

/s/

David Orloff
4/10/01 02:50:07 PM
MEDICAL OFFICER

**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
Office of Clinical Pharmacology and Biopharmaceutics

Date: 12-OCT-00
From: Robert M. Shore, Pharm.D.
Through: Hae-Young Ahn, Ph.D., Team Leader
To: Maureen Hess, PM.
Re: Filing of NDA 21-232/RS
Orfadin (nitisinone) oral capsules
Submitted 07-SEP-00

/S/

The sponsor has resubmitted the NDA on 07-SEP-00 after receiving a RTF letter. The resubmission contains responses to the RTF issues.

1. Pivotal BE issue

The sponsor has submitted the requested clinical efficacy analysis providing a comparison of the to-be-marketed capsule formulation to the clinical trial formulation.

2. Assay validation data

Validation data have been submitted for both the plasma tyrosine and nitisinone assays.

As such, the resubmission is acceptable and OCPB recommends that this NDA be filed.

CC: : NDA 21-232/RS, HFD-850(LeeP, Lesko), HFD-510(Hess, Lubas, Orloff, Wu, Hertig), HFD-870(AhnH, Malinowski), CDR.

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Date: January 14th, 2002
From: Nakissa Sadrieh, Ph.D.
Associate Director of Pharmacology and Toxicology, ODE II

To: NDA 21-232
Orfadin (Nitisinone) capsules

I have reviewed the Pharmacology and Toxicology data in the action package for NDA 21-232 (Orfadin). I concur that the application is approvable pending the sponsor's commitment to perform standard reprotoxicity battery Phase 4, as recommended in the supervisory pharmacologist's memo.

I would however like to highlight some observations which could impact the product package insert.

1. In the pre-NDA meeting minutes from Dec 17th, 1998, Dr. Steigerwalt, the then pharm/tox team leader, recommended that due to toxicities seen in the eye and the liver of animals, there may need to be some information in the package insert. This information should be included in the _____ ' _____ ' section of the label (this usually follows the _____ section, as per the CFR). This was not included in the present package insert. However, there were some clinical data regarding ophthalmologic care and risk of liver toxicity included in the "Precautions" section. This may be why the _____ section was omitted. The only reason to consider adding the animal data would be to emphasize the risk to patient by providing some dose multiples for the observed toxicities. Nevertheless, the clinical data supercede the animal data and are thus considered more informative. Therefore, I am not recommending an additional section in the _____ ' _____ ' section of the label.
2. In Dr. Hastings's (the then Acting Associate Director for Pharmacology and Toxicology) memo dated March 9th, 2001, it was indicated that mutagenicity and carcinogenicity of nitisinone should be considered as part of phase 4 commitments. In the present Action letter, the sponsor is no longer requested to commit to performing mutagenicity and carcinogenicity as Phase 4 commitments. The reason for no longer requesting these studies was not clearly stated. However, Dr Davis- Bruno, the supervisory Pharmacologist for HFD-510, requested a consult from the FDA/CDER/OPS (HFD-900) for a structure activity relationship for Orfadin. This consult assessed the potential 1) mutagenicity, 2) carcinogenicity, 3) teratogenicity, 4) adult human hepatic toxicity and 5) adult human immunotoxicity of Orfadin. The results indicated that Orfadin had negative response for mutagenicity, carcinogenicity and teratogenicity. It is my understanding that due to these results, the need for

Phase 4 commitments for mutagenicity and carcinogenicity have been presently dropped. I agree with this decision.

