CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-232

CORRESPONDENCE

January 17, 2001

Product	Date
Orfadin - NDA 21,232	**2001-01-12**
Title **Documentation to support answers to questions received from FDA**	Signature Stro

Question:
FDA wants a DRAFT of label incl. PIL

Response:

Please find enclosed copies

Copy sent to: Ron Leonardi by courier.

Date: 2000 01 12

Signature: Stro

Original to be handed to Regulatory Affairs SOAB

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004

WITHHOLD 8 PAGE (S)

Draft

Labeling

1/4/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ronald G. Leonardi, Ph.D.
President
R & R Registrations
P.O. Box 262069
San Diego, CA 92196-2069

1/4/02

RE: NDA # 21-232
Nitisinone
MACMIS ID# 10180

Dear Dr. Leonardi:

This letter responds to your July 19, 2001, request to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for comments on proposed launch materials to promote the use of nitisinone. The materials include a press release, a [redacted] three convention panels, and a reprint entitled "Diagnosis and management of tyrosinemia type 1" authored by Holme and Lindstedt. DDMAC provided comments on the press release, [redacted] and convention panels in a letter to you dated August 8, 2001.

DDMAC has completed our review of the reprint and has no comments at this time.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #10180 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Margaret M. Kober
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Margaret Kober
1/4/02 03:34:18 PM

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R & R REGISTRATIONS DUPLICATE

Ronald G. Leonardi, Ph.D., President

P.O. Box 262069
San Diego, California 92196-2069

N 0002
NEW CORRESP

August 23, 2001

NDA 21-232
ORFADIN™, Nitisinone

Food and Drug Administration
David G. Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857 - 1706

RE: Promotion; LAUNCH MATERIALS

Dear Dr. Orloff:
Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for ORFADIN™, Nitisinone.

Additionally, On May 3, 2001 the Agency faxed and subsequently mailed an "Approvable" Letter which noted that before this application (NDA 21-232) may be approved, it will be necessary for us to address a number of issues. We addressed those issues in our responses to the Agency of July 19, 2001.

In that response we submitted draft Launch promotion to the Division as well as DDMAC (HFD-42) (see **Attachment** 16 in July 19, 2001 submission) in response to the Agency's directive. Subsequently, on August 8, 2001 we received comments from the Agency (DDMAC) to our draft promotion. On August 16, 2001 we submitted the changed pieces in accordance with the Agency's request and noted that we would utilize these pieces in our first campaign.

→ submitted to 510??

Submitted herewith in duplicate are copies of the same pieces sent to DDMAC, namely, 1) the _____ 2) three "Convention panels", and 3) a Press Release. Also, please find enclosed a signed Form FDA 356h.

If you have any questions please do not hesitate to call or E-mail me at the numbers noted.

Sincerely,

Ronald G. Leonardi, Ph. D.
R & R REGISTRATIONS
for Swedish Orphan, AB

cc: Swedish Orphan, AB; Rare Disease Therapeutics, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 21-232

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Swedish Orphan, AB	August 23, 2001
TELEPHONE NO. *(Include Area Code)* (858) 586-0751 US (Sweden 46-8-402-8330)	**FACSIMILE (FAX) Number** *(Include Area Code)* (858) 586-1108
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* Drottninggatan 98 S111 60 Stockholm Sweden	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code telephone & FAX number)* IF APPLICABLE R & R Registrations P.O. Box 262096 San Diego, CA 92196

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-232

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nitisinone	**Orfadin**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any*
2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)	NTBC

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	**2, 5, and 10mg**	Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Launch material; Promotional

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED one — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (I), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50(k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Ronald G. Leonardi, Ph.D., President	August 23, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
PO Box 262069, San Diego, CA 92196	(858) 586-0751

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing 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 (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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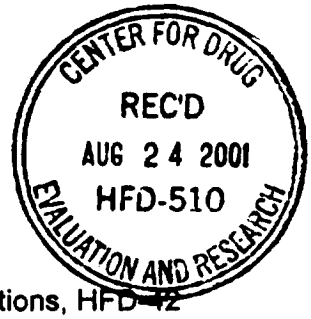
Please **DO NOT RETURN** this form to this address.

R & R REGISTRATIONS

Ronald G. Leonardi, Ph.D., President

P.O. Box 262069
San Diego, California 92196-2069



August 16, 2001

NDA 21-232
ORFADIN™, Nitisinone
MACMIS ID# 10180

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
Rm. 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: Agency letter dated August 8, 2001 regarding launch materials

Dear Director:

Reference is made to our New Drug Application (NDA 21-232) submitted to the Agency on September 7, 2000 for ORFADIN™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. On May 3, 2001 the Agency faxed and subsequently mailed an "Approvable" Letter.

Further, reference is made to a letter from DDMAC commenting on our July 19, 2001 submission of the initial launch material. We have revised the material and incorporated the Agency's comments received in the August 8, 2001 letter.

Submitted herewith in duplicate are our draft revised copies of the introductory promotional materials. It includes, ———————— 2) three "Convention panels", and 3) a Press Release.

If you have any questions please do not hesitate to call or E-mail me at the numbers noted.

Sincerely,

Ronald G. Leonardi, Ph. D.
R & R REGISTRATIONS
for Swedish Orphan, AB

cc: Swedish Orphan, AB; Rare Disease Therapeutics, Inc.

