CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-232

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

12 9 01

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-232/N-000	**SUBMISSION DATE: 7/19/01**
BRAND NAME:	**Orfadin®**
GENERIC NAME:	**Nitisinone 2, 5, and 10mg oral capsules**
REVIEWER:	**Hae-Young Ahn, Ph.D.**
APPLICANT:	**Swedish Orphan, AB,**
	Stockholm, Sweden
US AGENT:	**R&R Registrations, San Diego, CA**
TYPE OF SUBMISSION:	**Responses to "Approvable Letter"**

Submission:

Orfadin® (nitisinone; NTBC) is an orphan drug indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1, a disease caused by the deficiency of an enzyme at the tailend of the tyrosine degradation pathway. This enzyme deficiency causes accumulation of toxins which can lead to liver failure in infancy or hepatocellular carcinoma in childhood or adolescence. The proposed initial dose is 1 mg/kg/day divided for morning and evening administration and can be titrated based on clinical response biomarkers up to 1mg/kg BID. Capsules of 2, 5, and 10mg are proposed to be marketed.

The scientific data for Orfadin® in the original NDA were limited. There was a lack of certain studies (e.g. pivotal bioequivalence , food effect, drug interactions) which made it difficult to have a full understanding of this drug from a pharmacokinetic perspective. However, from the pharmacokinetic and clinical data that were available, Orfadin® could be linked to the efficacy seen in the clinical trials. After reviewing the original NDA for Orfadin®, the Agency sent the sponsor an 'approvable (AE) letter' that stated before the application may be approved, it would be necessary for the sponsor to address several deficiencies. Per clinical pharmacology and biopharmaceutics perspective, since the effect of food on the bioavailability of NTBC was unknown, it was recommended in the AE letter that 'the sponsor submit data that indicated how the drug product was actually administered during the clinical trial in relationship to food. These could include dosing diaries from patients or verbal recommendation made from clinical study staff. In addition, data on the palatability of the drug product in water was requested.'

The sponsor's response in this submission indicates that it is reasonable to assume that Orfadin® was given together with food in the majority of patients since the message given either orally or in the letter to a new local investigator was "We —— the NTBC with —— and dispense it in capsules (easy to open and mix the content with e.g., formula diet)". The sponsor also indicates that they have no data on the palatability of NTBC. It should be noted that the label recommends that for young children, capsules may be opened and the contents suspended in a small amount of water immediately before use.

The effect of food on Orfadin® pharmacokinetics is unknown. The clinical trial protocol has addressed neither the timing of the dose nor how the drug should be dispensed. The drug substance has low solubility in water (5 mg/L), and is less soluble in acidic conditions (<1 mg/L in 2M HCl). After discussion with the Division Director, Dr. Malinowksi, the following points are noted:

Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II has reviewed the submission submitted on 19-July, 2001 and finds it acceptable.

Please convey the Recommendation, Comments and Labeling Comments to the sponsor as appropriately.

Comments: (Comments are from the original clinical pharmacology and biopharmaceutics review but were not conveyed to the sponsor since the NDA was not approved.)
Since the capsules dissolve readily within 30 minutes and the minimum dissolution at 30 minutes was —— it is recommended that the dissolution specification be changed to the following:

Medium:	Phosphate buffer pH 6.8
Volume:	1000 mL
RPM:	50, Apparatus 2 (paddle)
Tolerance:	Not less than—% (Q= —— at 30 minutes

Labeling Comments: (note: underline text should be added.)
DOSAGE and ADMINISTRATION
The dose of nitisinone should be adjusted in each patient. The recommended initial dose is 1 mg/kg/day divided for morning and evening administration. Since an effect of food is unknown, nitisinone should be taken at least one hour before a meal..... For young children, capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

Hae-Young Ahn, Ph.D. _____
John Hunt, Deputy Director _____

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

/s/

Hae-Young Ahn
12/7/01 02:48:05 PM
BIOPHARMACEUTICS

John, A hard copy has been signed.

John P. Hunt
12/7/01 03:54:00 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-232 / N-000 BL	**SUBMISSION DATE:**	**25-JAN-01**
BRAND NAME:	**Orfadin™ 2, 5, and 10mg oral capsules**	
GENERIC NAME:	**Nitisinone; NTBC**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
APPLICANT:	**Swedish Orphan, AB, Stockholm, Sweden**	
US AGENT:	**R&R Registrations, San Diego, CA**	
TYPE OF SUBMISSION:	**Labeling**	

SYNOPSIS:

The sponsor has submitted labeling in response to FDA suggestions. The following changes are further suggested; only relevant parts of the labeling are included. Data from the HT-1 subjects (submission on 18-JAN-01 BZ) have not been fully reviewed and, as such, these data are not to be included in the labeling at this time.

ORFADIN™, nitisinone (INN) capsules

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CLINICAL PHARMACOLOGY

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Pharmacokinetics and Drug Metabolism

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No pharmacokinetic study has been conducted in children or HT-1 patients.

Absorption

The single dose pharmacokinetics of nitisinone have been studied in ten healthy male volunteers aged 19-39 years (median 32 years). Nitisinone, 1 mg/kg body weight, was administered as a capsule and a liquid. The median time for maximum plasma concentration was 3 hours for the capsule and 15 minutes for the liquid. The capsule and liquid formulation were found to be bioequivalent based on an anlysis of area under the plasma concentration-time curve and maximum plasma concentration (Cmax).

Metabolism

No information on the metabolism of nitisinone in humans is available.

Excretion

The effect of food on the pharmacokinetics of nitisinone has not been studied

Special Populations

Geriatric - No pharmacokinetic

Gender - The effect of gender on the pharmacokinetics of nitisinone was not studied.

Race - The effect of race on the pharmacokinetics of nitisinone was not studied.

Renal Insufficiency - The effect of renal insufficiency on the pharmacokinetics of nitisinone was not studied.

Hepatic Dysfunction - The effect of hepatic dysfunction on the pharmacokinetics of nitisinone was not studied.

Drug-Drug Interactions

No drug-drug interaction studies were conducted.

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PRECAUTIONS

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Drug Interactions

No drug-drug interaction studies were conducted.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 12-FEB-01

FT initialed by Hae-Young Ahn, Ph.D., Team Leader_____

CC: NDA 21-232/N-000 (orig.,1 copy), HFD-510(Yang), HFD-870(Ahn), CDR.

