CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-498

Clinical Pharmacology and Biopharmaceutics Review

Office of Clinical Pharmacology and Biopharmaceutics Review

Division of Pharmaceutical Evaluation III

NDA:	21-498
Generic	Nitazoxanide
(Brand®)	Cryptaz®
Submission Date:	May 28, 2002
Applicant:	Romark Laboratories, L.C.
Clinical Division	DSPIDP (HFD-590)
OCPB Division	DPE3 (HFD-880)
Type of Submission:	NDA
Reviewer:	Dakshina Chilukuri, Ph.D.
Team Leader	Barbara Davit, Ph.D.
Review Date	October 4, 2002

1. EXECUTIVE SUMMARY

The applicant is seeking approval of — Nitazoxanide Powder for Oral Suspension in NDAs — 21-498, respectively. The proposed indications are treatment of chronic diarrhea in . pediatric patients due to Cryptosporidium parvum (C. parvum) and Giardia lamblia (G.lamblia). Since patients took the drug with food in the pivotal clinical trials, the label specifies that the drug is to be taken with food.

Nitazoxanide is a salicylamide acetate ester, which has demonstrated in vitro activity against the intracellular parasite C. parvum. The pharmacokinetics of the drug has been characterized in healthy normal subjects and in AIDS patients. Pharmacokinetic studies in humans and experimental animals have failed to detect parent nitazoxanide in plasma, urine, or fecal samples. Nitazoxanide is rapidly desacetylated to tizoxanide (desacetylnitazoxanide) in biological fluids, most likely by a combination of nonspecific esterase activity and spontaneous hydrolysis. Thus, the plasma concentration-time curves of tizoxanide have been monitored in clinical and preclinical pharmacokinetic studies.

The applicant previously submitted an NDA 20-871 in 1997 for the approval of nitazoxanide tablets to treat AIDS patients with chronic diarrhea due to C. parvum. Following recommendations of the Anti-Infectives Advisory Committee, the applicant was issued a non-approvable letter indicating deficiencies in the application. The applicant has since submitted new — 21-498 for nitazoxanide powder for oral suspension — respectively, with additional data. — — The powder for suspension in NDA 21-498 is targeted for pediatric patients of ages 12 months to 11 years.

To support the approval of nitazoxanide — powder for oral suspension, the applicant conducted studies B099597, RM01/02-1015 and 198.637; a bioequivalence study of a suspension — formulations of nitazoxanide, a PK study in pediatric patients and a multiple dose study in healthy volunteers. Additional in vitro studies to evaluate intestinal permeability and the potential for interaction of nitazoxanide with cytochrome P450 enzymes were performed.

HFD-590 recommends approval for the nitazoxanide powder for oral suspension, NDA 21-498. — — Thus, the nitazoxanide powder for oral suspension will be approved for use in children.

TABLE OF CONTENTS

2. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in [redacted] 21-498 for Nitazoxanide [redacted] powder for oral suspension. The Human Pharmacokinetics and Bioavailability Section of ND. [redacted] 21-498 has met the requirements of the 21 CFR 320 and the clinical pharmacology labeling requirements of 21 CFR 201.56.

Administration with food: The bioequivalence data, when viewed together with the food-effect data and the efficacy data suggest that the food effect should be studied further. Food increases systemic bioavailability, but it may be that it is more advantageous to achieve high local concentrations in the gastrointestinal tract where the site of action is presumed to reside. The sponsor is advised to investigate the effect of food on tizoxanide availability from the powder for oral suspension formulation.

Drug Interaction Studies: Nitazoxanide showed potential to inhibit cytochrome P450 2C9. However, since only tizoxanide can be determined in the systemic circulation, the clinical relevance of this study is not clear. It is recommended that the applicant repeat the in vitro drug-drug interaction studies with tizoxanide.

In Vitro Transfer across the Epithelial Barrier: It is recommended that the applicant investigate in vitro transfer of tizoxanide across the digestive epithelium. This is because it is not known to what extent conversion of nitazoxanide to tizoxanide occurs prior to absorption through the gut wall.

Dissolution: Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method for the suspension (i.e., USP Apparatus 2, rotation speed of 100 rpm, and dissolution medium of phosphate buffer at pH 7.5 with 6% hexadecyltrimethyl ammonium bromide), is acceptable. Specification should be as follows:

- For the suspension, NLT [redacted]% (Q) of the labeled amount dissolved as nitazoxanide and tizoxanide combined at 30 minutes

[redacted]

Labeling: The proposed label for the powder for oral suspension is attached.

Phase IV commitments: The applicant is asked to address the Phase IV commitments by conducting the following studies:

- **In vivo study of the effect of food on pharmacokinetics following oral administration of Nitazoxanide for Oral Suspension**
- **In vitro study of the effect of nitazoxanide metabolites (tizoxanide and tizoxanide glucuronide) on cytochrome P450 enzymes**
- **Study of the in vitro transfer of tizoxanide across the epithelial barrier**

Please convey the recommendations and comments as appropriate to the applicant.