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Draft

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

8/2/2001

TRANSMITTED BY FACSIMILE

Ronald G. Leonardi, Ph.D.
President
R & R Registrations
P.O. Box 262069
San Diego, CA 92196-2069

RE: NDA # 21-232
Nitisinone
MACMIS ID# 10180

Dear Dr. Leonardi:

This letter responds to your July 19, 2001, request to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for comments on proposed launch materials to promote the use of nitisinone. The materials include a press release, [redacted] three convention panels, and a reprint entitled "Diagnosis and management of tyrosinemia type 1" authored by Holme and Lindstedt.

DDMAC has reviewed the proposed materials and offers the following comments that should be applied to these and all other current or future materials with the same or similar claims. Please note that our comments relate solely to the presentation of the promotional materials and do not in any way confer approval or acceptance of the proposed name. In addition, these preliminary comments are based on draft labeling. The promotional materials should be updated to reflect any changes made to the draft labeling prior to approval.

Press Release

The established name of the product (nitisinone) should accompany the proprietary name. We recommend that you revise the press release accordingly.

The indication presented in the first paragraph of the press release is incomplete because it does not identify nitisinone as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1). We recommend that you revise the materials to include the complete indication as expressed in the approved product labeling (PI).

The second sentence of the press release is grammatically incorrect.

The quote from Milton Ellis [redacted] is misleading because it implies a guarantee of efficacy for every nitisinone-treated patient. The claim overstates the benefits of nitisinone by implying a 100% cure rate.

The quote from Abbey Meyers [redacted] is misleading because it implies that nitisinone has a beneficial effect on productivity and overstates the effect on survival. These outcome claims are misleading without substantial evidence. We recommend that you either delete the claims or supply documentation to support their use.

The press release lacks fair balance because it fails to present any risk information. We recommend that you include information related to contraindications, warnings, precautions, and side effects associated with the use of nitisinone with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of nitisinone.

[redacted]

Convention Panels

The convention panels lack fair balance because they fail to present risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of nitisinone. In addition, the warning regarding high tyrosine levels is incomplete because it does not include information about toxic effects to the skin and nervous system.

The biochemical pathway depicted in the convention panels should be consistent with the corresponding information presented in the PI.

Reprint

We are currently reviewing the reprint of the article entitled "Diagnosis and management of tyrosinemia type 1" authored by Holme and Lindstedt. Upon completion of this review, we will provide comments on the reprint in a subsequent letter.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #10180 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Margaret M. Kober
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Margaret Kober
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/18/2001

TRANSMITTED BY FACSIMILE

Bo Allen
Rare Disease Therapeutics, Inc.
1101 Kermit Dr., Suite 608
Nashville, TN 37217-2126

RE: NDA # 21-232
Nitisinone
MACMIS ID# 10180

Dear Mr. Allen:

This letter responds to your June 27, 2001, request to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for comments on proposed launch materials to promote the use of nitisinone. The materials include two convention panels and a

DDMAC has reviewed the proposed materials and offers the following comments which should be applied to these and all other current or future materials with the same or similar claims. Please note that our comments relate solely to the presentation of the promotional materials and do not in any way confer approval or acceptance of the proposed name. In addition, these preliminary comments are based on draft labeling. The promotional materials should be updated to reflect any changes made to the draft labeling prior to approval. Final proposed launch materials may be submitted when the final approved product labeling (PI) is available.

Convention Panels

The indication presented in the convention panels is incomplete because it does not identify nitisinone as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1). We recommend that you revise the materials to include the complete indication as expressed in the PI.

The effect on overall survival featured in the convention panels represents a selective presentation of the more favorable results (29% to 88%) seen in patients presenting with HT-1 under 2 months of age. The less favorable results (60-74% to 94%) seen in patients presenting with HT-1 under 6 months of age should be included in this presentation to provide additional context for the claim. Similarly, the context that comparisons are based on historical controls should be included for this claim as well as the claim "reduced risk of liver transplantation or death due to liver failure".

The convention panels lack fair balance because they fail to present any risk information. We recommend that you include information related to contraindications, warnings, precautions, and side effects associated with the use of nitisonone with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of nitisinone.

The patient depicted in the convention panels is not representative of the results presented. The increased survival, based on historical controls, from 29% to 88% relates to patients presenting with HT-1 under 2 months of age and are rates for 2- and 4-year survival. We recommend choice of a younger model.

The biochemical pathway depicted in the convention panels appears to contain a typographical error (am1notransferase in place of aminotransferase).

[ ]

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #10180 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Margaret M. Kober
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Margaret Kober
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-232

INFORMATION REQUEST LETTER

11/9/01

R & R Registrations
Attention: Ronald Leonardi, Ph.D.
President
P.O. Box 262069
San Diego, CA 92196-2069

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.

We also refer to your July 19, 2001, submission responding to our May 3, 2001, approvable letter.

We are reviewing the chemistry, manufacturing and controls section of your July 19, 2001, submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:

1 Please amend the application to state that you agree 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.

The above three items may be submitted in one prior approval supplement.

Drug Product:

Post Approval Stability Commitments:

1. Two items in your Post Approval Stability Commitments should be modified to conform to the Revised Stability Protocol, provided in your March 30, 2001, amendment, using the following or similar wording:

   - Swedish Orphan AB commits to completing the ongoing stability studies (through the expiration period) on the three production (validation) batches of both the 2-mg and 10-mg strengths of capsules, manufactured at the Apoteket AB production site, according to the approved stability protocol.

   - One batch each of the 2-mg and 10-mg strengths of Orfadin will be placed on stability annually under the approved storage conditions and tested until the end of shelf life.