3. I would like to propose some additional changes to the label:

- A) In the “Nursing Mothers” section of the label, I noticed that in a cross-fostering reproduction toxicology study, pups that were exposed to Orfadin during lactation has significantly lower body weights than pups that were not exposed to Orfadin. Similarly, pups exposed to Orfadin only during lactation had more severe ocular lesions than pups that were exposed during lactation and gestation. This may indicate that the drug has the capacity to get excreted in breast milk. I therefore recommend a statement be added in the “Nursing Mothers” section that highlights these results and the possibility of drug excretion via breast milk. I suggest the following: *“Although the exposure was not quantified, naive pups that were exposed to Orfadin via breast milk showed signs of ocular toxicity and lower body weight. This suggests that Orfadin is excreted via breast milk in rats. It is not known whether nitisinone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitisinone is administered to a nursing woman.”*
- B) In the “Geriatric Use” section of the label, dose-selection for an elderly population is generally described. Since Orfadin is indicated for a pediatric population and the disease is unlikely in an elderly population, the benefit of that section is unclear. The first 2 sentences of that section provide the necessary information and should therefore be kept as they are. However, the third sentence that starts with “In general...” could be omitted, since it does not provide any additional information for the proposed use of the drug
- C) In the “Carcinogenicity, Mutagenicity, Impairment of Fertility” section of the label, a rat reprotoxicity study is described. It is indicated that the study was a single dose study. I recommend that we change the sentence to *“In a single dose-group study in rats given 100 mg/kg/day (12 times the recommended clinical dose based on relative body surface area), reduced litter size, decreased pup weight at birth and decreased survival of pups after birth was demonstrated.”* The reason for recommending this change is that when I initially read the statement as it is written now in the label, I thought that the rats were treated with nitisinone only once with 100 mg/kg. In fact the rats were dosed as in any standard segment 1 study, however only one dose group was included in the study.

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

/s/

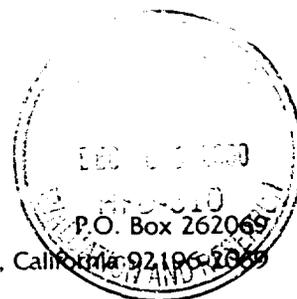
Nakissa Sadrieh
1/14/02 04:14:34 PM
PHARMACOLOGIST

**APPEARS THIS WAY
ON ORIGINAL**

R & R REGISTRATIONS

Ronald G. Leonardi, Ph.D., President

San Diego, California 92196-2669



December 4, 2000

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

BC
ORIG AMENDMENT

**RE: CMC Request from Dr. Markovsky
Revised Table of Contents for Drug Substance 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.

Further reference is made to Agency's Dr. Markovsky request for a correction of the Table of Contents for the Drug Substance Specification (Volume 2, page 369) for NTBC. Dr. Markovsky had noted that there were inconsistencies between the Table of Contents for the specifications and the actual specifications included, which were correct.

Submitted herewith in triplicate together with a completed and signed Form FDA 356h is a Chemistry Manufacturing and Control Amendment to NDA 21-232, which includes the corrected Table of Contents for the Drug Substance Specification.

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

Sincerely,

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

REVIEWS COMPLETED	
CSO ACTION	
CSO INITIALS	
CSO INITIALS	DATE

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

Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

WITHHOLD 1 PAGE (S)

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 Swedish Orphan, AB	DATE OF SUBMISSION December 4, 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) Nitisinone	PROPRIETARY NAME (trade name) IF ANY Orfadin	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)	CODE NAME (If any) NTBC	
DOSAGE FORM: Capsules	STRENGTHS: 2, 5, and 10mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 801)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 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)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
REASON FOR SUBMISSION	Request from Dr. Markofsky to correct Drug Substance specification page table of content to make consistent with actual specifications.	
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>one</u>	THIS APPLICATION IS	<input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> 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
2.	Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3.	Summary (21 CFR 314.50(c))
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)
	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 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 Ronald G. Leonardi, Ph.D., President	DATE December 4, 2000
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (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

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

Please DO NOT RETURN this form to this address.

R & R REGISTRATIONS

DUPLICATE

Ronald G. Leonardi, Ph.D., President

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

January 17, 2002

N 000C
NEW CORRESP

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: Package Insert for ORFADIN®, nitisinone

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.

Further reference is made to numerous phone calls to Mr. Samuel Wu of the Agency regarding Orfadin®, nitisinone labeling.

Submitted herewith by fax as well as by courier is the revised labeling (Package Insert) which includes all Agency suggested changes and revisions. Swedish Orphan accepts all changes made by the Agency and is described in this submission.

