R & R REGISTRATIONS

ORIG AMENDMENT
N-000-nc

Ronald G. Leonardi, Ph.D., President

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

January 26, 2001

NDA 21-232
ORFADIN™, Nitisinone

Food and Drug Administration
John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857-1706

RE: CMC Questions from Dr. Markovsky

1. **Drug Substance, expression of impurity profile specification and sample chromatogram**
2. **Storage of Drug Substance**
3. **Drug Substance, terminology used for degradation product specification**

Dear Dr. Jenkins:

Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for Orfadin™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's call of October 19, 2000 from Ms. M. Hess notifying Swedish Orphan, AB that NDA 21-232 was accepted for filing on September 8, 2000.

Reference is also made to Dr. Markovsky's questions on December 5, 7 and 26, 2000 regarding the Drug Substance and the way we expressed the impurity profile specification, and request for a sample chromatogram of the Drug Substance. Dr. Markovsky also wanted to know the type of container used for storing the drug substance. Further, he asked for a clarification of the terminology used to describe the specification for the degradation product. Following are the responses to each of Dr. Markovsky's questions.

1. The known impurities are expressed in area%. The unknown impurities are also expressed as Area%. A sample chromatogram with peaks identified is included.

[ ]

3. Regarding the specification terminology, "check limit", for the degradation product, [redacted] of not more than [redacted] (w/w) means the limit of [redacted] in the product at the expiry date.

A completed and signed Form FDA 356h is included with this letter. If you have any questions please do not hesitate to call or email me.

Sincerely,

Ronald G. Leonardi, Ph. D
for Swedish Orphan, AB

cc: Swedish Orphan, AB; Orphan Pharmaceuticals USA, Inc.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

NDA 21-232

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Swedish Orphan, AB	January 26, 2001
TELEPHONE NO. *(Include Area Code)* 46-8-412 9800	FACSIMILE (FAX) Number *(Include Area Code)* 46 8 412 9899
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Kungsgatan 37 S111 56 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 Phone (858) 586-0751 Fax (858)m 586-1108

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 (INN)	**Orfadin**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any*
2-(2-Nitro-4-trifluromethylbenzoyl) 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 December 5, 7 and 26, 2000 Request from Dr. Markofsky regarding Drug Substance.

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.

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	19. OTHER (Specify)

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3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
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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
[signature]	Ronald G. Leonardi, Ph.D., President	January 26, 2001

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

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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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ıse **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

January 25, 2001

DUPLICATE

NDA 21-232
ORFADIN™, Nitisinone

Food and Drug Administration
John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857-1706

RE: FDA's Ms. Su Yang's E-mail and phone call of January 19, 2001; Revised Package Insert copy and diskette

Dear Dr. Jenkins:

Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for Orfadin™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's phone call of October 19, 2000 from Ms. M. Hess notifying Swedish Orphan, AB that NDA 21-232 was accepted for filing on September 8, 2000.

Reference is also made to Ms. Su Yang's email of January 18, and phone call of January 19, 2001 requesting the revised package insert be sent to the Agency on diskette as well as hard copy in preparation for the internal "labeling" meeting January 30th. We have included three copies of the "final" package insert with 2 diskettes.

Additionally, Ms. Yang asked if nitisinone was an approved name. It is our understanding that Nitisinone is requested as an International non-proprietary name (INN).

A completed and signed Form FDA 356h is included with this letter. If you have any questions please do not hesitate to call or E-mail me.

Sincerely,

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

cc: Swedish Orphan, AB; Orphan Pharmaceuticals USA, 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

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Swedish Orphan, AB	January 25, 2001
TELEPHONE NO. *(Include Area Code)* (858) 586-0751 US (Sweden 46-8-412-9800)	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)*: Kungsgatan 37, S-111 56 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

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REASON FOR SUBMISSION December 7, 2000 Request from Ms. Su Yang for updates to the NDA – Labeling (Package Insert).

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

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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.

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Ronald W. Leonardi	Ronald G. Leonardi, Ph.D., President	January 25, 2001

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FORM FDA 356h (7/97)

R & R REGISTRATIONS DUPLICATE

Ronald G. Leonardi, Ph.D., President

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

NDA 21-232
ORFADIN™, Nitisinone

January 18, 2001

BM

DRUG AMENDMENT

Food and Drug Administration
John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857-1706

RE: FDA's Ms. Su Yang's E-mail of December 8, 2000;
1 Plasma concentrations of NTBC in children
2 Cross Validation of — and Plasma NTBC ——— assay

Dear Dr. Jenkins:
Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for Orfadin™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's phone call of October 19, 2000 from Ms. M. Hess notifying Swedish Orphan, AB that NDA 21-232 was accepted for filing on September 8, 2000.