Code: AE

/s/

Robert Shore
2/14/01 03:05:12 PM
BIOPHARMACEUTICS
further labeling suggestions.
hardcopy already finalized

Hae-Young Ahn
2/23/01 12:04:34 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-232/N-000 RS	**SUBMISSION DATE:**	**07-SEP-00**
BRAND NAME:	**Orfadin**	
GENERIC NAME:	**Nitisinone 2, 5, and 10mg oral capsules**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
APPLICANT:	**Swedish Orphan, AB, Stockholm, Sweden**	
US AGENT:	**R&R Registrations, San Diego, CA**	
TYPE OF SUBMISSION:	**NME (1P)**	

TERMS AND ABBREVIATIONS:

AUCa-b ..... area under the plasma-concentration-time curve from time a to time b
BW .... Body weight
Cmax... ..... Maximum plasma concentration
DMEDP ..... Division of Metabolic and Endocrine Drug Products
HT-1 .... Hereditary tyrosinemia type 1
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
T1/2..... ..... Half-life
TBM .... To be marketed
Tmax... ..... Time of Cmax

CONCENTRATION CONVERSION FACTOR:

3μmol/L NTBC ≈ 1μg/mL NTBC

SYNOPSIS:

The following is a survey of the studies included in Section 6 of this NDA:

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studies data form
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS STUDIES

DPE #_2__ NDA# 21-232 Category: __1P_ (_P or _S)

Clinpharm / Biopharm Briefing Date: 25-Jan-01 chem type: __ Route of Administration: _____oral_____

note: Categorize & count study types based on primary objective only. When there is more than one primary objective, flag counts associated with the same study with matching letters. If more than one multiple objective study, use a distinct letter for each one.

STUDY TYPE	no. submitted	no. reviewed	Outcome (i.e., effect on labeling or safety and efficacy
I. Clinical Pharmacology			
Mass balance:			
Isozyme characterization:			
Blood/plasma ratio:			
Plasma protein binding:			
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:	1a		
multiple dose:			
Patients-			
single dose:			
multiple dose:	1		
Dose proportionality - please indicate fasting or non-fasting			
fasting / non-fasting single dose:			
fasting / non-fasting multiple dose:			
Drug-drug interaction studies -			
in-vivo effects on primary drug:			
in-vivo effects of primary drug:			
in-vitro:			
Subpopulation studies -			
ethnicity:			
gender:			
pediatrics:			
geriatrics:			
renal impairment:			
hepatic impairment:			
			* indicate quality - scale 1=poor 2 3 4 5=excellent
PD:			*
PK/PD:			*
Population Analyses -			
data rich:			*
data sparse:			*
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:	1a		
alternate formulation as reference:			
Bioequivalence studies - please indicate single or multiple dose			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies:			
Dissolution:	1		
(IVIVC):			*
III. Other			
Genotype/phenotype studies:			
Chronopharmacokinetics:			
Literature / No. of Articles:			
Which Phase IV study(ies)requested:	N/A	N/A	

TOTAL NO. OF STUDIES SUBMITTED: _3___ **TOTAL NO. OF STUDIES REVIEWED: __3__**

Orfadin® (nitisinone; NTBC) is an orphan drug proposed for the treatment of hereditary tyrosinemia type 1, a disease caused by the deficiency of an enzyme at the tailend of the tyrosine degradation pathway. This enzyme deficiency causes accumulation of toxins which can lead to liver failure in infancy or hepatocellular carcinoma in childhood or adolescence. The proposed dosing will start at 0.5mg/kg PO BID and can be titrated based on clinical response biomarkers up to 1mg/kg BID. Capsules of 2, 5, and 10mg are proposed to be marketed.

What drug formulations have been studied?
The to-be-marketed formulation will be a mixture of only NTBC and starch in an immediate release hard gel capsule for oral administration. The clinical trials were performed with both the TBM formulation as well as a ——— containing formulation. Although the two formulations have not been shown to be bioequivalent in a pivotal study, there are pharmacokinetic and clinical data to support the similarity of the two formulations.

What is the dissolution method and specification?
The proposed method and specification are:

Medium:	Phosphate buffer pH 6.8, USP
Volume:	1000 mL
# caps:	12
Sinker:	Attached
RPM:	50
Time:	60 minutes
Tolerance:	——— (Q= ———)

Based on dissolution profiles submitted, OCPB recommends the time be changed to 30 minutes.

Were the analytical methods acceptable?
Both the ——————————————— assays are acceptable. The sponsor has been asked to submit data comparing the two assay but this has not been received at the time of this writing.

Are the clinical trial and TBM formulations bioequivalent?
Although a pivotal head-to-head study was not conducted, there is data that show the steady-state NTBC plasma concentrations achieved with the two formulations are similar.

What are the pharmacokinetic parameters of NTBC?
The half-life of NTBC is 54 hours. The AUC after administration of the ——— containing capsule is 603μg*h/mL and the Cmax is 8.2μg/mL. Median Tmax is 3 hours.

How do single and multiple doses compare?
Although NTBC is calculated to accumulate 7-fold if dosed as labeled, the actual accumulation is slow and occurs while doses increase slightly over years of therapy. One possible reason for this lack of expected accumulation is self-induction of metabolism (N.B. no metabolism study has been conducted)

What is the effect of food on the bioavailability of NTBC?
The effect of food on NTBC pharmacokinetics is unknown. The clinical trial protocol did not address the timing of the dose and no specific food effect study was submitted. ——————————

How does the human body metabolize / clear NTBC?
Neither *in vitro* nor *in vivo* metabolic studies have been conducted. It remains unknown how NTBC is cleared from the human body. ——————————

Have special populations been studied?
The clinical trial has been conducted in pediatric patients, the diseased population. The only formal pharmacokinetic study conducted (study CCT/96/001) enrolled healthy adults. Steady-state NTBC concentrations were determined in the clinical trial. No gender, age, hepatic or renal impairment studies have been conducted.

Have drug interaction studies been conducted?
No drug interaction studies have been conducted.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-232/N-000 RS submitted 07-SEP-00. Based on the data submitted in Section 6 along with the clinical indication, the overall Human Pharmacokinetic Section of this NDA is acceptable to OCPB. This recommendation, comments (p. 12), and labeling comments (p.12) should be sent to the sponsor as appropriate.

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(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

BACKGROUND:

Nitisinone (NTBC) received orphan designation for the treatment of HT-1 in May 1995; in July 1999 fast track designation was granted. The proposed indication is treatment of hereditary tyrosinemia type 1, a disease caused by the deficiency of an enzyme at the tailend of the tyrosine degradation pathway. Current therapy for this disease is dietary restriction of protein. This enzyme deficiency causes accumulation of toxins which can lead to liver failure in infancy or hepatocellular carcinoma in childhood or adolescence. NTBC inhibits an enzyme at the beginning of the tyrosine degradation pathway, thus limiting the production of toxic metabolites. Tyrosine accumulates but is cleared through other elimination routes. Proposed dosing will start at 0.5mg/kg PO BID and can be titrated based on clinical response biomarkers, up to 1mg/kg BID. Capsules of 2, 5, and 10mg are proposed to be marketed.