Labeling:

1. The initials —— should be removed from the nomenclature in the Description section of the package insert.

2. The route of administration of the drug product should be stated in the Description section of the package insert.

3. Please change your storage statement, in all of your labeling, from "Store Cold at 2-8^{0}C (36-

46^0F)" to either:

"Store refrigerated, 2-8^0C (36-46^0F)"
or
"Store in a refrigerator, 2-8^0C (36-46^0F)"

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Sheldon Markofsky, Ph.D.
Acting Chemistry Team Leader
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
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/s/

Sheldon Markofsky
11/9/01 03:10:27 PM

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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: May 3, 2001

To: Dr. Ronald Leonardi	**From:**
Company: R & R. Registrations	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) 827-6385

Subject: Crofadin (NDA 21-232) AE letter + Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: ☑ YES ☐ NO

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-232

DISCIPLINE REVIEW LETTER

2/14/01

Swedish Orphan, AB
R & R Registrations, Agent
Attention: Ronald G. Leonardi, Ph.D.
President
P.O. Box 262096
San Diego, CA 92196-2069

Dear Dr. Leonardi:

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

Our review of the Biopharmaceutics and Chemistry, Manufacturing and Controls sections of your submission are complete, and we have identified the following deficiencies:

Biopharmacetics Section:

> To elucidate the effect of food on the bioavailability of nitisinone, please submit data which indicate how the drug product was actually administered during the clinical trial in relationship to food. These can include dosing diaries from patients or verbal recommendations made from clinical study staff. In addition, please provide data on the palatability of the drug product in water.

Chemistry Section:

Drug substance

Drug Product

WITHHOLD 1 PAGE (S)

8) Please amend your application with the following Post Approval Stability Commitments using the following (or similar) wording.

- Swedish Orphan AB commits to 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 an approved up-dated version the Stability Protocol found in Vol. 1.3, pp. 196 of NDA 21-232.

- 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.

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

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

- Any batch stored under label conditions which 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.

9) Please amend your claim for a Categorical Exclusion from an Environmental Assessment with the following or similar wording:

> Swedish Orphan AB certifies that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Although not required for approval, please note that any future Prior Approval Supplement which provides for a new manufacturer of the drug substance should also include a qualification protocol for a new reference standard.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Kati Johnson
2/14/01 02:58:05 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-232

11/9/01

Swedish Orphan, AB
R & R Registrations, agent
Attention: Ronald G. Leonardi, Ph.D.
President
P.O. Box 262096
San Diego, CA 92196-2069

Dear Dr. Leonardi:

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

We also refer to our acknowledgment letter dated September 21, 2000, that stated the drug review classification for this application would be determined at the filing meeting.

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatment marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority review. The user fee goal date is March 8, 2001.

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

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

David Orloff
1/9/01 07:19:59 PM

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Electronic Mail Message

Date: 12/8/00 5:55:37 PM
From: Su Yang (YANGS)
To: leonardi@r-rregistrations.com
Subject: NDA 21232 Orfadin

Hi, Dr. Leonardi

Please refer to your letter page 2 paragraph 2 dated September 7, 2000. Our Pharm/Tox Reviewer would like to have the document you mentioned you would submit in that paragraph. If you have question, please let me know. Thanks,

Su Yang, DMEDP

/s/

Su Cha Yang
1/22/01 10:34:28 AM
CSO

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Electronic Mail Message

Date: 12/7/00 11:37:06 AM
From: Su Yang (YANGS)
To: leonardi@r-rregistrations.com
Subject: NDA 21-232 Orfadin

Hi, Dr. Leonardi:

Are the following information same as your original submission on December 1999?

1. Labels
2. Patent
3. Debarment
4. Financial Certification
5. Integrated Summary of Efficacy
6. Integrated Summary of Safety
7. Summary of Benefits/Risks
8. Safety Update

If not, please submit the most up-to-date information.
Thank you,

Su Yang, DMEDP

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/s/

Su Cha Yang
1/22/01 10:49:49 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND ——

JUL 7 1999

R.& R Registrations
Attention: Ronald G. Leonardi, Ph.D.
President
P.O. Box 262069
San Diego, CA 92196-2069

Dear Dr. Leonardi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food. Drug, and Cosmetic Act (the Act) for NTBC.

We also refer to your May 21, 1999, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating NTBC for treatment of Hereditary Tyrosinemia Type 1 as a fast track product.

We are granting fast track designation for the following reasons:

1. Hereditary Tyrosinemia Type 1 is a serious and life-threatening illness with a total worldwide population of less than 400 patients.

2. NTBC appears to improve survival and currently there is no pharmacologic therapy approved to treat this condition.

If you pursue a clinical development program that does not support use of NTBC for Hereditary Tyrosinemia Type 1. we will not review the application under the fast track development program.

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

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

May 16, 1995

Orphan Pharmaceutical USA, Inc.
Attention: Mr. Milton Ellis
President
1101 Kermit Drive, Suite 600
Nashville, TN 37217

Dear Mr. Ellis:

Reference is made to your orphan drug application of March 10, 1995 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of NTBC [2-(2-nitro-4-triflouromethyl-benzoyl)-1,3-cyclohexanedion]as an orphan drug (application #95-890).