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.

Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

R & R REGISTRATIONS

DUPLICATE

Ronald G. Leonardi, Ph.D., President

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

January 11, 2002

NDA 21-232
ORFADIN® capsules, Nitisinone

N 000 C
NEW CORRESP D

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: USAN name: Agency's phone Requests January 10, 2002.

Dear Dr. Orloff:

Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for ORFADIN® capsules, Nitisinone, and the Agency's approvable letter dated May 3, 2001.

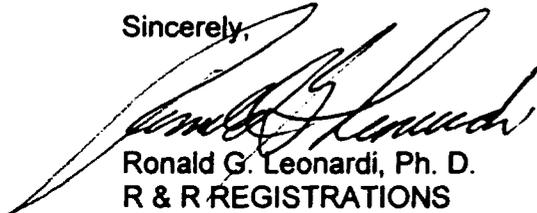
Further, reference is made to a telephone discussion with Mr. Samuel Wu on January 10, 2002, in which Mr. Wu requested that we commit to changing the suggested USAN name on the labeling should they not approve the use of the name "nitisinone".

The labeling changes requested by the Agency have been incorporated in the labels and package insert, which are enclosed.

Submitted herewith in duplicate is our commitment to utilize the USAN name of "nitisinone" or what ever it may be should "nitisinone" not be acceptable to USAN in all of our labeling. Also enclosed is a completed and signed Form FDA 356h. An E-mail copy of this submission is also sent to Mr. Samuel Wu.

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 International, AB

cc: Swedish Orphan International, AB; Rare Disease Therapeutics, Inc.
Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

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)

R FDA USE ONLY

APPLICATION NUMBER

NDA 21-232

APPLICANT INFORMATION

NAME OF APPLICANT Swedish Orphan, AB	DATE OF SUBMISSION January 11, 2002
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) Nitisinone	PROPRIETARY NAME (trade name) IF ANY Orfadin® capsules	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)	CODE NAME (if any) NTBC	
DOSAGE FORM: Capsules	STRENGTHS: 2, 5, and 10mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 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)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
REASON FOR SUBMISSION	Response to the Agency's November 9, 2001 "Information Request Letter".	
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>one</u>	THIS APPLICATION IS	<input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

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<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50(c))
<input type="checkbox"/>	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)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 308 (k) (1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50(k) (3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	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.
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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 Ronald G. Leonardi, Ph.D., President	DATE January 11, 2002
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (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

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

Please DO NOT RETURN this form to this address.

R & R REGISTRATIONS

DUPLICATE

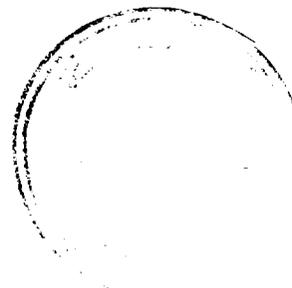
Ronald G. Leonardi, Ph.D., President

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

January 7, 2002

NDA 21-232
ORFADIN® capsules, 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



N 000 BL
ORIG AMENDMENT

RE: Response to Agency's Requests of December 28, 2001 and January 4, 2002.

Dear Dr. Orloff:

Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for ORFADIN® capsules, Nitisinone, and the Agency's approvable letter dated May 3, 2001.

Further, reference is made to an E-mail received on December 28, 2001 from Mr. Samuel Wu of the Agency's with labeling change requests and a change to the dissolution specification of the Orfadin capsules. Additionally reference is made to a telephone discussion with Mr. Samuel Wu on January 4, 2002, in which Mr. Wu requested a commitment date for the reproductive toxicology study to be performed for Orfadin capsules.

The labeling changes requested by the Agency have been incorporated in the labels and package insert, which are enclosed.

The dissolution specifications requested by the Agency have been changed and incorporated in the final product specification.

Lastly, we commit to the best of our abilities to submit reproductive toxicology study protocol on or before May 30, 2002, start the study on or before September 30, 2002 and report the results to the Agency on or before March 30, 2003.

