dysfunction associated with HT-1.

Nitisinone (NTBC, Orfadin) was originally developed as a potential herbicide and only later discovered to be a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an upstream enzyme of tyrosine metabolism. Blocking of tyrosine metabolism using nitisinone leads to dramatic reductions in succinylacetone and succinylacetate, apparently affecting the progression of liver disease and leading to marked reductions in the occurrence of porphyric crises.

Medical

Efficacy

Dr. Lubas has written a clear and thorough review of the clinical section of this NDA. The sponsors submitted data from an open-label treatment protocol initiated in 1991. Including safety update reports, the NDA contains efficacy and safety information on approximately 300 patients treated in 25 different countries through 1999, for a total exposure of approximately 1000 patient-years. The population studied constitutes the majority of the patients identified with this condition worldwide.

The sponsor presented data on drug levels and dose, plasma and urine tyrosine and tyrosine metabolites levels, plasma and urine levels of 5-aminolevulinate, RBC porphobilinogen synthase activity, as well as indices of liver function, alpha-fetoprotein, clinical imaging, and clinical outcomes. Laboratory indices were compared to baseline and clinical outcomes were compared to historical (published) series.

Of note, the original application for Orfadin was not filed. This refusal was based on the absence of sufficient information to bridge the clinical safety and efficacy data from the formulation used in the clinical trials up to 1998 to the to-be-marketed formulation used only later in the clinical studies. Resubmission contains adequate clinical information to bridge the formulations, establishing that the two are apparently therapeutically equivalent. Dr. Lubas has addressed these data in his review.

In sum, use of NTBC in patients with HT-1 resulted in marked improvement in survival and reduction in incidence of liver failure and transplantation as well as in cases of HCC compared to historical controls in the subgroup (most of the patients) with the early onset variant of the disease. All patient subgroups showed evidence of clinical improvement with regard to porphyric crises relative to historical controls, with only three incidents reported in the NDA from the clinical study and in follow up safety reports. The failure to demonstrate efficacy based on the former parameters for the other variants likely relates to issues of patient number and duration of treatment and follow up. It seems likely that early diagnosis and treatment of all patients with HT-1 will be of both short and long-term benefit.

Indices of liver function and injury, alpha-fetoprotein, and markers of renal function also improved markedly, on average.

The data submitted yield important information with regard to what are therapeutic nitisinone levels, as well as with regard to markers of favorable biochemical response that can be used in follow up of patients treated with Orfadin.

Safety

As Dr. Lubas makes clear in his review, the serious adverse events observed in this protocol are the result of the underlying disease. The most common adverse events attributed to drug are eye disorders including conjunctivitis, blepharitis, keratitis, eye pain, photophobia, and corneal opacities. These appear related to elevated plasma tyrosine levels, respond to dietary restriction in tyrosine and phenylalanine and/or reduction in NTBC dose, and are largely reversible.

A few patients experienced transient leucopenia and/or thrombocytopenia, with no episodes of bleeding or infection. These were not clearly related to Orfadin treatment as some episodes resolved without a change in dose. The safety updates confirm the findings in the original data submission with regard to safety and tolerability.

In conclusion, from a clinical standpoint, Orfadin may be approved as a safe and effective therapy for HT-1. This is the first medical therapy for this serious and life-threatening condition.

Labeling
Labeling remains to be finalized, however, there are no major labeling issues to resolve.

Biopharmaceutics
The capsule form of Orfadin is bioequivalent to oral solution. Absolute bioavailability was not determined in humans, though animal data suggest that the drug is highly bioavailable (>90%). The drug has a long half-life (54 hours) and a protracted duration of action, with tyrosine levels in healthy volunteers remaining elevated for several weeks. The original ———) and the to-be-marketed formulation ———starch) have not been studied in a rigorous bioequivalence study, but, as above, clinical trial data (efficacy, safety, drug levels as a function of dose) support therapeutic equivalence.

[ ]

Pharmacology/Toxicology
Predictive of toxicity in humans, eye findings in the animal predominated. For unclear reasons, rats and dogs were particularly susceptible, with rabbits, monkeys, and mice less prone at human equivalent doses. No data on plasma tyrosine levels were reported by the reviewer that might explain these differences. As above, the ocular adverse events are attributed to the elevated tyrosine levels that result from the mechanism of action of the drug as an inhibitor of a proximal step in tyrosine metabolism.

There is no evidence of teratogenicity or mutagenicity of NTBC.

Chemistry/ Microbiology
The application is approvable from the standpoint of ONDC, pending satisfactory response to certain deficiencies identified. The site inspection is scheduled for March 8, 2001.
A categorical exclusion from the environmental assessment appears warranted, though the chemist requires formal justification from the sponsor prior to granting the waiver.