STUDY SUMMARY INDEX

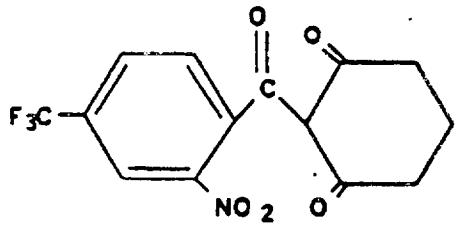
Protocol / Document Number	Title	Page
2000 010 02	A retrospective comparison of NTBC concentrations, laboratory data and Kaplan-Meier graphs between patients who received —— containing and patients who received starch containing NTBC formulations	p. 34

DRUG FORMULATION:

What drug formulations have been studied?

Nitisinone (2-(2-Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione), also known as NTBC, has a molecular formula of $C_{14}H_{10}F_3NO_5$ and a molecular mass of 329.23. Orfadin™ capsules will be manufactured at Apoteket AB, Gothenburg, Sweden.

The structural formula is shown below:



Clinical trials started in 1991 with the —— containing formulation prepared ——— ' for each patient. Fixed dose —— containing capsules (5, ——— and 10mg) were introduced in mid 1995. The 2mg starch-containing formulation became available in June/July 1996 while the 5 and 10mg starch-containing capsules were not introduced until March/April 1998. The ——— mg —— containing capsules were manufactured until October 1997. As a patient's supply of the ——— containing capsules ran out they were replaced with the starch-containing formulation.

As per Dr. Lubas, MO, the clinical data submitted in the original NDA (which was deemed RTF) was from 1991 to 1997 on about 200 patients. Since most of these clinical data had been generated with the —— -containing formulation, a link to the starch-containing formulation was needed. The sponsor then submitted a parallel-groups analysis of steady-state NTBC plasma concentrations in patients who received either the —— · or starch-containing formulation. The results are located in the Human Pharmacokinetic and Bioavailability section of this review. In addition, the sponsor submitted a similar analysis using the clinical data from these two patient groups; this was reviewed by Dr. Lubas.

Starch formulation (TBM)

Capsule strength Name of ingredient	2 mg capsules (amount/ capsule)	5 mg capsules (amount/ capsule)	10 mg capsules (amount/ capsule)
2-(2-nitro-4-trifluoromethyl-benzoyl)1,3-cyclohexandedione (NTBC)	2 mg	5 mg	10 mg
Starch, pregelatinised	—	—	—
Hard gelatine capsules ——	1 unit	1 unit	1 unit
-Gelatin	—	—	—
-Titanium Dioxide	—	—	—
Ink reference: 1007- Black (Black Iron Oxide ——			

formulation (clinical trials)

Capsule strength Name of ingredient	5 mg capsules (amount/ capsule)	mg capsules (amount/ capsule)	mg capsules (amount/ capsule)	mg capsules (amount/ capsule)	10 mg capsules (amount/ capsule)
2-(2-nitro-4-trifluoromethyl-benzoyl)1.3-cyclohexanedione (NTBC)	5 mg				10 mg
Hard gelatine capsules	1 unit	1 unit	1 unit	1 unit	1 unit
-Gelatin					
Capsule body colours % of gelatine capsule weight					
Capsule top colours % of gelatine capsule weight					

A bioequivalence analysis between the containing formulation and a liquid formulation was performed by the sponsor and is reviewed under Human Pharmacokinetics and Bioavailability Studies. The liquid formulation is listed below.

Liquid formulation

Name of ingredient	Amount
2-(2-nitro-4-trifluoromethyl-benzoyl)1,3-cyclohexanedione (NTBC)	2.0 mg

DISSOLUTION:

What is the dissolution method and specification?

The solubility data provided by the sponsor are shown below:

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Solvent	Solubility, µg/mL
Gastric juice (pH = 1.2)	3.0
Gastric juice + 0.25% SDS	19.7
Gastric juice + 0.5% SDS	34.3
Gastric juice + 1.0% SDS	66.0
Acetate buffer (pH = 4.5)	165
Acetate buffer + 0.25% SDS	191
Acetate buffer + 0.5% SDS	213
Acetate buffer + 1.0% SDS	247

To meet sink conditions (at least 3 times actual solubility) with the 10mg capsule using 1000mL of dissolution media, the solubility needs to be at least 30mcg/mL. This is not achieved with a media of pH 1.2 unless a surfactant is used. However, sink conditions are achieved with media at or above pH 4.5. As reported by the sponsor, in a 2M NaOH solution (calculated pH 13.7) solubility is 75mg/mL. A dissolution media of pH 6.8 was chosen by the sponsor for dissolution testing.

The proposed dissolution method and specification are as follows:

Medium: Phosphate buffer pH 6.8, USP
Volume: 1000 mL
caps: 12
Sinker: Attached
RPM: 50, Apparatus 2 (paddle)
Time: 60 minutes
Tolerance: ≥ — (Q= —)

Dissolution data were generated by the sponsor using only 6 capsules per batch (See Appendix). Both 2mg and 10mg capsules were tested. The data show that the dissolution is consistent between the batches. Below is a typical example.

Dissolution data for NTBC 10mg Capsule (Batch 1060952)

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	92.2	97.2	97.5	96.9

Since the capsules dissolve readily within 30 minutes and the minimum dissolution at 30 minutes was ——, it is recommended that the dissolution specification be changed to the following:

Medium: Phosphate buffer pH 6.8, USP
Volume: 1000 mL
caps: 12
Sinker: Attached
RPM: 50, Apparatus 2 (paddle)
Time: 30 minutes
Tolerance: ≥ —— (Q= ——)

ANALYTICAL METHODOLOGY:

Were the analytical methods acceptable?

The concentrations of NTBC in plasma in study CCT/96/001 were determined by [redacted]

The concentrations of NTBC in plasma in study 2000 010 02 were determined by an [redacted]

Both these assays are acceptable. The sponsor has been asked to submit data comparing these two assay but this has not been received at the time of this writing.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

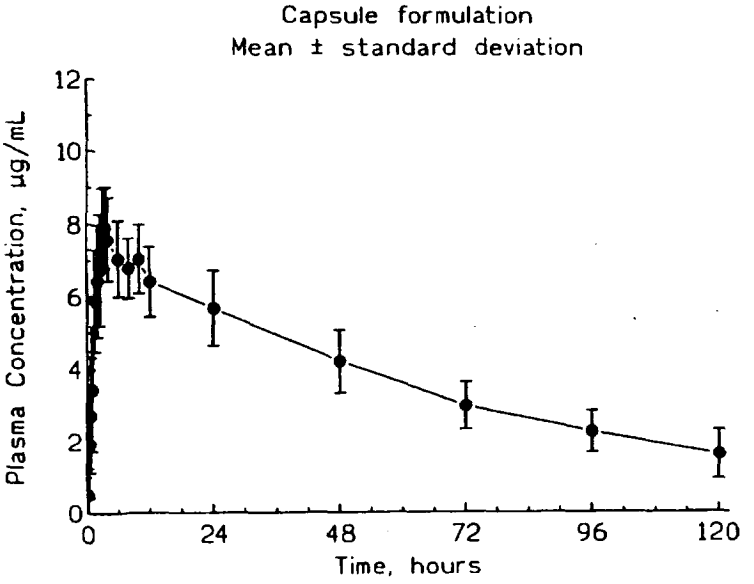
What are the pharmacokinetic parameters of NTBC?