We have completed the review of this application and have determined that NTBC qualifies for orphan designation for the treatment of tyrosinemia type I. Please note that it is NTBC and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if NTBC were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of NTBC as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Mr. Peter Vaccari at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

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ON ORIGINAL

1-18-02

Meeting Minutes

NDA #/Drug Name:	NDA 21-232 / Orfadin (nitisinone) Capsules
Meeting Date:	January 4, 2002
Time:	11:00 am
Location:	PKLN 14B45
Indication:	Treatment of Hereditary Tyrosinemia Type I
Sponsor:	Swedish Orphan
Type of Meeting:	Pre-Approval Safety Conference
Meeting Chair:	David Orloff, M.D., Division Director
Regulatory Project Manager:	Samuel Y. Wu, Pharm.D.
Participants:	John Jenkins, M.D., Director, OND David Orloff, M.D., Division Director, DMEDP Mary Parks, M.D., Deputy Director, DMEDP William Lubas, M.D., Medical Reviewer, DMEDP Toni Piazza-Hepp, Pharm.D., Associate Director, ODS Carolyn McCloskey, M.D., Epidemiologist, ODS Lanh Green, R.Ph., M.P.H., Team Leader, ODS Janos Bacsanyi, M.D., Safety Evaluator, ODS Paul D. Maher, M.D., Medical Officer, Orphan Drugs

Meeting Objective:
To discuss potential safety issues related to post-approval marketing.

Background:
Hereditary tyrosinemia type I (HT-1) is a rare genetic disease due to a deficiency in fumarylacetoacetase in the tyrosine catabolic pathway. This results in an accumulation of intermediate metabolites which are responsible for the liver and kidney toxicity observed in HT-1.

Nitisinone works by competitively inhibiting 4-hydroxyphenylpyruvate dioxygenase, an enzyme upstream of fumarlyacetoacetase in the catabolic pathway of tyrosine. and thereby prevents the accumulation of toxic metabolites. However, by blocking the catabolism of

tyrosine, nitisinone can also lead to potentially toxic elevations in serum tyrosine. Therefore, treatment with nitisinone requires the concomitant dietary protein restriction of phenylalanine and tyrosine.

Discussion Points:

Overall, there are no post-approval marketing safety concerns. This drug is used in a very small population, approximately — patients in the U.S., and has a limited distribution. With regular monitoring and follow-up, the incidence of adverse events such as eye disorders, thrombocytopenia and leukopenia can be reduced. In clinical trials a small percentage of patients still continue to develop porphyric crises, liver failure, and hepatic carcinoma which are part of the natural history of the disorder

Since the ramification associated with long term use , including carcinogenicity and reproductive toxicity, of nitisinone are unknown, the sponsor is encouraged to set up a registry to follow these patients. Although there is some concern with the use of the trade name, Orfadin, the potential for prescribing errors is reduced, again, due to its limited distribution.

Prepared by: _____, **Regulatory Project Manager**
Samuel Y. Wu, Pharm.D. **Date**

Approval: _____, **Meeting Chair**
David G. Orloff, M.D. **Date**

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

/s/

Mary Parks
1/18/02 02:55:17 PM
for Dr. Orloff

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: October 18, 2000 Time: 3:30 p.m. - 4:00 p.m. Location: PKLN 14B56

NDA 21-232 Orfadin (nitisinone) Capsules, 2, 5, 10 mg

Type of Meeting: Filing (internal)

Meeting Chair: Dr. David Orloff

Meeting Recorder: Ms. Maureen Hess

FDA attendees and titles:

Dr. David Orloff	Director, DMEDP
Dr. Bill Lubas	Medical Officer, DMEDP
Ms. Maureen Hess	Regulatory Health Project Manager, DMEDP
Dr. Duu-Gong Wu	Chemistry Team Leader, DMEDP
Dr. Hae-Young Ahn	Biopharmaceutics Team Leader, DPE II
Dr. Robert Shore	Biopharmaceutics Reviewer, DPE II
Dr. Jeri El Hage	Pharmacology Team Leader, DMEDP

Meeting Objectives:

Determine filing and review status of NDA 21-232 for the treatment of Hereditary Tyrosinemia Type 1.

Discussion Points:

Clinical: Fileable

Pharmacology: Fileable

Biopharmaceutics: Fileable

Chemistry: Fileable

Biostatistics: Not Needed, but will assist clinical and biopharmaceutics as needed.

DSI: Not Needed

Review Status: Priority

Decisions (agreements) reached:

The application will receive a Priority review. Review team was informed of the following timeline:

January 26, 2001: Final reviews, signed by team leader to the project manager.
February 5, 2001: Action package to Division Director
February 16, 2001: Action package to Office Director
March 8, 2001: User Fee Goal Date

Minutes preparer, Maureen Hess, MPH, RD /S/

Chair, David G. Orloff, MD /S/ 10-19-00

Concurrence:
RShore/10.19.00/DWu/10.19.00/HAhn/10.19.00/BLubas/10.19.00/TSahlroot/10.19.00

cc: NDA 21-232
HFD-510/Div. File
HFD-510/DOrloff/BLubas/HRhee/JElHage/DWu/RShore/HAhn/Tsahlroot/EGalliers
HFD-46/RBlay

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: May 16, 2000 Time: 11:30 a.m. – 12:30 p.m. Location: PKLN "C

NDA 21-232 Orfadin (Nitisinone)

Type of Meeting: Post Refuse to File

Meeting Chair: Dr. David Orloff

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Ronald Leonardi

FDA attendees and titles:

Maureen Hess, MPH, RD	Regulatory Health Project Manager, DMEDP
David Orloff, MD	Deputy Director, DMEDP
Todd Sahlroot, PhD	Statistical Team Leader, DOB II
Rob Shore, PhD	Biopharmaceutist, DPE II
Marlene Haffner, MD	Director, Office of Orphan Drugs
Tom Nguyen	Office of Orphan Drugs
Diane Centeno-Deshields	Office of Orphan Drugs
Bill Lubas, MD	Medical Officer, DMEDP
John Jenkins, MD	Acting Director, DMEDP

External participant and titles:

Mr. Milton Ellis	Orphan Pharmaceuticals, USA, President
Dr. Bo Hansen	Swedish Orphan AB, Toxicology Consultant
Dr. Ronald Leonardi	R & R Registrations, Regulatory Consultant
Ms Ruth Leonardi	R & R Registrations, Vice-President
Dr. Bo Lumholtz	

Meeting Objectives:

Meeting requested by R & R Registrations on behalf of Swedish Orphan AB to discuss the Agency's February 25, 2000, Refuse to File action taken on NDA 21-232.