Submitted herewith in duplicate is our response and a signed Form FDA 356h. An E-mail copy of this submission is also sent to Mr. Samuel Wu.

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

Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

R & R REGISTRATIONS

DUPLICATE

Ronald G. Leonardi, Ph.D., President

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

November 21, 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



N 000 BC
ORIG AMENDMENT

RE: Response to Agency's November 9, 2001, "Information Request Letter"

Dear Dr. Orloff:

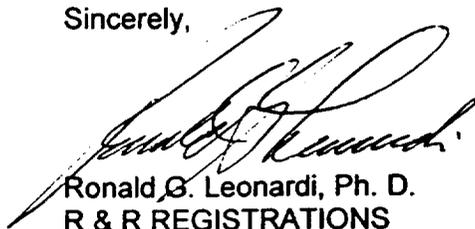
Reference is made to our New Drug Application (NDA 21-232) resubmitted to the Agency on September 7, 2000 for ORFADIN™, Nitisinone, an Orphan Drug designated product for the treatment of Hereditary Tyrosinemia Type I. Further reference is made to the Agency's call of October 19, 2000 from Ms. M. Hess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

Additionally, on November 16, 2001 we received the Agency CMC "Information Request Letter", dated November 9, 2001, which noted that while they were reviewing our July 19, 2001 response to the Agency's May 3, 2001 "Approvable Letter" to NDA 21-232, FDA had a number of comments and information requests that needed a respond before the Agency could continue its evaluation of our NDA.

Submitted herewith in duplicate along with a completed and signed Form FDA 356h is our response to the Agency's November 9, 2001 CMC "Information Request Letter". We have followed the Agency's numbering system. The document is formatted so that our response follows the Agency's question or comment. If additional documentation is need to respond to the question, we noted in our response to "Please see Attachment" with an associated number.

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.

Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

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 Swedish Orphan, AB	DATE OF SUBMISSION November 21, 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) Nitisinone	PROPRIETARY NAME (trade name) IF ANY Orfadin	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)	CODE NAME (if any) NTBC	
DOSAGE FORM: Capsules	STRENGTHS: 2, 5, and 10mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 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)	<input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER	
REASON FOR SUBMISSION	Response to the Agency's November 9, 2001 "Information Request Letter".	
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED <u>one</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> 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
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	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)
	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)
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	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)
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	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

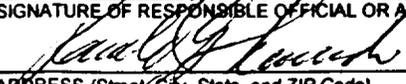
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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 Ronald G. Leonardi, Ph.D., President	DATE November 21, 2001
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (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

DUPLICATE

August 24, 2001

NDA 21-232
ORFADIN™, Nitisinone

AMENDMENT
N-000-BL



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: Labels and Labeling

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 labels and labeling (see Attachment 13 and 14 in the July 19, 2001 letter) in response to the Agency's comments and questions. Enclosed is a **change in format but not text** for our labels and labeling.

This change resulted because of technical difficulties in producing a package insert in the format as was described in our July 19 submission. As a result we have changed the presentation of the package. We are still using the same bottle and bottle label as described previously but now we have placed the bottle in a carton and placed a label on the carton. This is new. Further, the package circular will be printed on light weight paper and placed in the carton with the bottle. There is no change in text on the labels or package insert as compared to the July 19, 2001 submission. This is a format change only.

Submitted herewith in triplicate are printer proofs of the carton label, the bottle label and the Package insert along with 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,

A handwritten signature in black ink, appearing to read "Ronald G. Leonardi".

Ronald G. Leonardi, Ph. D.
R & R REGISTRATIONS
for Swedish Orphan, AB
cc: Swedish Orphan, AB; Rare Disease Therapeutics, Inc.

Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

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 Swedish Orphan, AB	DATE OF SUBMISSION August 24, 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

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(PROPOSED) INDICATION(S) FOR USE:

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REASON FOR SUBMISSION Labels and labeling

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CERTIFICATION

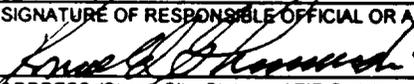
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Ronald G. Leonardi, Ph.D., President	DATE August 24, 2001
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (858) 586-0751

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R & R REGISTRATIONS

Ronald G. Leonardi, Ph.D., President

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

THIS IS A COMPLETE RESPONSE

July 19, 2001

NDA 21-232
ORFADIN™, Nitisinone

DUPLICATE

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: Agency's May 3, 2001, "Approvable Letter"; Swedish Orphan, AB's Response

Dear Dr. Orloff:

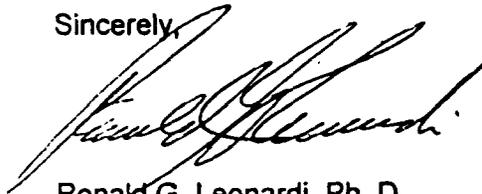
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If you have any questions please do not hesitate to call or E-mail me at the numbers noted.

Sincerely,



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

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

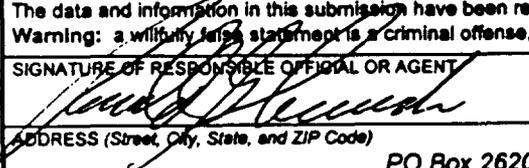
Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-rregistrations.com

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 Swedish Orphan, AB		DATE OF SUBMISSION July 19, 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			
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ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Nitisinone		PROPRIETARY NAME (trade name) IF ANY Orfadin	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)			CODE NAME (if any) NTBC
DOSAGE FORM: Capsules	STRENGTHS: 2, 5, and 10mg	ROUTE OF ADMINISTRATION: Oral	
(PROPOSED) INDICATION(S) FOR USE: Hereditary Tyrosinemia Type I (HT-1)			
APPLICATION INFORMATION			
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 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) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER			
REASON FOR SUBMISSION: Response to the Agency's May 3, 2001 "Approvable" letter			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED <u>one</u>		THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> 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, 610(k)s, IDEs, BMFs, and DMFs referenced in the current application)			

This application contains the following items: (Check all that apply)		
	1. Index	
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
	3. Summary (21 CFR 314.50(c))	
	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)	
	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)	
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	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) (8), 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:		
<ol style="list-style-type: none"> 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 Ronald G. Leonardi, Ph.D., President	DATE July 19, 2001
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (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		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Please DO NOT RETURN this form to this address.		

R & R REGISTRATIONS

DUPLICATE

Ronald G. Leonardi, Ph.D., President

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

March 30, 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



N 000 BZ
NDA ORIG AMENDME

RE: Agency's "Discipline Review Letter"; Swedish Orphan, AB's Response

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, 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, On February 15, 2001 the Agency faxed and subsequently mailed a "Discipline Review Letter" which dealt with the review of the Biopharmaceutics and Chemistry, Manufacturing and Control sections of NDA 21-232.

Submitted herewith in duplicate along with a completed and signed Form FDA 356h is our response to the Agency's "Discipline Review Letter". The document is formatted so that our responses follow the Agency's question. We have chosen to number each query consecutively (the Agency did not number each question separately but chose to use bullet points as subdivisions of questions). If additional documentation is need to respond to the question we have noted in our response to "Please see attachment" with an associated number.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Ronald G. Leonardi".

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

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

Advising & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

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 Swedish Orphan, AB	DATE OF SUBMISSION March 30, 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) Nitisinone	PROPRIETARY NAME (trade name) IF ANY Orfadin	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)	CODE NAME (If any) NTBC	
DOSAGE FORM Capsules	STRENGTHS: 2, 5, and 10mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 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)	<input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION	
	<input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT	
	<input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER	
REASON FOR SUBMISSION	Request from Dr. Markofsky for NTBC recrystallization procedure.	
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED <u>one</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	

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	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

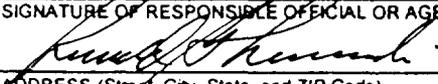
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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports 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 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 Ronald G. Leonard, Ph.D., President	DATE March 30, 2001
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (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)
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200 Independence Avenue, S.W.
Washington, DC 20201