Reference is also made to Ms. Su Yang's E-mail on December 8, 2000 requesting the information referred to in our September 7, 2000 response to the Refuse to File(RTF) letter regarding plasma concentrations in children (page 2, paragraph 2 of the letter). Enclosed with this letter is a report " Case Reports on Serum Nitisinone (NTBC) concentrations in 7 patients with Hereditary Tyrosinaemia Type 1" Report # 2000 010 07, December 20, 2000 which includes and discusses the plasma concentrations in 4 patients following the first nitisinone dose and in 3 patients after discontinuation of maintenance therapy.

Additionally, in a recent discussion with Dr. Shore, he noted that the data for NTBC plasma concentration of all patients submitted in the original NDA in Volumes 1.17 to 1.22 (Case Report Tabulations) does not need to be resubmitted (see section of the RTF letter noted above).

Further reference is made to the May 16, 2000 meeting with the Agency regarding the RTF letter in which a cross validation of the assays for plasma (serum) concentrations of NTBC was recommended. We have included with this submission a Methods Validation report of the cross validation of the ——— assays for NTBC, titled "Plasma (serum) NTBC – ——— assay, Methods validation", Report 2000 010 06, October 26, 2000.

A completed and signed Form FDA 356h is included with this letter. If you have any questions please do not hesitate to call or email me at the numbers noted.

REVIEWS COMPLETED

Sincerely,

Ronald G. Leonardi, Ph. D.
R&R REGISTRATIONS
for Swedish Orphan, AB
cc: Swedish Orphan, AB; Orphan Pharmaceuticals USA, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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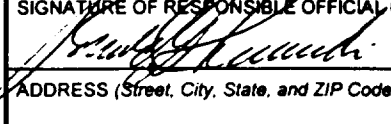
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. 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	January 18, 2001

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

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Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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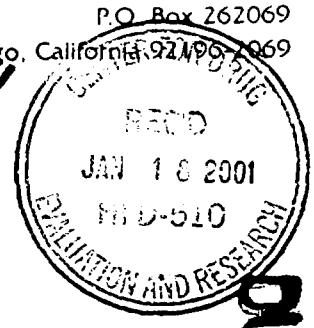
R & R REGISTRATIONS

Ronald G. Leonardi, Ph.D., President

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



DUPLICATE

January 17, 2001

NDA 21-232
ORFADIN™, Nitisinone

Food and Drug Administration
John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857-1706

RE: **FDA's Ms. Su Yang's call of December 7, 2000;**
Confirmation of Previously Submitted and Updated information.

Dear Dr. Jenkins:

Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for Orfadin™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's phone call of October 19, 2000 from Ms. M. Hess notifying Swedish Orphan, AB that NDA 21-232 was accepted for filing on September 8, 2000.

Reference is also made to Ms. Su Yang's E-mail on December 7, 2000 asking if the information noted below, as stated in the original submission of December 29, 1999, is applicable to the NDA submission of September 7, 2000 (response to Refuse to File letter) or were sections updated.

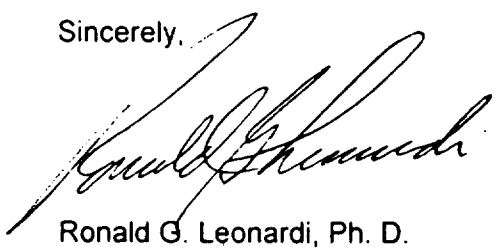
1. Labels
2. Patent
3. Debarment
4. Financial Certification
5. Integrated Summary of Efficacy (ISE)
6. Integrated Summary of Safety (ISS)
7. Summary of Benefit/Risks
8. Safety Update
9. Updated data for points 5 and 8

We have included with this submission three copies of Items 1 through 8 included in the original submission dated December 29, 1999 which are still applicable to the resubmission dated September 7, 2000. In addition we have added updated information (tab 9) submitted in the RTF response for points 5 and 8. Each part is clearly marked with a tab and a cover page to indicate contents of submission and reference to the original submission volume and page.