Discussion Points:

- The sponsor stated that they have no presentation per se and posed the following questions to the Agency, based on the April 29, 2000 background package.

1. Does the Agency agree with the proposed analysis as noted in our protocol to support the bioequivalence of the formulations?

   The Division stated that the proposed analysis is unnecessary, adding that it prefers an analysis of the new formulation vs. old formulation and then a comparison between the two. The Agency requested that the sponsor focus on interpatient analysis rather than intrapatient analysis. The Agency added that it would like to see Kaplan Meier plots of survival, grouping all patients treated only with the new formulation. In addition, two other plots are also requested. The plots should be of dose normalized serum NTBC concentration vs. time for all patients treated only with the new formulation and all patients treated only with the old formulation. The Agency also requested the sponsor to demonstrate that the biochemical markers of effectiveness (e.g., succinyl acetone levels) are the same with both formulations. The sponsor acknowledged the Agency's recommendations.

2. Is it acceptable to use bioequivalence statistical principles under the conditions described in the protocol (e.g., randomization of treatment order not possible)?

   Formal statistical tests and confidence intervals will not be required.

3. Can the Agency accept the NTBC plasma/serum concentrations as a primary efficacy variable presented in the data package?

   The Agency requests that the data be presented as discussed in question #1.

4. Does the Agency agree with the primary efficacy variables chosen?

   The Agency agrees with the primary efficacy variables.

5. Can the Agency accept the validation of the methods for tyrosine and NTBC?

   The Agency stated that it would be acceptable for filing purposes, but it does recommend that the sponsor perform a cross-validation of the — assays for NTBC.

6. Will the Agency accept the use of 90% confidence intervals for the secondary variables?

   Not applicable, this pertains to the original protocols, which will be revised as discussed in question #1.

7. Can the Agency accept the dissolution data in light of the products solubility profiles at different pH's?

   The Agency offered the following comments/recommendations.

   The Agency stated that the dissolution testing conducted using the paddle apparatus at — rpm is unacceptable. The acceptable speeds are 50 or 75rpm for the paddle apparatus. The Agency referred the sponsor to the guidance for industry, "Dissolution Testing of Immediate Release Solid Oral Dosage Forms", August 1997. The Agency directed the sponsor to the following internet address: http://www.fda.gov/cder/guidance/1713bp1.pdf

   The pH — solution is not acceptable without justification. The recommended pH is 6.8. The other pHs submitted are acceptable.

   Regarding sink conditions, the Agency reminded the sponsor that sink conditions are at least three times the volume needed to reach maximum solubility.

   Twelve capsules should be used to set the final specification.

   The Agency recommended that the sponsor determine the appropriate BCS case for this drug.

Decisions (agreements) reached:

- The sponsor will revise and submit the NDA for filing as recommended by the Agency.

Minutes preparer, Maureen Hess, MPH, RD /S/

Chair, David Orloff, MD /S/

Concurrence: RShore/5.25.00/BLubas/5.31.00/DOrloff/6.2.00/TSahlroot/6.6.00/JJenkins/6.8.00

Cc:
NDA 21-232
HFD-510/Div. File
HFD-510/MHess/BLubas/TSahlroot/DOrloff/RShore/HAhn/
HF-35/MHaffner/DCenteno-Deshields/TNguyen
HFD-102/JJenkins

Meeting Date: February 10, 2000 Time: 2:30 p.m. - 3:00 p.m. Location: PKLN 1456

NDA 21-232 Orfadin (nitisinone)

Type of Meeting: Guidance

Meeting Chair: David Orloff, MD

External participant lead: Ronald Leonardi, PhD

Meeting Recorder: Maureen Hess, MPH, RD

FDA attendees and titles:
Robert Shore, PhD, Biopharmaceutics Reviewer, DPE II
Hae-Young Ahn, PhD, Biopharmaceutics Team Leader, DPE II
David Orloff, MD, Deputy Director, DMEDP
Bill Lubas, MD, Medical Officer, DMEDP
Maureen Hess, MPH, RD, Regulatory Health Project Manager, DMEDP
Su Yang, MSN, RN, Regulatory Project Manager, DMEDP

External participant attendees:
Ronald Leonardi, PhD R & R Registrations

Meeting Objectives

Meeting requested by FDA to discuss the biopharmaceutical section of the NDA and information that is still needed in order to file the application.

Discussion Points:

- The Agency stated that based upon its preliminary review of the biopharmaceutical information in the NDA, it notes that the clinical trial formulations ——— and the to-be-marketed formulations —starch—— are different. Because formulation changes can affect bioavailability of a drug substance and therefore the efficacy and safety of the drug, biopharm needs a "link" between the two formulations. Usually, a bioequivalence study would be used to "link" the formulations. The Agency stated that a bioequivalence study is not in the NDA submission and this is a filing issue, especially since the majority of the clinical data seems to have been generated with the clinical trial formulation. The sponsor replied that it does not have bioequivalence data. The Agency inquired if it is possible to identify patients that received the to-be-marketed formulation. The sponsor stated that there are a total of 207 patients in the submission with 35 of those in the United States. The —starch formulation was not introduced in the US until 1998. Data on clinical safety and efficacy were collected until 1999. The sponsor added that it has efficacy data in a small number of European patients, but none in US patients. The Agency stated that it will need to have data on a substantial number of patients who have received the new formulation. The Agency requested the sponsor to submit a listing of patients that have received the new

formulation and to identify those patients who were switched from the old formulation to the new formulation. The sponsor agreed to do so. The Agency advised the sponsor that the filing date is February 26, 2000, so this information will need to be submitted quickly. The sponsor understood the urgency.