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R & R REGISTRATIONS

Ronald G. Leonardi, Ph.D., President

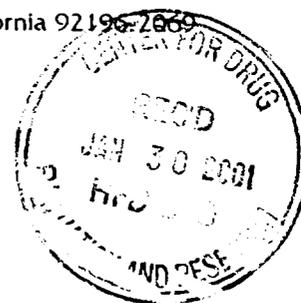
January 29, 2001

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

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

ORIGINAL AMENDMENT
DUPLICATE



**RE: Question from Dr. Shore:
December 15, 2000; raw data for Table 8.1 in September 7, 2000 submission
January 2, 2001; timing of 12 month blood samples**

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 made to a request from Dr. Robert Shore on December 15, 2000 to obtain the raw data in electronic format for Table 8.1 (Volume 1 of 2, page 038 of the September 7, 2000 submission). He noted that the raw data was in Appendix 5 of that volume, but needed the electronic version. The data tables were sent to Dr. Shore via email on January 8, 2001. Enclosed are 2 diskettes with the same information.

Further reference is made to a question from Dr. Robert Shore on January 2, 2001 regarding the time between the ingestion of the capsule and obtaining the blood sample at the 12 month time point. There is limited amount of data available as can be seen in the attachment to this letter.

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.

Sincerely,

A handwritten signature in black ink, appearing to read "Ronald G. Leonardi".

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

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

RENEWALS COMPLETED
ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> OTHER
DATE

Advlsing & Serving the Pharmaceutical Industry

Phone 858 586-0751

Fax 858 586-1108

leonardi@r-registrations.com

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 Swedish Orphan, AB	DATE OF SUBMISSION January 29, 2001
TELEPHONE NO. (Include Area Code) (Sweden 46-8-412-9800)	FACSIMILE (FAX) Number (Include Area Code) Sweden 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 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 (858) 586-0751, fax (858) 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) Nitisinone (INN)	PROPRIETARY NAME (trade name) IF ANY Orfadin	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 2-(2-Nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione (IUPAC)	CODE NAME (if any) NTBC	
DOSAGE FORM: Capsules	STRENGTHS: 2, 5, and 10mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hereditary Tyrosinemia Type I (HT-1)

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 801)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 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	
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	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
REASON FOR SUBMISSION	December 15, 2000 and January 2, 2001 Request from Dr. Shore for updates to the NDA.	
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>one</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	

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X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
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	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

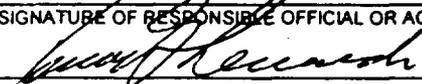
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5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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The data and information in this submission have been reviewed 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 Ronald G. Leonardi, Ph.D., President	DATE January 29, 2001
ADDRESS (Street, City, State, and ZIP Code) PO Box 262069, San Diego, CA 92196		Telephone Number (858) 586-0751

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Washington, DC 20201

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268	8	000314: 6.00 am	000314: 9.40 am
272	8	991205: 8.00 pm	991206: 8.30 am

In conclusion the nitisinone serum concentrations measured in the NTBC-study has been performed on blood samples sent to the main investigators at specific dates but in most cases time of day for sampling and for nitisinone intake have not been recorded. The nitisinone serum concentration measured is most likely randomly related to the intake of nitisinone. For the statistical analysis visit windows were defined and only the value closest to the visit 8 (12 month from the start of nitisinone treatment) used. If values were missing between two existing values they were interpolated with the mean of the value closest before and closest after the missing value.

The treatment objective is a complete suppression of the tyrosine metabolism to avoid generation of down stream toxic metabolites. In the analysis of the clinical study population it could be concluded that the probability of recurrence after previous normalisation was at the 1% level for the primary biochemical efficacy variables at serum concentrations of nitisinone between 37 µmol/L and 70 µmol/L. The safety profile for nitisinone allows the treating physicians to aim a trough value of nitisinone within this concentration window during maintenance therapy.

Ib Bo Lumholtz, M.D.
Company's medical officer

**APPEARS THIS WAY
ON ORIGINAL**