In addition we have only included three copies of a draft label and package insert for the 2mg capsule. The labels for the 5mg and 10 mg capsule are identical and will be submitted upon request. The text of the package insert has not been revised to reflect the Agency's fax and E-mail of a revised draft of proposed package insert text sent from Dr. Shore on December 28, 2000. However, the draft label shows the intended format of the label and package insert to be used for the marketed Orfadin™ capsule vials.

A completed and signed Form FDA 356h is included with this letter. 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; Orphan Pharmaceuticals USA, Inc.

**APPEARS THIS WAY
ON ORIGINAL**

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	January 17, 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-trifluromethylbenzoyl) 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 December 7, 2000 Request from Ms. Su Yang for updates to the NDA.

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))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	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)
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	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	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)
X	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

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.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Ronald G. Leonardi, Ph.D., President	January 17, 2001

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

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R & R REGISTRATIONS DUPLICATE

Ronald G. Leonardi, Ph.D., President

P.O. Box 262069
San Die[illegible]

November 3, 2000

NDA 21-232
ORFADIN™, Nitisinone

Food and Drug Administration
John Jenkins, M.D., Acting Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857 - 1706

RE: CMC Request from Dr. S. Markofsky
Supporting Documentation for NTBC ———

Dear Dr. Jenkins:
Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for ORFADIN™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's call of October 19, 2000 from Ms. M. Hess notifying Swedish Orphan, AB that NDA 21-232 was accepted for filing on September 8, 2000.

Additionally, reference is made to Agency's, Dr. S. Markofsky, request for information on ——— procedure for NTBC the Drug Substance of Orfadin, Nitisinone. He noted that the ——— is described adequately in Volume 1.2 page 149 of the NDA, but he could not find any description of the process used by —— He requested that we find out what we had or what we could get and fax it to him as well as sending it to the NDA as an Amendment.

On November 2, 2000 we faxed the enclosed information to Dr. Markofsky.

Submitted herewith in duplicate along with a completed and signed Form FDA 356h is a Chemistry Manufacturing and Control Amendment to NDA 21-232, which is composed of 19 pages describing ——— procedure for NTBC (Orfadin). This description was submitted to Swedish Orphan AB's IND —— as Amendment Serial #006, on November 27, 1996, pages 94 to 112.

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; Orphan Pharmaceuticals USA, 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	November 3, 2000
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*
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Capsules	**2, 5, and 10mg**	Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

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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

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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Request from Dr. Markofsky for NTBC recrystallization procedure.

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

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CERTIFICATION

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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.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Ronald G. Leonardi, Ph.D., President	November 3, 2000

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R & R REGISTRATIONS

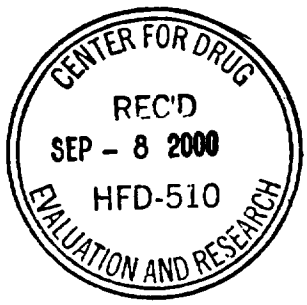
DUPLICATE
ORIG AMENDMENT
15 2

Ronald G. Leonardi, Ph.D., President

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

NDA 21-232
ORFADIN™, Nitisinone

September 7, 2000



Food and Drug Administration
John Jenkins, M.D., Acting Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857 - 1706

RE: NDA 21-232, ORFADIN™, Nitisinone
Response to Agency's February 25, 2000 "Refuse to File" letter;

ATTN: Ms. Maureen Hess, CSO

Dear Dr. Jenkins:
Reference is made to our New Drug Application (NDA 21-232) submitted to the Agency on December 27, 1999 for ORFADIN™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's "Refuse to File" (RTF) letter of February 25, 2000 which noted two areas upon which the Agency based its refusal to file NDA 21-232.

Also, reference is made to the meeting held with the Agency on May 16, 2000 which modified point one of the Agency's RTF letter among other comments and requested the Inter-patient analysis and not an Intra-patient analysis.