Dakshina Chilukuri, Ph.D. /S/
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Barbara Davit, Ph.D. /S/
Briefing Day 10/11/02
cc: HFD-590, HFD-880 and CDR (Biopharm).

3. Summary of Clinical Pharmacology Findings

Bioequivalence of the suspension formulations

The applicant studied the bioequivalence between nitazoxanide powder for oral suspension diluted to 100 mg 5 mL and nitazoxanide 500 mg tablet. The pharmacokinetic parameters determined were: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$). area under the plasma concentration versus time (AUC_t) curve and area under the plasma concentration curve versus infinite time (AUC_{inf}). The results showed that the bioavailability of the nitazoxanide active metabolite tizoxanide was 41% lower for the suspension formulation compared to the tablet formulation and the bioavailability of tizoxanide glucuronide was 30% lower for the suspension compared to the — The 90% confidence intervals of the test/reference ratios were shifted towards lower values and were outside the acceptable limits of 0.8-1.2.

Pharmacokinetics in pediatric patients

The applicant determined the time-course of plasma concentrations of major nitazoxanide metabolites: tizoxanide and tizoxanide glucuronide in healthy pediatric volunteers. The pharmacokinetic parameters determined were the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), and area under the plasma concentration versus time (AUC_t) curve and area under the plasma concentration curve versus infinite time (AUC_{inf}). The plasma concentrations of tizoxanide and tizoxanide glucuronide observed for the adolescents administered nitazoxanide were similar to those previously observed in healthy volunteers. Plasma concentration of the two metabolites was almost identical for the 12-47 month age group (100 mg dose) and the 4-11 year age group (200 mg dose). Plasma concentrations and pharmacokinetic parameters in children receiving the suspension dosage form were approximately one-third of those observed in adolescents receiving tablets. It is not clear if this is due to age-related differences in nitazoxanide absorption, or due to the fact that the tablet is better absorbed than the suspension. The C_{max} and AUC_t observed for tizoxanide in children receiving the 500 mg tablet were calculated to be 28% and 25% lower, respectively, than those observed in healthy adult volunteers (Study B099597). The T_{max} appears to be comparable between children and adults

Multiple Dose Pharmacokinetics

The applicant evaluated the safety and tolerability of nitazoxanide in healthy subjects after multiple dose of 0.5 g b.i.d. and 1 g b.i.d. in fed conditions for 7 days and to determine the time course of plasma concentration of nitazoxanide major metabolites, tizoxanide (T) and tizoxanide glucuronide (TG) after the first and the last dose, and to determine whether accumulation is likely to occur. The pharmacokinetic parameters determined were maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration versus time (AUC_t) curve from 0 until the last measurable time point, area under the plasma concentration versus time (AUC_{τ}) curve from 0–12 hours and area under the plasma concentration curve versus infinite time (AUC_{inf}), Minimum (or trough) plasma concentration during the dosing interval (C_{min}), Peak to trough fluctuation calculated as PTF = (C_{max} - C_{min})/C_{av}. The pharmacokinetics of both tizoxanide and tizoxanide glucuronide were both affected by repeated administration of 1g b.i.d. nitazoxanide and the pharmacokinetics of tizoxanide glucuronide was affected by repeated administration of 0.5g b.i.d. nitazoxanide. The PK of tizoxanide was not affected by repeated administration of 0.5g b.i.d. nitazoxanide. This indicates that accumulation occurred upon repeated administration of nitazoxanide.

In vitro drug metabolism studies

The applicant determined the interaction of nitazoxanide with the cytochrome P450 family of enzymes, specifically those most involved in drug metabolism: CYP1A2, CYP2D6, CYP3A, CYP2C9 and CYP2C19 The potential for interaction of nitazoxanide with different human cytochrome P450 isoforms was investigated. Among the different isoforms, CYP2C9 displayed the highest inhibitory potency, which was 10-fold higher than the other isoforms. The clinical significance of these studies is not clear. Nitazoxanide has never been detected in the systemic circulation. It is more appropriate to conduct in vitro metabolism studies using the tizoxanide, which is present in measurable amounts in plasma after nitazoxanide dosing.

__In vitro drug transport studies__

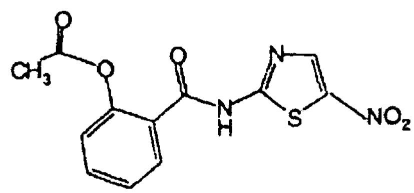
An *in vitro* investigation was to study the absorption of nitazoxanide across the epithelial barrier according to the mode (mucosal or serosal) of administration of the drug with respect to its intracellular absorption. Nitazoxanide was found to pass through the digestive epithelium in vitro and the overall magnitude of this passage is similar after apical and basolateral administration. Both transcellular and paracellular mechanisms appear to be involved in the transport of nitazoxanide. However, nitazoxanide is rapidly metabolized to tizoxanide and the concentrations of nitazoxanide cannot estimated in plasma. It is not known to what extent this conversion before gut absorption. It is recommended that the applicant conduct similar studies with tizoxanide.