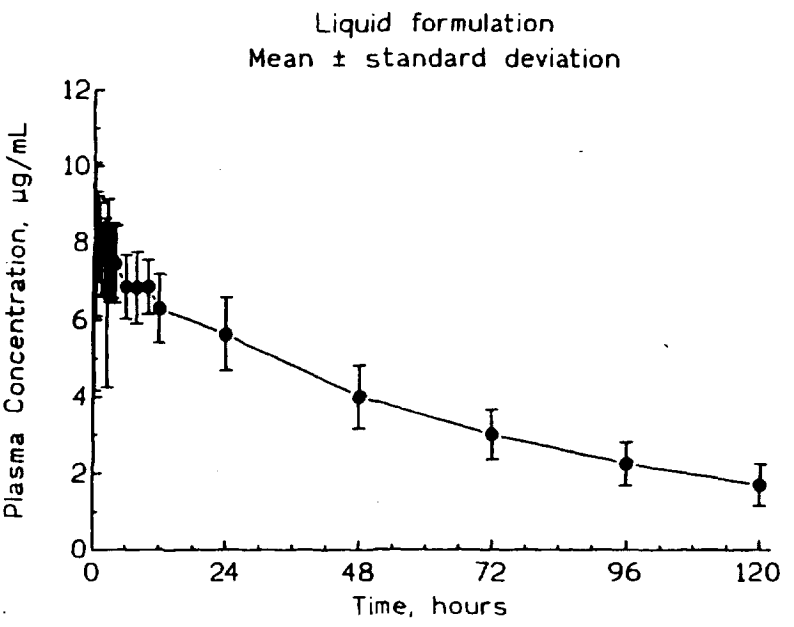
A bioequivalence study was conducted which compared the [redacted]-containing Orfadin® capsule with a liquid formulation (see drug formulation section for formulation details; see Appendix for study details). Ten healthy adult subjects received either the capsule or liquid in a cross-over study. Blood samples were taken up to 120 hours. It is noted that the half life of NTBC is calculated to be 54 hours. Therefore, sampling was performed for only about 2 half lives and extrapolated AUC is > 10%. Summary NTBC pharmacokinetic parameters from the non-compartmental analysis are listed below.

	AUC	AUClast	Cmax	Tmax	Half life
Capsule	602 (26%)	460 (20%)	8.22 (13%)	3 hr (1.5-3.5)	54 hr (24%)
Liquid	602 (24%)	464 (19%)	8.98 (14%)	0.25 hr (0.25-3.5)	54 hr (15%)

AUC expressed as µg*h/mL; Cmax expressed as µg/mL.
Tmax expressed as median (range); all other data expressed as mean (cv).

The NTBC half-life calculated from each formulation is the same. Tmax from the liquid occurs sooner than for the capsule, as expected. Below are plots of the average NTBC plasma concentrations for each formulation.





The table below summarizes the bioequivalence analysis, using the liquid as the reference.

Parameter	Point estimate (90%CI)
AUC	1.00 (0.94-1.06)
AUClast	0.99 (0.96-1.02)
Cmax	0.92 (0.86-0.97)

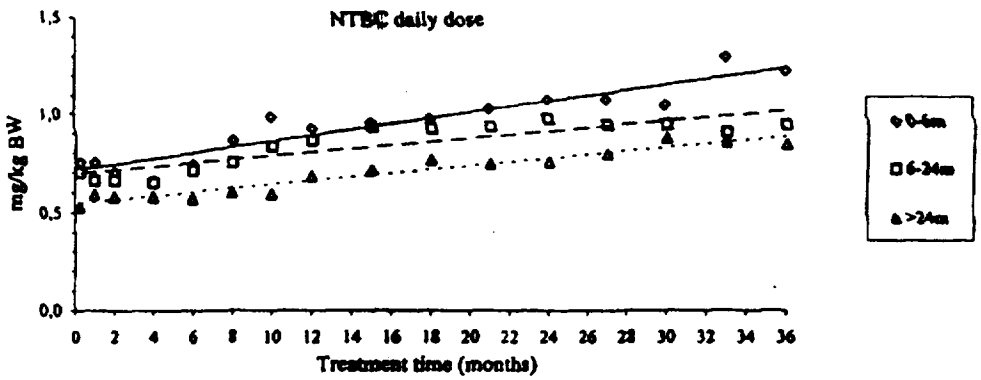
Both the liquid and ——— containing capsule are bioequivalent demonstrating that these formulation changes had little impact on the pharmacokinetic profile of NTBC.

Are the clinical trial and TBM formulations bioequivalent?

A formal pivotal bioequivalence study between the clinical ——— and TBM (starch) capsule formulations has not been conducted. Originally, this was a RTF issue. In lieu of this pivotal study the sponsor, as per FDA request, has submitted a parallel-group steady-state bioequivalence analysis. The SAS output from this analysis is located in the Appendix. This study (2000 010 02) compared a single steady-state plasma NTBC concentration from patients either receiving the ——— or the starch formulation for 12 months in the clinical trial. The ——— and starch groups had 17 and 29 patient samples, respectively. Plasma NTBC concentrations were log-transformed and averaged in each group. An ANOVA estimate of the 90% confidence interval about the ratio of these averages was calculated. The point estimate of the starch/ ——— ratio is 0.98 with a 90%CI of 0.8 to 1.2. Nothing is known about the timing of doses prior to the NTBC plasma sample but with a half-life of 54 hours the fluctuation in plasma NTBC concentrations is expected to be minimal. Although this is not a definitive bioequivalence analysis it does demonstrate relative similarity between the two formulations even with many unknown variable factors. In addition, the Medical Officer reviewed a similar analysis using clinical data and found that the starch- and ——— -containing formulations were similar.

How do single and multiple doses compare?

The first plot below shows the increase in dose as a function of time. For all three groups the daily dose (mg/kg BW) increases as the patients age. Also, the youngest patients had the highest doses. The reason for this dose increase is unknown but could include a change in sensitivity to the drug as the disease progresses.