- The Agency stated that there was no report on drug levels in the NDA and this was information that was requested to be included in the NDA at the pre-NDA meeting in December 1998. The sponsor stated that it realizes that these data were requested, but it could not be obtained and they didn't want to hold up the filing of the NDA. The Agency stated that this information will be needed, but at this time, for filing purposes, the sponsor should focus on obtaining the data needed on the new formulation.

Decisions (agreements) reached:

- The sponsor will submit to the NDA a listing of patients that have received the new formulation.

- Data on drug levels will be needed.

Post Meeting Action Items:

- On February 18, 2000, the sponsor submitted additional information. Upon review, it was determined that there was still not enough information to evaluate the drug for safety and effectiveness and a refuse to file letter was issued on February 25, 2000.

Minutes preparer, Maureen Hess, MPH, RD /S/

Chair, David Orloff, MD /S/

cc:
NDA 21-232
HFD-510/Div. File
HFD-510/RShore/HAhn/BLubas/DOrloff/MHess

Concurrence: RShore/3.1.00/HAhn/3.2.00/DOrloff/3.2.00/BLubas/3.6.00

Meeting Date: December 17, 1998 Time: 3:00 p.m. – 4:30 p.m. Location: PKLN "M"

IND —— NTBC

Type of Meeting: pre-NDA

Meeting Chair: Dr. David Orloff

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Ronald Leonardi

FDA attendees and titles:

Ms. Maureen Hess	CSO, DMEDP
Dr. Shelley Markofsky	Chemist, DNDC II
Dr. David Orloff	Medical Team Leader, DMEDP
Dr. Ron Steigerwalt	Pharmacology Team Leader, DMEDP
Dr. Lee Pian	Biostatistician, DOB II
Dr. Todd Sahlroot	Statistical Team Leader, DOB II
Dr. Jim Wei	Biopharmaceutist, DPE II
Dr. Hae-Young Ahn	Biopharmaceutical Team Leader, DPE II
Dr. John McCormick	Medical Officer, Orphan Drugs
Ms. Laura Governale	Orphan Drugs

External participant and titles:

Mr. Milton Ellis	Orphan Pharmaceuticals, President
Dr. Staffan Ekberg	Swedish Orphan AB, Medical Director
Ms. Annika Bergman	Swedish Orphan AB, Regulatory Affairs
————	———— Toxicology Consultant
Dr. Ronald Leonardi	R & R Registrations, Regulatory Consultant

Meeting Objectives:

Meeting requested by the sponsor of IND —— to discuss the application of an NDA for the use of NTBC in Hereditary Tyrosinemia type 1.

Discussion Points:

- The sponsor presented a brief overview of the toxicology program. The sponsor stated that the work on the toxicology program was done under GLP's, but was not audited. The Agency inquired if the sponsor has a report that can be retranscribed, so that it can review actual numbers. The firm responded that it does have that

information. The Agency advised the sponsor to submit that information in the NDA.

- The sponsor presented a clinical background, including biochemical markers in patients. The sponsor stated that survival is dependent on the age of the patient at first symptom. The Agency inquired if a correlation can be made between the response of a particular biochemical marker and a clinical response? The sponsor replied that it has not studied that and there is enormous individual variability. The Agency inquired if the patients are monitored for cataract formation. The sponsor replied that the patients are monitored and have had one report of crystal formation that was reversible, but have had thirteen reports documenting some type of eye problem. The firm added that there is no clear connection between the occurrence of eye problems and high tyrosine plasma levels. The Agency inquired if there was anything seen in animals, such as increased blinking or red eyes. The firm responded that there were some reports, but those were concerning corneal opacities.

Additional questions posed to the Agency by the sponsor in a pre-meeting package:

IND [redacted]

Drug: NTBC
Sponsor: Swedish Orphan AB
Indication: Treatment of Hereditary Tyrosinemia Type 1

1. Request for a Fast Track designation with a rolling review.

The Agency agrees that a Fast Track designation and a rolling review is appropriate for this drug and indication. However, the sponsor needs to make official requests for Fast Track designation and a rolling review. These must be separate requests, but may be made concurrently.

The sponsor also needs to submit a schedule for submission of information necessary to make the application complete.

2. **Pharmacology/Toxicology**:

The data the sponsor has is limited, but does have most of the individual animal data. Most of the work was not performed in compliance with GLP's. This is all the work the sponsor intends to perform on NTBC.

The Division is willing to work with the information that the sponsor has available. However, some issues need to be addressed in the label. Of concern are the eye and liver toxicities. These should be addressed in an animal toxicity section included in the label. Also, Phase 4 commitments may be an avenue of addressing concerns, if necessary.

IND —

Drug: NTBC
Sponsor: Swedish Orphan AB
Indication: Treatment of Hereditary Tyrosinemia Type 1

Other Pharmacology Issues:

None

3. **Clinical:**

The patient population has been divided into United States, Canada and the rest of the world (ROW) to attempt to show that there appears to be no major effect of regional treatment on critical parameters.

Does the Agency see any problem with using the entire patient population in support of the NDA?

No, the Agency does not have a problem if the entire patient population is used in support of the NDA.