Submitted herewith in duplicate are responses to the "Refuse to File" (RTF) letter. As agreed at the May 16 meeting, a report on the comparison of patients receiving —— formulation and starch formulation of NTBC has been performed. This report, presented under Tab 1, in Vol. 1, contains patient serum concentrations of NTBC, laboratory variables (erythrocyte PBG synthase, plasma succinylacetone, U-succinylacetone, and U-5-aminolevulinic acid) and Kaplan-Meier plots. In addition, enclosed under Tab 2 (Vol. 1, p 168) is the "Periodic Safety Update Report" (PSUR) covering data up to December 31, 1999. Although the Agency did not require an intra-patient analysis as originally requested (patients first receiving the —— formulation, switching to the NTBC starch formulation) we have enclosed it as an Appendix in Volume 2 (pp 211 – 268).

With regard to Point 2 of the Agency's RTF letter, we have enclosed a detailed description of the amino acid analysis method, the method validation for tyrosine plasma concentrations as well as validation of the assay used to estimate NTBC levels in patient's plasma samples. In addition the ———— and validation report, used to determine NTBC in plasma in the pharmacokinetic study is enclosed. These reports may be found in Volume 2, Tabs 3A, 3B and 3C, pages 001 to 090.

Additionally and further to this same point, the Agency noted at our May 16, 2000 meeting that the validation information and data for tyrosine and NTBC assay would be acceptable for filing purposes but recommended that the sponsor perform a cross-validation of the two assays for NTBC. This is not completed at this time but will be submitted within the next few weeks.

Further, reference is made to the above noted RTF letter and three points stated by the Agency to be unrelated to the refusal to file the application but recommending that we consider submitting this information in our resubmission. Most of this information is enclosed in Vol. 2 under Tabs. 4 to 11, pages 091 to 210. However, we have not completed the collection and analysis of the plasma concentrations of NTBC in children which was one of the Agency's suggestions under point 1 of this section (unrelated to the RFT). This will be completed shortly and will be submitted along with a resubmission of the plasma NTBC concentrations collected in all study subjects (which were mostly children) previously presented in NDA 21-232, Volumes 1.17 to 1.22 (Case Report Tabulations).

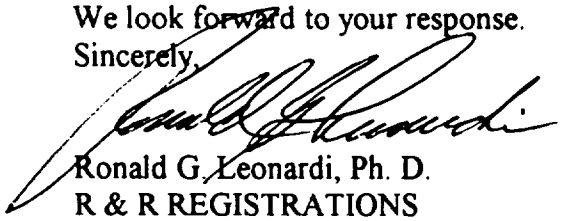
With regard to this same point (second point one) the Agency requested solubility profiles, dissolution data and justification of dissolution method as well as specifications for NTBC capsules. This information is presented in Vol. 2 under Tabs 4 to 10, pages 091 to 146.

Under Point 2 of this section (unrelated to the RTF) the Agency requested submission of the pharmacokinetics data from study CCT/96/001 (capsule and liquid bioavailability study) in electronic format. This data is enclosed on a labeled CD in Volume 2 in a plastic cover numbered page 269.

Lastly, the Agency requested that we submit any information available (e.g., published literature) that pertains to the metabolism and excretion of NTBC in humans. We have searched the literature and have not found any literature that pertains to the metabolism and excretion of NTBC in humans. All published information we have, has been submitted in NDA 21-232 previously. If there is any specific reference (s) the Agency would like please let us know and we will prepare copies for submission.

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

Sincerely,



Ronald G. Leonardi, Ph. D.
R & R REGISTRATIONS
for Swedish Orphan, AB
cc: Swedish Orphan, AB; Orphan Pharmaceuticals USA, Inc.; Office of Orphan Product Development (HF-35)

R & R REGISTRATIONS

ORIGINAL
NEW CORRESP
NC

Ronald G. Leonardi, Ph.D., President

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

December 29, 1999

CENTER FOR DRUG
REC'D
DEC 30 1999
HFD-510
EVALUATION AND RESEARCH

NDA 21-232
ORFADIN™, Nitisinone

Food and Drug Administration
Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD 510
5600 Fishers Lane
Rockville, MD 20857 - 1706

RE: Amendment to Item 19, Financial Certification
New Drug Application (NDA) 21-232 for ORFADIN™, Nitisinone

4/13/00
/S/

ATTN: Ms. Maureen Hess, CSO

Dear Dr. Sobel:

Reference is made to our New Drug Application (NDA 21-232) submitted to the Agency on December 27, 1999 for ORFADIN™, Nitisinone an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I.