DSI/Data Integrity
No DSI inspections were requested. The open-label nature of the study, the fact that the data submitted were essentially culled from clinical records, and the quality of the submission received led to the conclusion that an inspection would yield no useful information in the assessment of data integrity.

Financial disclosure

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature
The OPDRA reviewer recommended against the name Orfadin, citing potential for confusion with Rifadin (rifampin capsules or injection), Coumadin (tablets and injection), Claritin (tablets and syrup), and Oraphen-PD (acetaminophen elixir).

The Division has decided to permit the sponsor's proposed name. Orfadin (nitisinone) tablets is a treatment for an extremely rare disease that will likely not even be available in the vast majority of pharmacies in the United States. Hereditary tyrosinemia Type 1 is a condition that is and will continue to be treated by a small number of specialists around the country. Care is likely to be intensive, with frequent follow up because of the serious morbid and mortal risks associated with the disease that are unlikely to be completely eradicated by apparent effective therapy with NTBC. Drug is likely to be dispensed through hospital or clinical research center formularies. Furthermore, it is not an intrinsically toxic drug.

Conclusions from studies investigating possible confusion with marketed drugs are problematic because the test name is not one with which practitioners are familiar (as it is not yet marketed and/or advertised). Notwithstanding these limitations of the methodology, OPDRA identified four specific drugs with which Orfadin might potentially be confused and addressed them in the consult.

The Division feels that there is little reason for concern for the reasons discussed above in addition to the following: Coumadin is a tablet and is unlikely to be prescribed to children (the population, at least initially, treated with Orfadin). Claritin is available in tablet or liquid dosage forms for symptomatic disease. Even if the drugs were confused, substitution would merely result in non-relief of symptoms for the intended Claritin user and deterioration leading to clinical evaluation in the HT-1 patient. Rifampin capsules are in 150 and 300-mg denominations. Orfadin doses range from 2-10 mg daily. Oraphen is an elixir.

In sum, the Division feels that the proposed name is acceptable.

Recommendation
From the standpoint of clinical safety and efficacy, this application may be approved. The ONDC review identified numerous minor deficiencies that preclude approval at this time. Therefore, the application is APPROVABLE pending resolution of the deficiencies. OCPB has recommended two phase 4 studies.

1/4/02

Memo to Division Files (This review supercedes the prior entry dated 11/29/01.)

NDA 21,232
Sponsor: Swedish Orphan AB
USAN Name: Nitisinone **Proprietary Name Orfadin™**
Category: New Drug Product
Indication: Treatment of Hereditary Tyrosinemia 1 (HT-1)

Medical Officer Review of the Periodic Safety Update covering the time period Jan. 1, 2000 to April 30, 2001 submitted June 21, 2001 in Response to Agency's May 3, 2001 Approvable Letter.

SAFETY UPDATE REPORT FROM JAN. 1, 2000 – April 30, 2001
A total of 281 patients were already on Orfadin™ at the beginning of this Safety Update. 37 new patients were enrolled during this treatment period. These data correspond to an additional 383 patient treatment years.

There were 3 deaths during the course of this safety update: one due to liver failure, one due to liver cancer and one due to a relapse of Hodgkin's lymphoma. There were 6 cases of liver failure and 5 cases of suspected liver cancer (4 verified), which are likely due to the natural history of HT-1 and not to the consequence of Orfadin™ therapy. In general the incidence of these adverse events is similar to what had been seen during the original NTBC Study and earlier Safety Update Reports. Data in this safety update confirm that there continues to be a small incidence of liver failure, and liver neoplasm despite present therapy. The currently proposed label recommends regular follow up of serum α-fetoprotein and liver imaging to screen for HCC. This should adequately address this concern.

Table 1 Summary of Patients with Serious Adverse Events in NTBC Study and SURs

# of pts in current SUR (n=318)	Adverse Event or Reason for Withdrawal	Outcome	NTBC Study (n=207) 441 pt-years 2/23/91-8/21/97 (pts/100 pt-yrs)	SUR 1 (n=262) 290 pt-years 8/22/97-12/31/98 (pts /100 pt-yrs)	SUR 2 (n=281) 254 pt-years 1/1/99-12/31/99 (pts /100 pt-yrs)	**SUR 3 (n=318) 383 pt-years 1/1/00-4/30/01 (pts /100 pt-yrs)**
6	Liver failure or GI bleed	death or transplant	3.2	3.8	2.0	**1.6**
1	Suspected HCC but not verified at surgery	transplant	1.4	0.3	0.8	**0.3**
4	Verified HCC	transplant	2.0	0.3	0.8	**1.0**
2	Elective/Unk	transplant	1.6	1.7	1.6	**0.6**
0	Porphyria	death	0	0	0.8	**0**
0	Cirrhosis		0	0	0.8	**0**

There were no Serious Adverse Events in the NTBC Study, Safety Update or Safety Addendum Reports that could be directly attributed to treatment with Orfadin™.