4. Question Based Review

4.1. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Nitazoxanide 500 mg tablets and powder for oral suspension contain nitazoxanide, which is a N-(nitrothiazolyl) salicylamide compound and has a chemical name of 2-acteoxy-N- (5-nitro-thiazol-2-yl) benzamide ($C_{12}H_9N_2O_5S$). It is insoluble in water, ethanol, chloroform and acetone and soluble in DMSO and pyridine. It has a pKa of 5.81 measured in ethanol/water (1:1 v/v) and is also insoluble in aqueous solutions of low pH and soluble in aqueous solutions of high pH. Nitazoxanide has the following structural formula:



Powder for Oral Suspension (100 mg in 5 mL). The composition of the commercial tablet formulation is as follows:

Ingredient	Amount (mg/tablet)
Tablet core	
Nitazoxanide	500

The composition of the powder for oral suspension formulation is as follows:

Ingredient	Unit Formula (g/bottle)
Nitazoxanide	1.2
Sodium benzoate	
Sucrose	
Xanthan gum	
Microcrystalline cellulose & carboxymethylcellulose sodium	
Citric acid anhydrous	
Sodium citrate dihydrate	
strawberry powder	

4.2. Clinical Pharmacology

4.2.1. Dosage and Administration

What is the proposed dosage and route of administration?

The proposed dosage is one tablet (500 mg) orally twice-daily with food. For younger patients, the dosage (oral suspension to be administered with food) is as follows:
Age 4-11 years: 10 mL (200 mg nitazoxanide) every 12 hours for 3 days.
Age 12-47 months: 5 mL (100 mg nitazoxanide) every 12 hours for 3 days.

What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics data?

Efficacy and safety information was collected from the following five clinical studies using the proposed three-day regimen:

[redacted]	A double-blind placebo-controlled study in adults with diarrhea caused by G.lamblia or E.histolytica
RM-NTZ-98-002	A double-blind placebo-controlled study in adults and children with diarrhea caused by C.parvum
RM-NTZ-98-010	A double-blind metronidazole-controlled study in children with diarrhea caused by G.lamblia
RM02-3007	A double-blind placebo-controlled study in HIV-seronegative children with diarrhea caused by C.parvum
RM02-3007	A double-blind placebo -controlled study in HIV-seropositive children with diarrhea caused by C.parvum

One of the above-mentioned studies (RM-NTZ-98-002) evaluated the efficacy of both the 500-mg tablet and the pediatric suspension and another study [redacted] evaluated the efficacy of tablets and the remaining studies evaluated the efficacy of the pediatric suspension.

The doses of nitazoxanide administered for each of the above-mentioned studies were the same and are given below:

Adults and adolescents (≥12 years):	One nitazoxanide 500 mg tablet every 12 hours for 3 days with a meal
Children age 4 to 11 years:	10 mL of nitazoxanide suspension every 12 hours

	for three days with a meal
Children age 12 months to 47 months:	5 mL of nitazoxanide suspension every 12 hours for three days with a meal

The above-mentioned studies were all conducted in foreign countries where the infections are endemic. The studies were monitored by the applicant to ascertain the quality.

In Table 1 are presented the results of efficacy and safety from Study RM-NTZ-98-002

Table 1 **RM-NTZ-98-002: Summary of Efficacy Data**

	Nitazoxanide	Placebo	P[a]
Clinical response			
All subjects	39/49 (80%)	20/49 (41%)	<.0001
All children	21/24 (88%)	9/24 (38%)	.0004
Age 1-3	10/11 (91%)	4/11 (36%)	.01187
Age 4-11	11/13 (85%)	5/13 (38%)	.0207
Adults and adolescents	18/25 (72%)	11/25 (44%)	.0423
Parasitological response			
All subjects	33/49 (67%)	11/50 (22%)	<.0001
All children	18/24 (75%)	5/25 (20%)	.0001
Age 1-3	8/11 (73%)	3/11 (27%)	.0431
Age 4-11	10/13 (77%)	2/14 (14%)	.0016
Adults and adolescents	15/25 (60%)	6/25 (24%)	.0104
Median time from initiation of treatment to passage of last unformed stool			
All subjects	3 days	>6 days	0006
All children	3.5 days	>6 days	.0001
Age 1-3	4 days	>6 days	
Age 4-11	3 days	>6 days	
Adults and adolescents	3 days	>6 days	.0493