Enclosed with this submission, in duplicate, is an amendment to NDA 21-232, Item 19, which consists of a completed and signed FDA Form 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators" and a list of all investigators. The Form certifies that no investigators participated in any financial arrangements or had any proprietary interest in the product or significant equity in the sponsor whereby the outcome of the study could be affected.

/S/ 1/19/00

If there is any additional information you need 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

REVIEWS CO
CSO ACT
☐ LETTE
/S/
CSO INIT
4/10/00
DATE

/S/
4/10/00

R & R REGISTRATIONS

Ronald G. Leonardi, Ph.D., President

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

December 27, 1999

New Drug Application (NDA)
Orfadin™, Nitisinone

Food and Drug Administration
Center for Drug Evaluation and Reasearch
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

RE: ORIGINAL NEW DRUG APPLICATION (NDA)
ORFADIN™, NITISINONE (NTBC)
ORPHAN DESIGNATED PRODUCT
FAST TRACT DESIGNATED PRODUCT

Ladies and Gentlemen:

Pursuant to Section 505 (b) (1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, Swedish Orphan, AB, Drottninggatan 98, S-111 60 Stockholm, Sweden is submitting an original New Drug Application containing Chemistry, Manufacturing and Control data, Pre-clinical data, and Clinical data to support the safe and effective use of Orfadin™, nitisinone for the treatment of Hereditary Tyrosinemia Type 1 (HT-1).

It should be noted that this Product and Indication have been granted both Orphan Drug Designation (less than 50 patients in the United States- see clinical note below) and Fast Tract Designation by the Agency (see Volume 1.1, pp 12 to 15).

The Archival copy of this NDA consist of 47 volumes (see Volume 1.1, p 36, Item 1, Index of the NDA). Volume 1.1 contain our Cover letter, a completed and signed 356h Form, draft labeling, the NDA's overall Table of Contents, and the Summary of the NDA as well as responses to Items 13 to 19 of the 356h Form. This volume is also submitted with each of the Technical Review Sections of the NDA.

The Archival copy of the NDA also contains 15 volumes of Technical Review Sections (Volume 1.2 to 1.16) as well as 10 volumes of Case Report Tabulations (Volumes 1.17 to 1.26) and 21 volumes of Case Report Forms (Deaths and Dropout due to Serious Adverse Events) (Volumes 1.27 to 1.47).

The Technical Review Sections are; Chemistry Manufacturing and Controls (Vols. 1.2 to 1.4). The Drug Substance and Drug Product are described in Vols. 1.2 and 1.3 while Methods Validation information is contained in Volume 1.4.

Pre-Clinical data is contained in 3 Volumes (1.5 to 1.7) while the Human Pharmacokinetics and Bioavailability data, which is limited, is presented in Volume 1.8.

The Clinical data Section (Volumes 1.9 to 1.12) and the Statistical Section (Volume 1.13 to 1.16) contain the data from treatment of most of the worlds HT-1 patients with Orfadin™, nitisinone.

Hereditary tyrosinemia type 1 (HT-1) is a rare disease with poor prognosis. In patients with HT-1, toxic metabolites accumulate in liver and kidney because of deficiency of fumarylacetoacetase, the last enzyme in the tyrosine catabolic pathway. Typically, fatal outcome results from either liver failure during infancy or hepatocellular carcinoma during childhood or adolescence. No pharmaceutical therapy is available for HT-1, and liver transplantation is the only effective treatment.

The mechanism of action of Orfadin™, Nitisinone is to inhibit the enzyme 4-hydroxyphenylpyruvate dioxygenase, thereby preventing the formulation of toxic metabolites of tyrosine. The goal is to achieve an efficient inhibition of this enzyme in the patient. Several biochemical parameters which directly or indirectly reflect the degree of inhibition were measured in the clinical study, and the data demonstrates that the goal could be reached in all patients.

The Clinical study as presented in this NDA was performed by 96 local investigators at 87 different hospitals in 25 countries. The Efficacy data presented was obtained over a period covering more than six years (start February 23, 1991 to August 21, 1997) and includes 207 patients with a diagnosis of HT-1 verified by the presence of succinylacetone in the urine and plasma. Orfadin™, nitisinone was administered orally twice daily. The dose is individualized based on response data but in general was 1mg/Kg body weight as a total daily recommended dose. The median duration of treatment was 22.2 months with a range of 0.1 months to 77.9 months.