This second plot shows the dose normalized NTBC concentrations. The NTBC concentration almost doubled during this time period. In patients with a start age 0-6 months, the dose normalized NTBC serum concentration was about 20 μmol/L per mg/kg daily dose at the beginning of NTBC treatment and increased to about 40 μmol/L per mg/kg after three years. Increases in the 6-24 month group were similar. In patients with start age >24 months the dose normalized NTBC concentration was about 30 μmol/L per mg/kg at the beginning of NTBC treatment and increased to about 60 μmol/L per mg/kg after three years.

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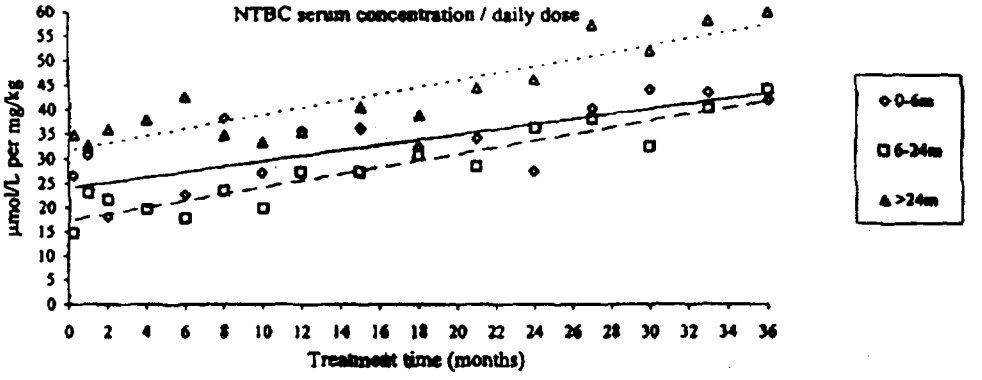

With a half-life of 54 hours and twice a day dosing the accumulation of the drug in the body is calculated to be 7 fold $\left[1/(1-e^{-k\tau}); k = 0.013\,hr^{-1}; \tau = 12\,hr\right]$. One reason that this accumulation was not seen maybe self-induction of NTBC metabolism.

What is the effect of food on the bioavailability of NTBC?

No food effect study was conducted. The labeling currently has no indication of when to take the dose in relationship to a meal and the clinical study protocol indicates 'Besides the instructions to administer the daily dose at two separate occasions, no specific dose interval or any specific timing of the dose were recommended.' The labeling does indicate that the capsules can be opened and the contents suspended in a small amount of water for administration to young children. However, it is possible that the contents may be sprinkled on food or that the whole capsule may be administered with a meal.

How does the human body metabolize / clear NTBC?

No data are available to address this topic. One rodent study summary indicates 'the majority of the urinary radioactivity was present as two polar metabolites.'

Have special populations been studied?

No studies have been conducted to explore the effects of gender, renal disease, or hepatic impairment on the pharmacokinetics of NTBC.

Have drug interaction studies been conducted?

Neither *in vitro* nor *in vivo* drug interaction studies have been conducted.

DISCUSSION:

The scientific data available for Orfadin® in section 6 of this NDA are limited. There is a lack of certain studies (e.g. pivotal bioequivalence , food effect, drug interactions) which makes it difficult to have a full understanding of this drug from a pharmacokinetic perspective. However, from the pharmacokinetic and clinical data that are available, the TBM formulation can be linked to the efficacy seen in the clinical trials.

Further study of the metabolism of, and food effect on, NTBC are to be conducted.

COMMENTS TO BE SENT TO SPONSOR:

1) Since the effect of food on the bioavailability of NTBC is unknown, it is recommended that the sponsor submit data which indicate how the drug product was actually administered during the clinical trial in relationship to food. These can include dosing diaries from patients or verbal recommendation made from clinical study staff. In addition, data on the palatability of the drug product in water is requested.

[ ]

LABELING COMMENTS:

1) Under the Pharmacokinetic section pharmacokinetic data [redacted] from the [redacted] containing capsule (Study CCT/96/001) are to be included. There are data to support the similarity between the [redacted] and starch-containing formulations. The following FDA proposed labeling change was sent to the sponsor on 28-DEC-00.

Pharmacokinetics and Drug Metabolism

The sponsor needs to include data showing plasma concentrations following oral administration of the to-be-marketed drug product. It is not enough to state that [redacted] *A comparison of AUC and Cmax for the capsule formulation should be determined if the capsule is ingested whole or if the capsule is opened and resuspended in water prior to administration. Information on solubility and drug food interactions would be useful since medications are routinely mixed with foods in pediatric patients to make the drugs more palatable. Were the clinical trials done under fed and/or fasted conditions?*

The sponsor should also include what information is known about metabolism, distribution and excretion of the drug product in this section

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Robert M. Shore, Pharm.D. /S/ 25-JAN-01
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 17-JAN-01

CPB Briefing 25-JAN-01
attendees: Malinowski, Hunt, Lazor, Ahnh, Sahajwalla, Lubas, Shore.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 1/25/01

CC: NDA 21-232/N-000 RS (orig.,1 copy), HFD-510(Yang), HFD-870(Ahn)

DFS Code: AE

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Appendix 1a. Draft Labeling from Sponsor

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Appendix 1b. Counter-proposed Labeling from FDA

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Labeling

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Appendix 2. Study Summaries

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Name of Company: Swedish Orphan AB Name of Finished Product: Nitisinone (NTBC) 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexandione	Individual study table referring to part of the dossier Volume: Page:	(For national authority use only)

Title of study:
A retrospective comparison of NTBC concentrations, laboratory data and Kaplan-Meier graphs between patients who received — containing and patients who received starch containing NTBC formulations.

Clinical trial id: NTBC Study: Inter-patient analysis	Document number: 2000 010 02

Principle Investigators:
[ ]

Study centres:
Samples from patients in 24 countries were analysed at the ——— Hospital (Australia 1+0, Austria 4+1, Belgium 2+1, Canada 10+9, Chile 1+0, Czech Republic 0+1, Denmark 2+0, Finland 1+1, France 2+0, Germany 6+1, Hungary 1+1, Israel 0+3, Italy 1+2, Japan 0+1, Netherlands 0+1, Norway 1+3, Poland 0+1, Portugal 0+1, Saudi Arabia 1+3, Spain 3+9, Sweden 1+0, Turkey 1+3, UK 1+6, USA 16+5 patients in the starch and — group, respectively).

Publication:

Studied period: First day in analysis: 1 January 1996 Last day in analysis: 16 March 2000	Phase of development: III

Objective:
To adequately link the bioavailability and clinical activity of the to-be-marketed formulation of NTBC, containing pregelatinized starch as — constituent, to the formulation delivered by Swedish Orphan AB that was used in the clinical documentation in the NDA, containing — as — constituent.