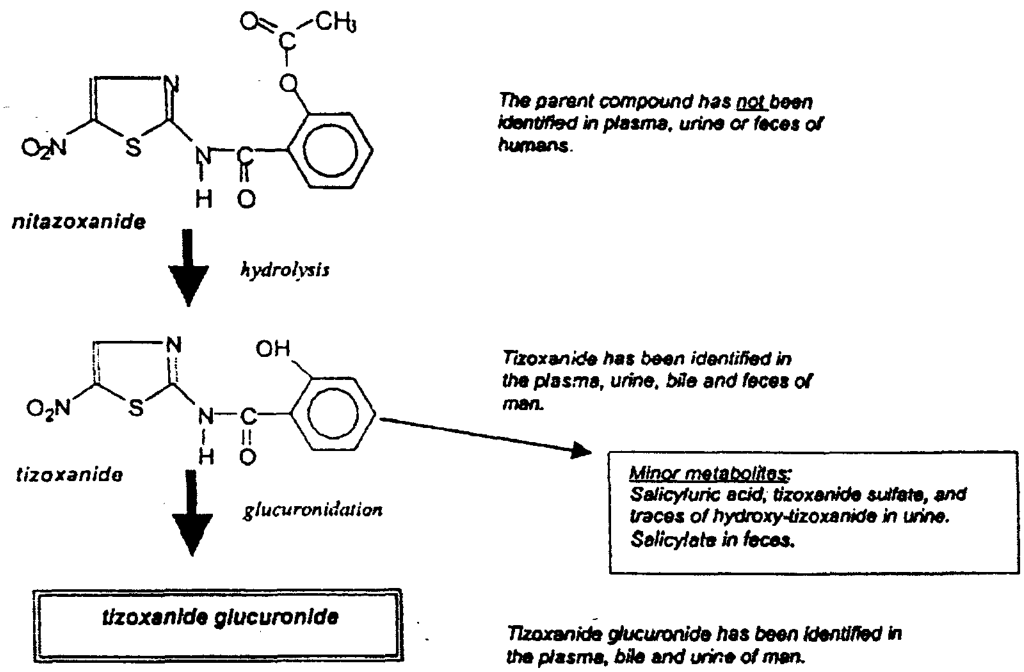
[a] Fisher's exact test, one-sided

Are the active moieties in serum appropriately identified and measured to assess pharmacokinetic parameters and exposure/response relationships?

Following oral administration in humans, nitazoxanide is rapidly hydrolyzed in plasma to an active metabolite, tizoxanide (desacetyl-nitazoxanide), which possesses antimicrobial activity comparable to that of nitazoxanide. Tizoxanide then undergoes conjugation by glucuronidation. Tizoxanide glucuronide, also an active metabolite (but less active than nitazoxanide and tizoxanide) is excreted in urine and bile, and tizoxanide is excreted in the urine, bile and feces.

The following schematic shows the metabolic pathway of nitazoxanide.

Fig. 4.6.4 Metabolism of nitazoxanide



The pharmacokinetic parameters of tizoxanide and tizoxanide glucuronide following administration of the tablet and suspension dosage forms are given below in Table 4.6.6

Table 4.6.6 Pharmacokinetic parameters of tizoxanide in plasma

Population	Dose (mg)	Dosage form	C_{max} (µg/ml)	AUC_t (µg•h/ml)	T_{max} (h)	Reference
Adults	500	tablet	10.4	41.8	3.0	Study 198.637
12-17 yrs	500	tablet	9.12	39.5	4.0	Study RM01/02-1015
4-11 yrs	200	suspension	3.0	13.5	2.0	Study RM01/02-1015
12-47 months	100	suspension	3.11	11.7	3.5	Study RM01/02-1015

Table 4.6.7 Pharmacokinetic parameters of tizoxanide glucuronide in plasma

Population	Dose (mg)	Dosage form	C_{max} (µg/ml)	AUC_t (µg•h/ml)	T_{max} (h)	Reference
Adults	500	tablet	10.4	64.7	4.5	Study 198.637
12-17 yrs	500	tablet	7.27	46.5	4.0	Study RM01/02-1015
4-11 yrs	200	suspension	2.84	16.9	4.0	Study RM01/02-1015
12-47 months	100	suspension	3.64	19.0	4.0	Study RM01/02-1015

4.3. Intrinsic Factors

Are there any gender differences observed for nitazoxanide?

No significant differences between men and women were observed for the combination tablet.

Are there any age differences observed for nitazoxanide?

Regression analysis on the effect of age and body weight on clearance was performed and as shown below in Figures 2 and 3, no effect of age and body weight on clearance was observed. Table 2 shows the slope, intercept, R^2 and p-value of the regression analysis. As seen in the table, the p-value indicated a significant effect of age on clearance of tizoxanide. However, with due consideration to the R^2 and the fact that increase of clearance is only two-fold in the age range studied, there does not appear to be a clinically meaningful effect of age on clearance.

Figure 2: Relationship of age and clearance.

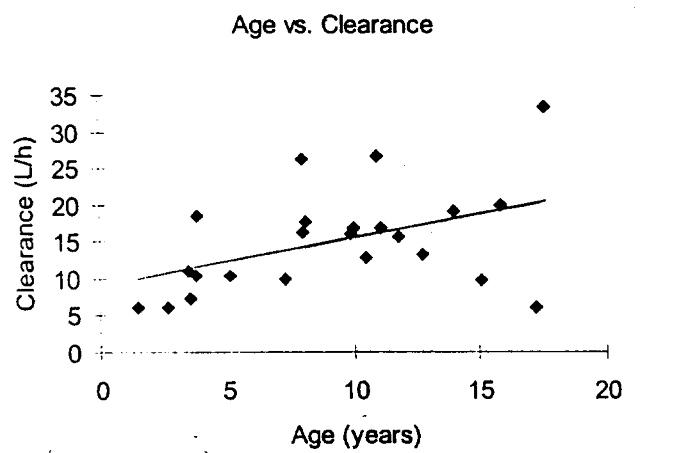


Figure 3: Relationship of body weight and clearance.