The Safety data comprised the information from the Clinical Study Report (treatment exposure 441 years; 207 patients) and a Safety Addendum (treatment exposure 13 years; 24 patients).

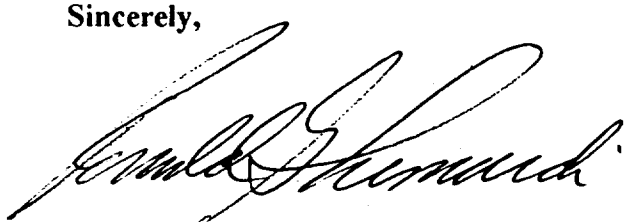
The study has shown that Orfadin™, Nitisinone significantly reduced the risk of death in liver failure, prevented occurrence of potentially fatal porphyric crises and prevented symptoms of tyrosinemic kidney disease. For some patients, however, liver transplantation was necessary. The treatment was well tolerated and there were very few serious adverse effects with a causal relationship to therapy.

We understand that the information contained in this submission of our New Drug Application, unless otherwise made public by Swedish Orphan, AB or its affiliates, is confidential. Further, if for any reason, FDA officials should, at any time, believe that disclosure of this confidential material should be made to any member of the public, we expect that the Agency will first contact us on the issue of such disclosure.

Swedish Orphan, AB and the undersigned, their U.S. agent for this application, are prepared to discuss the contents of this submission to assist and expedite Agency review.

Please do not hesitate to contact me at the address noted above or at 858-586-0751 or E-mail me at leonardi@r-rregistrations.com.

Sincerely,



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

cc: Swedish Orphan, AB and Orphan Pharmaceuticals U.S. A.

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
21-232

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Swedish Orphan, AB	
TELEPHONE NO. *(Include Area Code)* 858 586-0751	**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 Stockholm, Sweden 111 60	**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) Pending

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(if any)*
Nitisinone	ORFADIN	

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

(PROPOSED) INDICATION(S) FOR USE:
Hereditary Tyrosinemia type I (HT-1)

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 2 8 1999
CDR

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ 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

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

NUMBER OF VOLUMES SUBMITTED 47 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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)*	
X	1. Index
X	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	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)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	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))
X	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)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
X	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify)

CERTIFICATION

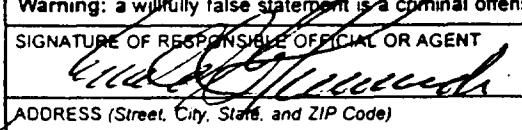
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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 reviewed 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.,Pres	12/27/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O.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 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 (0910-0338)
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.

FORM FDA 356h (4/97)

Meeting Date: December 17, 1998 Time: 1:30 p.m. – 2:30 p.m. Location: PKLN "M"

IND —— NTBC

Type of Meeting: pre-NDA (CMC)

Meeting Chair: Dr. Shelley Markofsky

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Ronald Leonardi

FDA attendees and titles:

Ms. Maureen Hess	CSO, DMEDP
Dr. Duu-Gong Wu	Chemistry Team Leader, DNDC II
Dr. Shelley Markofsky	Chemist, DNDC II
Dr. John Gibbs	Director, DNDC II
Dr. David Lewis	Chemist, DNDC II

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. Erling Ehrin	Apoteket, Chemist
Dr. Ronald Leonardi	R & R Registrations, Regulatory Consultant

Meeting Objectives:

Meeting requested by the sponsor to discuss the chemistry issues that need to be addressed prior to submission of the NDA.

Discussion Points:

- The sponsor presented information on the nomenclature and the description of NTBC.
- The sponsor informed the Agency that —— is no longer manufacturing the drug and that ———— (also known as ——) is now synthesizing the drug.
- In order to help the sponsor with the chemistry portion of the NDA, the Agency provided the sponsor with the June 4, 1992 version of "New Drug Application Chemistry Review Format and Content Guide". The Agency also provided the sponsor with a list of deficiencies, based on the sponsor's November 20, 1998

background package and proceeded to go over this deficiency list with the sponsor.