Methodology:
Patients who have been treated with NTBC formulations containing pregelatinized starch as constituent from the start of NTBC treatment (starch treatment group) were compared with patients who have been treated with NTBC formulations containing — as constituent, delivered by Swedish Orphan AB, from the start of NTBC treatment (— treatment group) in a parallel group analysis.

Number of subjects (planned and analysed):
Starch treatment group: 55 patients.
— treatment group: 53 patients.

Main criteria for inclusion:
The analysis was performed on patients receiving NTBC only from Swedish Orphan AB. Patients who started NTBC treatment between and included 1 January 1996 and 31 December 1999 were included.
Starch group: Patients who had used only pregelatinized starch containing formulations from the start of NTBC treatment.
— group: Patients who started their NTBC treatment with a — containing formulation and had an order date for the delivery of the first pregelatinized starch containing formulations.

Test product and batch number:
The NTBC substance was synthesized by ———— (batch number 10912/94). The pregelatinized starch containing formulations were distributed as hard gelatine capsules containing 2, 5 and 10 mg NTBC and pregelatinized starch

Reference therapy:
The — containing formulations were distributed as hard gelatine capsules containing 5, — and 10 mg NTBC and ————

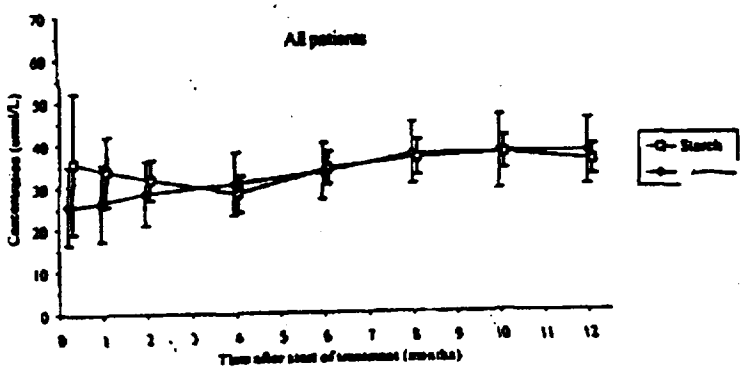
Name of Company: Swedish Orphan AB Name of Finished Product: Nitisinone (NTBC) 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexandione	Individual study table referring to part of the dossier Volume: Page:	(For national authority use only)
		Document number (cont'd): 2000 010 02

Duration of treatment:
In the starch treatment group the treatment time until 31 December 1999 varied between 1 and 32 months. In the —— treatment group the treatment time until the order date of the first delivery of a starch NTBC formulation varied between 1 week and 29 months, and the treatment time until 31 December 1999 varied between 1 and 47 months.

Criteria for evaluation:
NTBC serum concentration during 12, 18 and 24 months. Urine and plasma succinylacetone, erythrocyte PBG-synthase and urine 5-ALA during 12 months. Occurrence of death, liver transplantation, liver cancer, and liver failure leading to death or liver transplantation.

Statistical methods:
No formal hypothesis testing using pre-determined significance levels was performed.
NTBC serum concentration: Descriptive statistics was presented for each treatment group from the start of NTBC treatment until the 12-month, 18-month and 24-month visit. A 90% two-sided confidence interval for the difference between the treatment groups after 12 months (335-395 days) of NTBC treatment was calculated.
Laboratory variables: Each laboratory variable was presented using frequency tables, describing the proportion of normalized patients at 0-13, 14-29, 30-44, 45-59, 60-89, 90-120, 121-150, 151-182, 182-242, 243-303 and 304-364 days after start of NTBC treatment.
Survival analyses: The occurrence of death, liver transplantation, liver cancer, and liver failure leading to death or liver transplantation was presented as Kaplan-Meier graphs for each treatment group. The difference between treatment groups was analysed using the Gehan-Wilcoxon test.

Summary – conclusions:
The NTBC serum concentrations were similar for the starch and —— treatment groups. In the analysis of all included patients who were followed for at least 12 months after start of NTBC treatment, the mean dose normalized NTBC serum concentration at the 12-month visit window was 2.0 µmol/L (5%) lower in the starch than in the —— treatment group, with a 90% two-sided confidence interval of –4.3 – 8.4 µmol/L. It is reasonable to conclude that the starch and —— containing NTBC formulations are bioequivalent with regard to NTBC serum concentrations.



NTBC serum concentrations (mean ±2SEM) in all patients followed until the 12-month visit or later (29 patients in the starch group and 17 patients in the —— group).

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		Document number (cont'd): 2000 010 02

Summary – conclusions (cont'd):

The urine succinylacetone values normalized very fast in both the starch and —— treatment groups, and all patients had normal values within a few weeks. The plasma succinylacetone values normalized considerably slower. After six months of NTBC treatment there were still patients with abnormal values, but after 12 months all patients were normalized in both the starch and —— groups. The erythrocyte PBG-synthase and urine 5-ALA values also normalized very fast in both the starch and —— groups, and almost all patients were normalized within a few weeks. However, three patients was not normalized during the first year of NTBC treatment, two in the starch with regard to erythrocyte PBG-synthase and one in the —— group with regard to urine 5-ALA. It can be concluded that there was no difference between the starch and —— containing formulations concerning the efficacy on the laboratory variables urine and plasma succinylacetone, erythrocyte PBG-synthase and urine 5-ALA.

Death and transplantation due to liver failure can be regarded as the treatment failures observed in the survival analyses, since there were no cases of hepatocellular carcinoma or other cases of withdrawals directly related to the illness. The treatment groups were very similar regarding the probability of preventing death or transplantation due to liver failure, two patients died due to liver failure in the starch group and one in the —— group. Further three patients in the —— group were transplanted due to liver failure after the shift to starch formulations.

The treatment groups were very similar regarding the probability of preventing death due to any reason. Two patients in the starch group died, one due to liver failure and one due to complications of prematurity, and one patient in the —— treatment group died due to liver failure.

In addition to the three patients who died due to liver failure, one patient died due to complications of prematurity, two patients were transplanted due to suspected liver cancer which was not verified later and two patients had elective liver transplantation, all five in the starch treatment group. The probability of preventing death or liver transplantation due to any reason was lower in the starch group compared to the —— group. However, the confidence limits were wide and overlapping, and the p-value for the difference between the treatment groups was 0.090 according to the Gehan-Wilcoxon test. Three patients were transplanted in the —— group shortly after (3-5 weeks) the shift to starch containing formulations, two due to liver failure and one as elective, and further two transplantations were performed 5 and 16 months after the shift.

In summary of the survival analyses, no difference could be seen between the treatment groups. The probability of preventing treatment failure seems to equal for both the starch and —— containing formulations, although the limitations of the analyses do not allow a definite conclusion.

As an overall conclusion, the starch containing and —— containing NTBC formulations are equal regarding bioavailability and clinical activity.