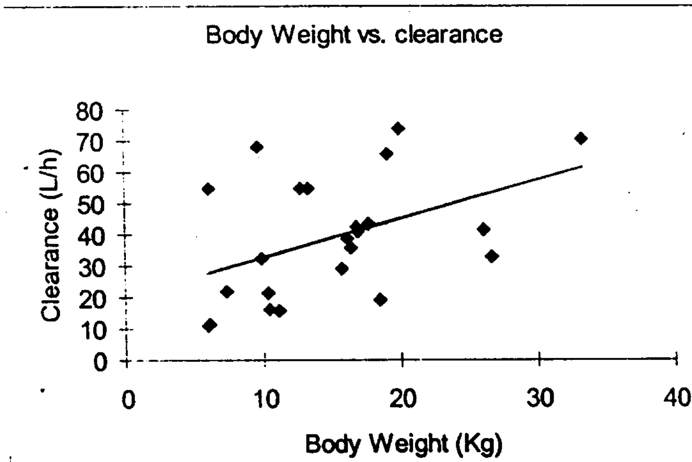


Table 2. Slope, Intercept and R^2 of the regression analysis

	Age vs. clearance	Body Weight vs. clearance
Slope	0.65	1.23
Intercept	9.08	20.41
R^2	0.2	0.2
p-value	0.0327	0.0336

4.4. Extrinsic Factors

Does food affect the bioavailability of nitazoxanide?

Food prolonged the rate of appearance of tizoxanide in plasma and increased the extent of systemic exposure. Administration of nitazoxanide tablets following a high-fat (48% of kcal as fat) meal compared with the fasted state resulted in a 116 ± 83% (range 6% to 289%) increase in AUC and 73 ± 81% (range -26% to 248%) increase in C_{max}. The median T_{max} was greater when nitazoxanide was given with food (3.25 vs 2 hr).

Desacetyl-NTZ pharmacokinetic parameters in 18 fed and fasted healthy male subjects receiving a single 1000 mg dose of NTZ						
Parameter	Cmax (µg/mL)	Tmax (hr)	AUCt (µg*hr/mL)	AUC∞ (µg*hr/mL)	T1/2 (hr)	MRT (hr)
Fasted	8.57±2.50	2	31.7±9.81	32.7±11.6	2.83±2.13	3.94±1.23
Fed	13.8±4.53	3.25	61.4±21	58.3±21.8	2.06±0.98	4.72±1.18

Confidence intervals and point estimates were:

90% confidence intervals and point estimates, comparison of fed(test):fasted(reference) for AUCt and Cmax		
	AUCt	Cmax
Point estimate	1.86	1.57
90% CI	1.56,2.25	1.33,1.89

Based on the above results, it is clear that administration of nitazoxanide with food results in higher exposure. Results from the efficacy studies indicated that nitazoxanide, which was administered in children as a suspension was more effective in treating the diarrhea compared to adults who were administered tablets. A comparison of the exposure of tizoxanide and tizoxanide glucuronide between the suspension and tablet dosage forms indicated a greater exposure (41%) for tablets compared to suspension. When this data is viewed in conjunction with the food-effect study, it suggests that food increases the absorption of the metabolites of nitazoxanide, but the increased exposure may actually result in a decreased efficacy due to removal of the drug from the site of action, which is the gastrointestinal tract. Stated otherwise, the increased exposure of tizoxanide and tizoxanide glucuronide with food may actually result in reduced efficacy, since the site of action of the drug is the gastrointestinal tract. Thus, a recommendation is being made to further study the effects of food on efficacy of nitazoxanide.

Is there an in vitro basis to suspect in vivo drug-drug interactions?

The potential for interaction of nitazoxanide with different human cytochrome P450 enzymes was investigated. Among the different isoforms, CYP2C9 displayed the highest inhibitory potency, which was 10-fold higher than the other isoforms. The clinical relevance of these findings is not clear, since nitazoxanide has never been detected in the systemic circulation.

Is the drug an inhibitor and/or an inducer of CYP enzymes?

Nitazoxanide showed little potential to inhibit other CYP 450 enzymes.

4.5. Biopharmaceutics

Are the proposed dissolution methodology and specifications acceptable?

In the previous submission (NDA 20-871), the applicant evaluated stability of the 500 mg to-be-marketed nitazoxanide tablets with a dissolution method using 20% DMSO/80% phosphate buffer pH 7.5 as the media. During development, the applicant tested various media with a variety of surfactants, and found that, with the exception of the DMSO/phosphate solution, nitazoxanide solubility was low and degradation to tizoxanide was rapid. The applicant requested that: (1) the requirement of dissolution testing be waived; and (2) tablet disintegration be used to support product stability. However, the company's request for a waiver for dissolution testing was not granted.