- In reviewing the Agency's deficiency list, the sponsor noted the following potential problems:

  Batch records for the drug substance are not available. The Agency responded that it needs to know in detail how the drug is made, so if changes are made at a later date it can determine the appropriateness and track the changes. The Agency inquired if the firm has retained samples. The firm stated that it does have samples. The Agency commented that those samples could be used to compare with the new —— product. The Agency added that —— will also need to be inspected and encouraged the firm to get a DMF from ——

  The firm stated that the only stability data they have is what has been submitted in the background package. The Agency commented that it prefers to have data that show one year at room temperature and six months at accelerated conditions. The Agency added that it needs justification that once the drug is made it is still viable and good. The Agency inquired how long the drug would be stored after it has been made. The firm responded that it would be shelved for about three years. The Agency stated that based on the current stability data, the drug might end up with a reduced expiration date, if there is that much of a lag time before use. The firm stated that it might be possible to manipulate the product as far as production and holding.

The Agency continued reviewing the deficiency list with the sponsor:

- The Agency stated that the sponsor will have to show that the product produced by the old company —— and the new company —— is bioequivalent.

- The Agency stated that the quality controls need to be explained and better defined. The firm agreed to do so.

- The Agency stated that as far as detecting impurities, the firm will need a reference standard and if there is not one currently, a reference standard will have to be made.

- The Agency stated that —— as an assay for drug substance is not acceptable and the firm will need to use the HPLC method. The Agency added that there is a guidance for HPLC that has been issued and encouraged the sponsor to reference that guidance. The firm agreed.

- The Agency commented that in addition to what is outlined in the deficiency list, the Agency will also need information on the complete container/closure system, including auxiliary packaging materials. The firm stated that they ——

The sponsor stated that it feels confident that they will be able to meet all the issues raised by the Agency. The Agency encouraged the sponsor to contact them if any issues cannot be resolved or if other questions arise.

Signature, minutes preparer: /S/

Concurrence, Chair: /S/

APPEARS THIS WAY
ON ORIGINAL

DATE: February 28, 2001

SUBJECT: ADRA Review of NDA 21-232 Action Package

FROM: Leah Ripper, ADRA, ODE II

Drug: Orfadin (nitisinone) Capsules
Indication: As an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.
Type action: Not sure at this time – AP or AE. No action letter with package.
RPM: Su Yang, phone 7-6385
Date Orig NDA Rec'd: 9/8/00
User Fee Goal Date: 3/8/01
Date NDA Package Rec'd: 2/28/01

This is a 505(b)(1) application. Patent info received.

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, the applicant should be asked to submit a signed 356h, countersigned by their US agent.**

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

EER: **Two facility inspections pending**, scheduled for 3/7 and 3/10/01. EES report should be in action package even when inspection(s) are not completed.

Environmental Assessment: Categorical exclusion was requested. **Request is pending additional info from applicant.**

Postmarketing Study Commitments: Dr. Jenkins has suggested P/T commitments.

DSI: No clinical audits were requested.

Safety Update: Safety data through 12/31/99 have been submitted and reviewed. No documentation of receipt of the 4-month safety update. **Applicant should be asked to provide a safety update.**

Trade Name Review: OPDRA did not recommend use of the tradename Orfadin. DD memo documents division decision finding name acceptable.

Financial disclosure: **Please provide the applicant's forms submitted with form FDA 3454 for the Action Package.** Statement in DD memo is adequate.

The Exclusivity Summary needs to be completed.

An ePeds Page needs to be completed and added to the package.

If not already done, HF-35 should be notified that this orphan drug might be approved soon; this could be done by inviting them to the Pre-AP Safety Conference.

Was the sponsor ever asked to obtain a USAN for the drug?

OPDRA had some comments on the labels. Have these been conveyed to the applicant? Action Package does not contain updated labels.

The following documents were in DFS but not in the action package. I have added them to the Action Package. (Note: When I printed the 2/23/00 review on my personal printer, the labeling and formulation pages attached were all black. However, the pages could be viewed on the screen and printed OK when I sent the print order to our office printer which has much more memory than my personal printer does.)

2/25/00 RTF Letter
2/23/00 Clin Pharm Filing Review
2/23/01 Clin Pharm Labeling Review

The following documents were in the package but not in DFS. MHess' may no longer be available.

10/18/00 Memo of filing mtg, MHess
12/17/98 Memo of Pre-NDA (CMC) Mtg, MHess
12/17/98 Memo of Pre-NDA Mtg, MHess
2/17/01 DD Review, DOrloff

/s/

Leah Ripper
4/11/01 12:42:09 PM
CSO

APPEARS THIS WAY
ON ORIGINAL