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Date of the report:
14 August, 2000

A single dose, crossover, pharmacokinetic study of two formulations (capsule and liquid) of NTBC in healthy volunteers. (protocol CCT/96/001)

Volunteers
Ten healthy, non-smoking males with a median age of 32 years (range 19-39 years) participated in the present study. Their median weight was 73.9 kg (range 63-95.5 kg). All subjects were within 10% of ideal body weight according to the Metropolitan Life Tables.

Study design
The study was an open, balanced randomized 2-way cross over design. The washout period between treatments was at least 14 days All volunteers were randomized for the treatment order prior to initiation of the study.
The scheduled dose of NTBC was 1 mg/kg, based on the body weight determined on Day 1 of Period 1. The drug was always administered along with 150 mL of water. The actual dose was 0.99 mg/kg (median value; range: 0.95-1.02 mg/kg).

Dosage forms
The capsule formulation consisted of NTBC and —— in a hard shell gelatin capsule , —— Four different strengths of capsules were available, 5,.— and 10 mg. The liquid formulation used had a concentration of 2 mg/mL. It was prepared by dissolving NTBC in ———— buffer and finally adjusted to pH 7.0.

Plasma Samples
Blood samples (9 mL) for the analysis of NTBC were taken into lithium heparin polypropylene monovettes prior to dosing (0 h) and 15, 30, 45 min, 1, 1.5, 2, 2.5 3, 3.5, 4, 6, 8, 10, 12, 24, 48, 72, 96 and 120 h after drug administration. The samples were centrifuged (1500 g at 4 °C for 10 min). The plasma fractions were isolated and stored frozen at -20 °C until analysis.

Bioanalytical procedure
The concentration of NTBC in plasma was assayed by ————————————

[ ]

Pharmacokinetics
The pharmacokinetics of NTBC in man were evaluated by pharmacokinetic modeling as well as by non-compartmental technique. Initial estimates for the pharmacokinetic modeling were obtained by the —— stripping program. The final estimates of the pharmacokinetic parameters were obtained by the PC-NONLIN program (ver. 2.0) As weight in the fitting procedure the reciprocal values of the measured plasma concentrations were used. Estimates of the maximum plasma concentration (Cmax), time for maximum plasma concentration (Tmax) and area under the plasma concentration time curve (AUC) were obtained from the fitted curves. The optimal pharmacokinetic models were established by visual inspection of the fitted plasma concentration time curves (lin and log scales) and from values of weighted squared residuals using the F-ratio test (HG Boxenbaum et al. J. Pharmacokin. and Biopharm. 2, 123 (1974)).
The area under the plasma concentration time curve was also evaluated by non-compartmental technique using the trapezoidal rule. The area from the last sampling time to infinity was calculated from the measured plasma concentration and the estimated terminal half-life time.

Statistics
In statistical evaluation of data involving Tmax and Cmax in treatment where the maximum plasma concentration occurred prior to the fist sampling the measured concentration value obtained at 15 min was used.

The paired differences of pharmacokinetic parameters, i.e. after administration of NTBC as capsule and liquid formulations formulation, were evaluated by the Pitman randomization test based on Wilcoxon matched paired sign rank test (GE Dallal Computers and Biomedical Research 21, 9 (1988)). Bioequivalence was established by the Westlake's 95% interval for untransformed values (WJ Westlake J. Pharm. Sci. 61, 1340 (1972, WJ Westlake Biometrics 32 741 (1976)) and the Hauschke-Steinijans nonparametric test for bioequivalence (D Hauschke et al. Int. J. Clin. Pharmacol. Ther. Toxicol. 28, 72 (1990)).

Results

Plasma concentration data from all subjects after the administration of NTBC as capsule and liquid formulations are given in Tables 1 and 2. The pharmacokinetic modeling were considered appropriate in all patients after intake of NTBC as a solution as well as capsules. However, due to very rapid absorption, the maximum plasma concentration appeared prior to the first sample, i.e. 15 min after administration, in six of the patients after intake of the liquid formulation of NTBC. Typically, the two compartment model with a zero order absorption phase was used for describing the plasma concentration time profile after intake of the liquid formulation of NTBC. The plasma concentration time profiles after intake of the capsule formulation of NTBC were typically most accurate described by the one compartment model with a first order absorption phase. The results from the pharmacokinetic modeling using data from all volunteers after administration of the two different formulations are given in Figures 1-20. Mean and standard deviation plasma concentration data of NTBC after administration of the two different formulations are given in Figures 21-24. The main pharmacokinetic parameters obtained for the pharmacokinetic modeling, i.e. AUC, Cmax, Tmax and terminal half life time, T½ are summarized in Table 3 and 4.
The results form non-compartmental analysis of the data are given in Table 5 and 6.
The statistical comparison of the pharmacokinetics of NTBC in man after administration as liquid and capsule formulations is summarized in Table 7. The statistical comparisons were based on data from the pharmacokinetic modeling. Moreover, a test was also performed of AUC values calculated by the trapezoidal rule. There were no statistical differences in AUC and T½ for the two formulations, and the values of AUC and T½ for the two formulations were also found to be bioequivalent. Cmax and the quotient Cmax /AUC were higher for the liquid formulation as compared to the capsule. Neither Cmax nor Cmax /AUC did fulfill the criteria for bioequivalence of the two formulations by the nonparametic test. According to the Westlake's test for bioequivalence the Cmax values of the two formulations did not fulfill the criteria for bioequivalence. This finding is in contrast to the results obtained by testing Cmax/AUC for the two formulations by the Westlake's test.
The results from pharmacokinetic modeling showed that the time for maximum plasma concentration was within 2 hours for liquid formulation and within the range ——— hours for the capsule formulation. In six of the volunteers the time for maximum plasma concentration of NTBC occurred within 15 minutes after administration.
The inter individual variation of the bioavailability, expressed as AUC, and the absorption rate, expressed as Cmax /AUC, did not differ for two formulations of NTBC (the F-test). The coefficients of variation of AUC were 25.6 and 23.7% (data from pharmacokinetic modeling), 25.6 and 24.3% (data from non-compartmental analysis) and of Cmax /AUC 16.0 and 14.7% for the capsule and liquid formulation, respectively.

Discussion

The present study compares the pharmacokinetics of NTBC in healthy volunteers after administration as capsule and liquid formulations. The results in the present study confirm our previous results from a pharmacokinetic study in the rats of a rapid absorption of NTBC after oral administration. The results furthermore indicate that the absorption rate is somewhat higher after administration of the liquid formulation as compared to the capsule formulation. The fairly low inter individual variation of the pharmacokinetics facilitates a proper dosing of the drug.