It was recommended[1] that the company develop a dissolution method using pH 6.8 borate buffer + laurylsulfate, since of the conventional surfactants tested with pH 6.8 borate buffer, the addition of 6% laurylsulfate appeared to result in the highest solubility of nitazoxanide. The applicant was asked to assay both nitazoxanide and tizoxanide and report the concentrations of each as well as the concentrations of the two combined over time. Further, it was recommended that the applicant develop a dissolution method using pH 7.5 phosphate buffer + 6% hexadecyltrimethyl ammonium bromide. Since the desacetylation of nitazoxanide is temperature dependent, it was also recommended that studies of nitazoxanide dissolution be conducted at 25°C rather than at 37°C.

In this submission, the applicant submitted dissolution data in the medium containing 6% hexadecyltrimethylammonium bromide for both the suspension and tablet dosage forms. The applicant's choice of medium, temperature, and apparatus is acceptable. The applicant was asked to evaluate lower paddle speeds. The proposed specification for the suspension is acceptable. For the tablet a specification will be suggested based on evaluation of additional dissolution data at the lower paddle speeds.

Apparatus:	Paddle (USP Apparatus 2)
Dissolution medium:	Phosphate Buffer pH 7.5 with 6% hexadecyltrimethyl ammonium bromide
Volume:	900 mL
Bath temperature:	25 ± 0.5 °C
Rotation speed:	100 rpm
Specifications:	NLT( )% (Q) of the labeled amount dissolved as nitazoxanide and tizoxanide combined at 30 minutes (powder for suspension)

[1] B. Davit, Clinical Pharmacology/Biopharmaceutics Review, NDA 20-871

The following two tables illustrate the dissolution data obtained for nitazoxanide powder for suspension and tablets.

Table 7.15 Summary of the dissolution performance for the nitazoxanide 500 mg tablet

Dosage form	Test Conditions [Apparatus, Medium, Speed of Rotation]	Lot no.	Media temperature	Collection time	Units tested	Mean % dissolved for units tested: Nitazoxanide	Tizoxanide	Sum
500 mg tablet	—	97E06	37°C	30 minutes	6	52.75	18.28	71.03
		97E06	37°C	45 minutes	6	51.43	25.09	76.52
		97E06	37°C	60 minutes	6	48.56	31.01	79.57
	paddle apparatus with peak vessels and covers to retard evaporation	97E06	25°C	15 minutes	6	33.00	2.92	35.92
		97E06	25°C	30 minutes	6	55.12	3.51	58.63
		97E06	25°C	45 minutes	6	57.90	8.65	66.55
	Medium	97E06	25°C	60 minutes	6	56.88	13.96	70.84
	pH buffer 7.5 + 6% hexadecyltrimethyl-ammonium bromide	97E07	25°C	15 minutes	6	49.31	4.68	53.99
		97E07	25°C	30 minutes	6	65.69	4.45	70.14
		97E07	25°C	45 minutes	6	64.97	9.37	74.34
	Speed of Rotation 100 rpm	97E07	25°C	60 minutes	6	62.40	14.69	77.09
		97E13	25°C	15 minutes	6	40.14	4.49	44.63
		97E13	25°C	30 minutes	6	60.65	4.87	65.52
		97E13	25°C	45 minutes	6	60.83	9.62	70.45
		97E13	25°C	60 minutes	6	56.06	12.19	68.25
	Same as above, but sample tray was cooled to 10°C before injection and — run time was reduced from 30 minutes to 15 minutes to reduce degradation	97E06	25°C	30 minutes	6	57.27 Range: —	2.17 Range: —	59.44 Range: —
		97E07	25°C	30 minutes	6	65.69 Range: —	2.53 Range: —	68.22 Range: —
		97E13	25°C	30 minutes	6	60.77 Range: —	2.36 Range: —	63.13 Range: —

Table 7.17 Summary of the dissolution performance for the nitazoxanide powder for oral suspension

Dosage form	Test Conditions [Apparatus, Medium, Speed of Rotation]	Lot no.	Media temperature	Collection time	Units tested	Mean % dissolved for units tested: Nitazoxanide	Tizoxanide	Sum
100 mg/5 ml powder for oral suspension	Apparatus	26726[1]	25°C	5 minutes	1[a]	58.7	1.6	60.3
	—	26726	25°C	10 minutes	1[a]	74.2	5.0	79.2
	paddle apparatus with	26726	25°C	15 minutes	1[a]	75.6	7.9	83.5
	peak vessels and covers	26726	25°C	30 minutes	1[a]	74.9	10.9	85.8
	to retard evaporation	26726	25°C	45 minutes	1[a]	72.1	12.5	85.6
	Medium pH buffer 7.5 + 6% hexadecyltrimethyl-	26751	25°C	15 minutes	4[b]	80.1 Range: —	2.2 Range: —	82.3 Range: —
	ammonium bromide	26752	25°C	15 minutes	4[c]	75.4 Range: —	4.3 Range: —	79.7 Range: —
	Speed of Rotation 100 rpm	121201[2]	25°C	15 minutes	4[b]	79.4 Range: —	1.5 Range: —	80.9 Range: —
	Other Sample tray cooled to 10°C — run time: 15 minutes	03117[3]	25°C	15 minutes		??	??	??
200 mg dispersible tablet	Same as above	112590[4]	25°C	15 minutes		??	??	??