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ON ORIGINAL

IND ——

Drug: NTBC
Sponsor: Swedish Orphan AB
Indication: Treatment of Hereditary Tyrosinemia Type 1

The sponsor feels that the preliminary findings indicate that the same patient treatment with ———— product or Swedish Orphan's product does not change the safety and efficacy of NTBC. Does the Agency agree?

The Agency believes that the label will have to assure safe, effective and optimal use and if there is evidence that this treatment should be titrated, that information may have to be teased out of currently available data.

Other Clinical Issues:

None

4. **Statistics:**

To summarize the study NTBC plus diet was compared with dietary treatment alone that came from historic data (van Spronson, et. al., 1994). The sponsor concludes "the survival" probability for patients with early presentation of HT-1 is significantly increased by combined NTBC and dietary treatment, compared with dietary treatment alone."

Is there a statistical analysis plan to compare NDA data with the historic data on the primary endpoint?

The sponsor stated that there is no formal statistical analysis plan. The sponsor presented the data in the form of a Kaplan-Meier curve and inquired if this would satisfy the statistical component. The Agency replied that a Kaplan-Meier presentation of the data is sufficient, but will still need an idea of overall outcomes. The Agency requested the sponsor to be as descriptive as possible in the NDA submission.

Will there be confidence intervals for the estimates of survival?

N/A

What are the cut-offs of the age group for the early presentation of HT-1?

N/A

5. **Biopharmaceutics:**

The Agency requests that the sponsor submit any pharmacokinetic information either from in-house or literature.

The Agency requests the measurement of two plasma samples from each patient in the ongoing clinical trials to assess NTBC levels in patients. The sponsor agreed to do so. The Agency also requested comparable plasma levels in children. The sponsor informed the Agency that it already has that data and will include that information in the NDA.

The Agency informed the sponsor that it will be necessary to perform three different solubility profiles at different pH's using gastric fluid, intestinal fluid and a buffer. The Agency added that if the pH change is <1, water may be used as a dissolution medium.

6. **DSI**:

The sponsor stated that there are two ongoing trials (both foreign) that DSI could audit and they will supply detailed information on these sites.

7. **Orphan Drug Products:**

Has an application been made for orphan status? Yes, in 1995.

Decisions (agreements) reached:

- The sponsor will include data in the NDA regarding the toxicology program in such a format, so that the actual numbers can be reviewed by the division.
- Fast Track desgination and a rolling review is appropriate for this drug and indication. The sponsor agrees to comply with the administrative requirements.
- The sponsor will submit the statistical data of the NDA in the form of a Kaplan-Meier curve. The sponsor will also include overall outcomes and descriptive information.
- The sponsor will perform the necessary solubility profiles and obtain the requested plasma samples for inclusion in the NDA.
- The sponsor will supply information on the foreign study sites prior to submission of the NDA.

Signature, minutes preparer: /S/

Concurrence Chair: /S/ 12-22-99

APPEARS THIS WAY
ON ORIGINAL

DATE: January 8, 2002, and January 17, 2002 1-17-02

SUBJECT: ADRA Review of NDA 21-232 Action Package

FROM: Leah Ripper, ADRA, ODE II

Drug: Orfadin (nitisinone) Capsules Classification: 1 P,V
Indication: As an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.
Type action: AP RPM: Samuel Wu, phone 7-6416

Date Orig NDA Rec'd:	09/08/00
User Fee Goal Date:	03/08/01
AE letter issued:	05/03/01
RS rec'd:	07/20/01
Date NDA Package Rec'd:	01/07/02
User Fee Goal Date:	01/20/02

This is a 505(b)(1) application. Patent info received.
EER: AC 5/21/01
Environmental Assessment: Categorical exclusion
Postmarketing Study Commitments: 1 commitment for reprotox battery
DSI: No clinical audits were requested.
Safety Update: SU submitted in resubmission; lock date was 4/30/01. Reviewed in MOR dated 1/4/02.
Trade Name Review: OPDRA did not recommend use of the tradename Orfadin; therefore, division did not send to OPDRA for update review. DD memos #1 and #3 document division decision finding name acceptable.
Financial disclosure: See #10 below.

1. The form 356h included in the package is signed only by the applicant's agent. Has the applicant ever signed a 356h for this NDA? If not, before approval, the applicant should be asked to submit a signed 356h, countersigned by their US agent.

   1/17/02: Correctly signed form was submitted 7/19/01

2. Debarment certification is not signed. Before approval, applicant should be asked to submit a statement signed by a responsible officer of the applicant, countersigned by the applicant's domestic agent.

   1/17/02: Correctly signed form was submitted 7/19/01

3. The Exclusivity Summary needs to be completed.

   1/17/02: PM will complete after approval.

4. The ePeds Page needs to be updated.

1/17/02: PM will complete after approval.

5. Generic name is — Letter should include a commitment to obtain a USAN and to change the labeling if the USAN is different from the —

1/17/02: Name has been submitted to USAN Council and will be considered at February meeting. Firm has agreed to change labeling if another name is chosen. Agreement is in AP letter.

6. The package contains letter from DDMAC re: their review of launch materials. Has MO reviewed the launch materials? Add a copy of the ——— and the press release to the package.

1/17/02: Launch materials reviewed in Dr. Lubas' January MOR (not yet finalized). PM to convey comments to DDMAC for any necessary action.

7. Was the dissolution spec in the 12/7/01 ClinPharm review sent to the applicant? Did they respond agreeing to it? If not, should be in AP letter.

1/17/02: Received in 1/7/02 submission.

8. Haven't received draft labeling and labels yet. Revised version was expected today.

1/9/02: Added to package

9. Dr. Koepke's comments on the CMC section of the previous action package are not in this package and I don't have a copy. Does the division have a copy?