Adverse events, which may be causally related to Orfadin™ are eye symptoms, thrombocytopenia and leucopenia.

Table 2 Summary of Patients with Other Adverse Events in NTBC Study and SURs									
		NTBC Study Report 2/23/91-8/21/97		Safety Update 1 8/22/97-12/31/98		Safety Update 2 1/1/99-12/31/99		**Safety Update 3 1/1/00-4/30/01**	
		Pts	Pts/(100 pt-yrs)	Pts	Pts/(100 pt-yrs)	Pts	Pts/(100 pt-yrs)	**Pts**	**Pts/(100 pt-yrs)**
Blood Disorders	Thrombocytopenia	6	1.4	2	0.7	1	0.4	**0**	**0**
	Neutropenia	2	0.5	2	0.7	0	0	**0**	**0**
	Leucocytosis	0	0	0	0	0	0	**1**	**0.3**
	Leucopenia	4	0.9	0	0	1	0.4	**0**	**0**
Eye Disorders	Blepharitis	2	0.5	0	0	0	0	**0**	**0**
	Conjunctivitis	4	0.9	1	0.3	1	0.4	**1**	**0.3**
	Corneal Opacity	4	0.9	4	1.4	2	0.7	**1**	**0.3**
	Eye Pain	3	0.7	2	0.7	2	0.7	**0**	**0**
	Keratitis	5	1.1	3	1.0	2	0.7	**1**	**0.3**
	Photophobia	4	0.9	1	0.3	1	0.4	**0**	**0**

Eye symptoms, including conjunctivitis, corneal opacity and keratitis, continue to be seen in this safety update. They are presumed to result from tyrosinemia induced by treatment with Orfadin™ and are not due to the drug itself. The incidence of eye symptoms in this latest safety update is similar to what had been seen earlier. The currently proposed label has been drafted to recommend adherence to a tyrosine and phenylalanine restricted diet to maintain plasma tyrosine levels below 500 μmol/L in order to avoid eye toxicity (see **WARNINGS** section of label). This should adequately address this concern.

Transient thrombocytopenia and leucopenia were not seen in this safety update but instead there was the first report of a single patient with three transient episodes of mild leukocytosis over a 5 month period. The clinical significance of these epidoses is unclear and these may simply reflect transient leukocytosis from undiagnosed viral illnesses. The currently proposed label recommends regular monitoring of platelet and white blood cell counts to help identify these events (see **WARNINGS** section of label). This should adequately address this concern.

All other adverse events occurred with an incidence of less than 2% and were unlikely to be related to Orfadin™ therapy.

Conclusion-The incidence and type of adverse events in this safety update report was similar to what had been seen during the original NTBC Study and earlier safety updates. Currently proposed labeling adequately addresses these concerns and no new labeling is necessary. The sponsor has adequately addressed the medical issues related to the approvability of Orfadin™ for the treatment of HT-1.

Recommendations-Orfadin™ may be approved for the treatment of HT-1.

11/29/01

William Lubas, MD-PhD
FDA/CDER/ORM/ODEII/DMEDP
Medical Officer William Lubas, MD-PhD

cc: David Orloff, MD (Division Director)
cc: Mary Parks, MD (Medical Team Leader, Deputy Division Director)
cc: Samuel Wu (Project Manager)

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/s/

William Lubas
1/4/02 12:13:34 PM
MEDICAL OFFICER

David Orloff
1/4/02 02:56:25 PM
MEDICAL OFFICER

Mary Parks
1/4/02 03:55:03 PM
MEDICAL OFFICER

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ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21232/000**
Priority: **1P** Org Code: **510**
Stamp: **28-DEC-1999** Regulatory Due: **20-JAN-2002**
Action Goal: District Goal: **09-MAY-2001**
Applicant: **SWEDISH ORPHAN**
C/O R AND R REGISTRATIONS
262096
SAN DIEGO, CA 92196
Brand Name: **ORFADIN (NITISINONE) 2/5/10MG CAPSULES**
Established Name:
Generic Name: **NITISINONE**
Dosage Form: **CAP (CAPSULE)**
Strength: **2, 5, 10 MG**

FDA Contacts:

M. HESS	**(HFD-006)**	**301-594-5461**	**, Project Manager**
S. MARKOFSKY	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
D. WU	**(HFD-510)**	**301-827-6375**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 21-MAY-2001 by EGASM
ACCEPTABLE on 03-MAY-2001 by EGASM
WITHHOLD on 30-MAR-2001 by P. LEFLER (HFD-324) 301-827-0062

Establishment: **9611567**
APOTEKET
PRISMAVAGEN 2
KUNGENS, KURVA, SW SE-141 75
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **21-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: **9616033**
APOTEKET
S-401 20
HISINGBACKA, , SW
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **21-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

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