[a] Tests conducted December 6, 2001; [b] Tests conducted January 16, 2002; [c] Tests conducted January 17, 2002

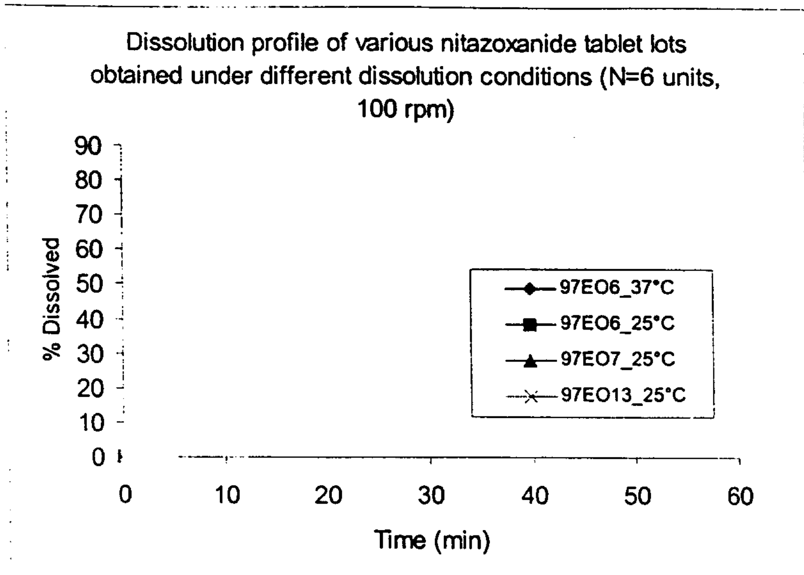
[1] Lot no. 26726 was used in pharmacokinetic study RM01/02-1015 and is identical to the lots used in the adequate and well-controlled studies.

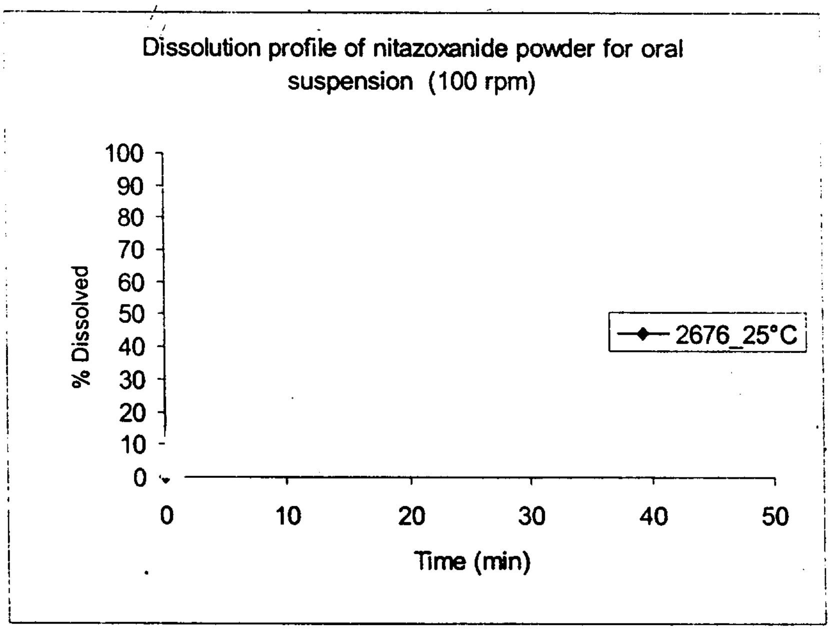
[2] Lot no. 121201 is a pilot lot of nitazoxanide powder for oral suspension produced with the red dye to be used in the proposed formulation. The dissolution is similar to that of batches 26726, 26751 and 26752 which were produced with the red dye (— used in batches of powder for oral suspension that were used in the adequate and well-controlled clinical studies.

[3] Lot 03117 is a batch of powder for suspension produced by — that used red dye — instead of the proposed red dye — and it used a strawberry flavoring from a different supplier. This lot is identical to lot 5-809 used in uncontrolled studies no. CL-NTZ-95-001 and PRC-94-NTZ-03.

[4] The dispersible tablet was used to treat children age 4-11 years enrolled in study no. PRC-94-NTZ-03 (an uncontrolled study).

The dissolution data were plotted and are shown below in the following two figures.