[redacted]

The pharmacokinetic profile after repeated, i.e. chronic, treatment is dominated by the long terminal half-life time of NTBC. The large inter individual variation of the time for maximum

plasma concentration observed is most likely of a minor importance in the clinical use of NTBC as capsule and liquid formulations.
The results from the non-compartmental analysis of the data are in close agreement with findings from the pharmacokinetic modeling of the data. However, the interindividual variation of the Tmax values using the non-compartmental analysis were less pronounced.

Conclusion
The pharmacokinetics of the capsule and liquid formulations of NTBC are essentially equivalent. The capsule formulation can therefore be substituted by the liquid formulation for clinical use. The low inter individual variation of the area under the plasma concentration time curve facilitates a proper dosing of the drug.

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Appendix 3. Assay Performance

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Appendix 4. Dissolution Data

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Table 1.

Dissolution profile for NTBC 10 mg capsules

Dissolution medium: Phosphate buffer pH 6.8

Volume of medium: 1000 mL

Rotation speed: 50 rpm

Batch No capsules:1049030

Batch No trituration: 1029713

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	86.1	94.4	95.5	95.3

Table 2.

Dissolution profile for NTBC 10 mg capsules

Dissolution medium: Phosphate buffer pH 6.8

Volume of medium: 1000 mL

Rotation speed: 50 rpm

Batch No capsules:911G2769

Batch No trituration: 909G2704

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	88.7	96.7	97.4	97.1

Table 3.

Dissolution profile for NTBC 10 mg capsules

Dissolution medium: Phosphate buffer pH 6.8

Volume of medium: 1000 mL

Rotation speed: 50 rpm

Batch No capsules:908G2566

Batch No trituration: 908G2546

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	83.5	92.7	94.4	94.3

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Table 4.

Dissolution profile for NTBC 2 mg capsules

Dissolution medium: Phosphate buffer pH 6.8

Volume of medium: 1000 mL

Rotation speed: 50 rpm

Batch No capsules:910G2747

Batch No trituration: 909G2704

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	86.9	93.6	93.9	93.7

Table 5.

Dissolution profile for NTBC 2 mg capsules

Dissolution medium: Phosphate buffer pH 6.8

Volume of medium: 1000 mL

Rotation speed: 50 rpm

Batch No capsules:1033913

Batch No trituration: 911G2782

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	89.3	96.3	96.5	95.8

Table 6.
Dissolution profile for NTBC 2 mg capsules
Dissolution medium: Phosphate buffer pH 6.8
Volume of medium: 1000 mL
Rotation speed: 50 rpm
Batch No capsules:1045112
Batch No trituration: 1029713

	% dissolved after (min)			
Sample	15	30	45	60
1				
2				
3				
4				
5				
6				
Mv	93.1	100.1	99.9	99.1

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Appendix 5. SAS Files

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OBS	SUBJ	TRT	CONC	LCONC
1	30			
2	31			
3	32			
4	33			
5	34			
6	35			
7	36			
8	37			
9	38			
10	39			
11	40			
12	41			
13	42			
14	43			
15	44			
16	45			
17	46			
18	1	Starch		
19	2	Starch		
20	3	Starch		
21	4	Starch		
22	5	Starch		
23	6	Starch		
24	7	Starch		
25	8	Starch		
26	9	Starch		
27	10	Starch		
28	11	Starch		
29	12	Starch		
30	13	Starch		
31	14	Starch		
32	15	Starch		
33	16	Starch		
34	17	Starch		
35	18	Starch		
36	19	Starch		
37	20	Starch		
38	21	Starch		
39	22	Starch		
40	23	Starch		
41	24	Starch		
42	25	Starch		
43	26	Starch		
44	27	Starch		
45	28	Starch		
46	29	Starch		

Analysis Variable : CONC

TRT= [redacted]

N	Mean	Std Dev	Minimum	Maximum
17	37.9294118	16.0725607	[redacted]	[redacted]

TRT=Starch

N	Mean	Std Dev	Minimum	Maximum
29	35.8551724	9.7493804	[redacted]	[redacted]

General Linear Models Procedure

Class Level Information

Class	Levels	Values
SUBJ	46	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46
TRT	2	[redacted] Starch

Number of observations in data set = 46

General Linear Models Procedure

Dependent Variable: CONC

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	46.11124261	46.11124261	0.30	0.5875
Error	44	6794.64701826	154.42379587		
Corrected Total	45	6840.75826087			

R-Square	C.V.	Root MSE	CONC Mean
0.006741	[redacted]	12.42673714	36.62173913

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRT	1	46.11124261	46.11124261	0.30	0.5875

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRT	1	46.11124261	46.11124261	0.30	0.5875

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
[redacted] vs. Starch	2.07423935	0.55	0.5875	3.79588082

General Linear Models Procedure

Dependent Variable: LCONC

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.00391128	0.00391128	0.02	0.8755
Error	44	6.92685020	0.15742841		
Corrected Total	45	6.93076148			

R-Square	C.V.	Root MSE	LCONC Mean
0.000564	[redacted]	0.39677250	3.53475548

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRT	1	0.00391128	0.00391128	0.02	0.8755

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRT	1	0.00391128	0.00391128	0.02	0.8755

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
[redacted] vs. Starch	-0.01910358	-0.16	0.8755	0.12119844

General Linear Models Procedure

Least Squares Means

TRT	CONC LSMEAN	LCONC LSMEAN
[redacted]	37.9294118	3.52271192
Starch	35.8551724	3.54181550

SAS data file (orfadin.dat) and command file for bioequivalence analysis.

```
---
1    1    2    556   7.50   445.3
1    2    1    661   9.50   477.5
2    2    2    755   10.00  582.8
2    1    1    816   9.91   606.6
3    2    2    591   8.20   460.3
3    1    1    624   10.00  471.5
4    1    2    345   6.39   281.6
4    2    1    332   6.50   293.5
5    1    2    867   8.82   540.7
5    2    1    792   11.10  548.4
6    1    2    423   6.96   355.2
6    2    1    433   8.00   360.5
7    2    2    663   8.80   475.1
7    1    1    579   7.96   464.4
8    2    2    594   8.20   485.3
8    1    1    587   8.75   468.5
9    1    2    523   8.13   411.2
9    2    1    549   9.00   444
10   2    2    706   9.20   562.9
10   1    1    647   9.11   504.3
---
```

```
data orfadin;
 infile 'a:\orfadin.dat';
 input subject period form AUC Cmax AUClast;
 lcmax = log(cmax);
 lauc = log(auc);
 lauclast = log(auclast);
 run;
proc glm data=orfadin;
 class subject period form;
 model lcmax lauc lauclast = subject period form;
 lsmeans subject period form / cl alpha=0.1;
 estimate  'Cap/Liquid' form -1 1;
run;
```

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/s/

Robert Shore
1/25/01 04:43:15 PM
BIOPHARMACEUTICS
NDA approvable

hardcopy already finalized

Hae-Young Ahn
2/2/01 03:29:32 PM
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