1/17/02: Neither the review division nor Dr. Duffy was able to find a copy.

10. The financial disclosure information dated 7/1/09, which is a part of the 7/19/01 submission, ———————————
Need a MOR that addresses this since the original submissions said there were no financial interests to disclose.

1/17/02: See Dr. Lubas' January MOR (not yet finalized). See also my telecon memo of 1/17/02. Information submitted is acceptable.

Outstanding Items:

I am still working with the chemists on the exact working of the chemistry agreements in the AP letter.

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

/s/

Leah Ripper
1/17/02 06:45:46 PM
CSO
No DDR action required

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: December 28, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

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

SUBJECT: NDA review issues and recommended action

Background
In a letter of May 3, 2001, the Division and Office took an "approvable" action on the application for nitisinone capsules for the treatment of Hereditary Tyrosinemia Type 1 (HT-1). The deficiencies related mainly to CMC issues.

[redacted]

The sponsor was asked to address the absence of reproductive toxicity information for nitisinone, and to address the potential for a food effect on bioavailability by providing information on how the product was administered in the trials up to that point.

The sponsor was asked to commit to completion of ongoing and additional stability studies.

Revised draft labeling was appended to the action letter.

The sponsor responded to the AE letter on July 19, 2001. A CMC IR letter was sent to the sponsor on November 9, 2001. The sponsor responded on November 21, 2001.

Clinical
Dr. Lubas has reviewed the Periodic Safety Update covering the period January 1, 2001 to April 30, 2001. He concludes that the spectrum and frequency of adverse events is consistent with the previously reviewed experience and that the only serious AEs that are likely attributable to drug are ocular, related to the tyrosinemia induced by the drug, particularly in the setting of inadequate restriction of dietary tyrosine and phenylalanine. It is important to note as well that

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leucopenia and thrombocytopenia have also been observed in nitisinone-treated patients. These have occurred with low frequency and have not resulted in clinical sequelae (i.e., infection, bleeding). The label adequately addresses the safety concerns with this drug.

Biopharmaceutics

The sponsor provided ample evidence to support the conclusion that, for the most part, Orfadin was given with food in the clinical experience to date. However, the effect of food (e.g., a high fat meal) on Orfadin pharmacokinetics is not known. There is no recommendation for a food-effect study. Rather, OCPB recommends labeling under Dosage and Administration as follows: "Since an effect of food is unknown, nitisinone should be taken at least one hour before a meal."

I concur with these recommendations. Orfadin dose is individualized and adjusted based on pharmacodynamic measurements (biochemical intermediates in tyrosine metabolism). The drug itself is apparently non-toxic. No further characterization of a food effect is necessary for safe and effective use.

Pharmacology/Toxicology

The AE letter requested that the sponsor address the absence of reproductive toxicology information on nitisinone. The sponsor has responded to the satisfaction of the toxicology team. There are currently no HT-1 patients treated with Orfadin who are of childbearing age. To date, the use of this drug has been for what has always been a life-threatening pediatric inherited metabolic disease. The sponsor estimates that in 3-5 years, 2-3 patients will reach childbearing potential. The sponsor has committed to performing a standard reprotoxicity battery in phase 4. Pharm/Tox recommends approval.

Chemistry/ Microbiology/Compliance

Dr. Markofsky has reviewed the responses to the CMC deficiencies and has found them satisfactory. The issues surrounding the absence, currently, of a drug substance manufacturer have been resolved (see agreements, below). The sponsor has addressed the deficiencies related to the drug product. Dr. Markofsky has a single, minor typographical recommendation on labeling. The original OC withhold recommendations were based on review of the Forms 483 and the investigators' recommendations only. The OC now states cGMP compliance status is acceptable. ONDC now recommends approval.

The sponsor has made the following agreements (which will be reiterated in the action letter):

1. Swedish Orphan, AB will provide information on characterization and proof of structure for the drug substance as a PA supplement once a new manufacturer has finalized the drug substance manufacturing process.

[ ]

Labeling

NDA #
Drug:
Proposal:
01/04/02

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The sponsor has accepted our previous labeling revisions. The changes suggested by OCPB and ONDC have been conveyed.

OPDRA/nomenclature
OPDRA had originally recommended against the proprietary name "Orfadin." The Division accepts the name for the reasons discussed in my previous memo to this NDA.

Recommendation
This application may be approved with attendant agreements and Phase 4 commitments. A recommendation to the sponsor to establish a voluntary registry of HT-1 patients treated with nitisinone in order to collect information on clinical outcomes (e.g., survival, ocular and hematologic adverse events, intellectual/neurological development, hepatocellular carcinoma, renal function) with long-term treatment with nitisinone is included in the draft action letter.

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/s/

David Orloff
1/4/02 12:19:32 PM
MEDICAL OFFICER

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MEMORANDUM

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

DATE: April 10, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

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

SUBJECT: Addendum to Division Director memo dated February 17, 2001

This addendum is to note the following:

1. The inspection of the manufacturing facility for this product (Apoteket, Hisingbacka, Sweden) was performed as scheduled on March 8, 2001. A Form-483 was issued. The final report has not been submitted to the file. The overall recommendation from P. Alcock (HFD-324) is "withhold." The approvable letter has been amended to note that satisfactory inspections of all manufacturing facilities will be required before approval.

[redacted]

3. The application does not contain adequate reproductive toxicology information, and this will have to be addressed in the sponsor's response to the approvable action. The Division recommends that the reproductive toxicology studies be part of a Phase 4 commitment, and we intend to elaborate further details in post-action correspondence with the sponsor.

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Drug:
Proposal:
04/10/01