If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Table 2 and Figure 3 shows the comparison of plasma profiles for the suspension and tablet formulations. The suspension formulation was found to be not bioequivalent to the tablet formulation. The exposure of tizoxanide was found to be 41% less than the tablet formulation. When this finding was correlated with the results of the efficacy study, it is interesting to note that the efficacy in children, who were administered the suspension was found to be greater than in adults, who were administered tablets. This suggests that the better efficacy of tizoxanide in children may be the direct result of the higher drug concentrations in the gastrointestinal tract, which is the site of efficacy for this drug. In other words, the higher exposure of tizoxanide observed upon administration of tablets may actually result in lesser amount of the drug available at the site of action, that is, the stomach thus leading to less efficacy compared to the suspension dosage form.

Table 1. PK parameters of tizoxanide derived from the individual tizoxanide plasma profiles

PK parameter	Test 100 mg/5 mL suspension	Reference 500 mg tablet	p-value	Test/reference ratio	
				Point estimate	90% CI
Cmax (µg/mL)	6.91	11.7	<0.001	59	51-68
AUC_t(µg-h/mL)	33.6	47.5	<0.001	71	63-80
AUC_{inf}(µg-h/mL)	33.9	47.8	<0.001	71	63-80
T_{max} (h)	1.50	1.50	0.067	-0.5h	-1.0 to 0.0 h
$T_{1/2}$ (h)	1.46	1.38	0.365		

Values are medians for tmax and t1/2

1: probability associated with the hypothesis of no difference between formulations (Koch's test for tmax. ANOVA for the other parameters)

2: expected geometric means test/reference ratio (%) and standard 90% CI, derived from ANOVA, except for tmax: non-parametric 90% CI of the treatment difference.

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Figure 3. Comparison of the plasma profiles of tizoxanide and tizoxanide glucuronide for the tablet and suspension formulations.

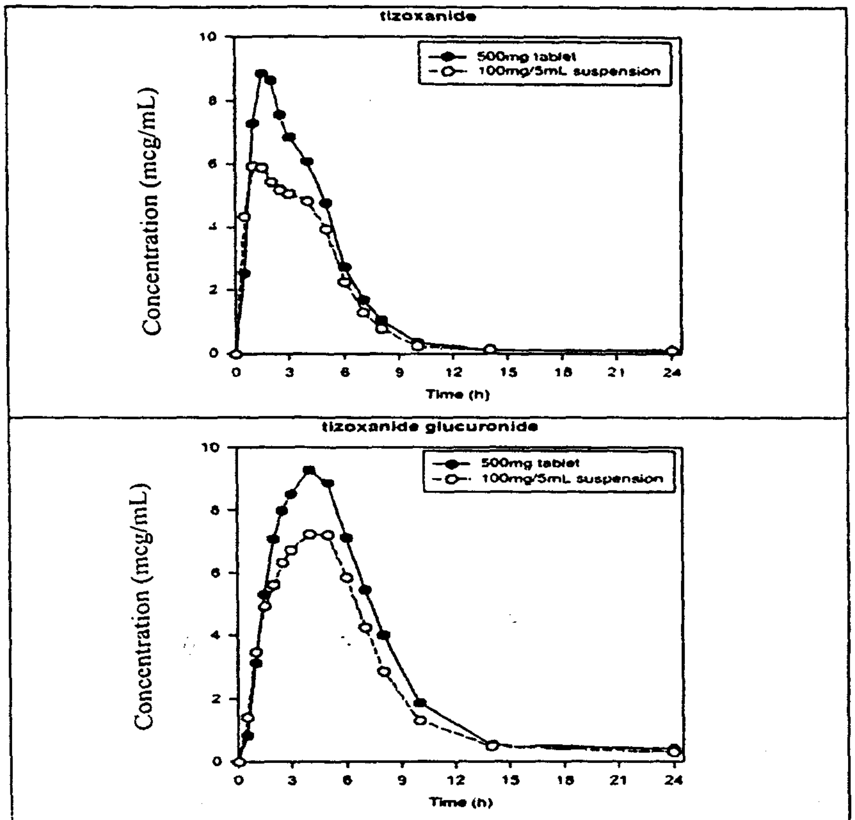

Figure 1: Average tizoxanide (top) and tizoxanide glucuronide (bottom) plasma concentration vs. time profiles; Values are geometric means.

4.6. Analytical Methodology

What analytical methodology was used to determine nitazoxanide?

Clinical Pharmacokinetic studies Study B099597, RM01/02-1015 and 198.637:

The following assays were validated and used to determine nitazoxanide, tizoxanide and tizoxanide glucuronide in plasma from the above-mentioned studies. A review of the analytical methodology is presented below:

— **Conditions:**

Mobile phase:

Column: .

Internal Standard: nifuroxanide

Detection: Mass Spectrometer

Linearity: — – — μg/mL for tizoxanide and — μg/mL for tizoxanide glucuronide.

QC samples: — and μg/mL for tizoxanide and — μg/mL for tizoxanide glucuronide, respectively.

Recovery: Average recovery was found to be close to 100 % at every level.

Limit of Quantitation: — μg/mL for tizoxanide and — μg/mL for tizoxanide glucuronide.

Specificity: The extraction and chromatographic procedures allowed a good separation of the components of interest from endogenous compounds.

6 pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Dakshina Chilukuri
11/22/02 09:02:51 AM
BIOPHARMACEUTICS

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