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APPLICATION NUMBER:

21-618

21-681

21-682

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA NUMBER:	**21-618, 21-681, 21-682**
SUBMISSION DATE:	**16 July 2003**
BRAND NAME:	**Tindamax®**
GENERIC NAME:	**Tinidazole**
DOSAGE FORM AND STRENGTH(S):	**Tablet (250 mg, 500 mg)**
INDICATION(S):	**For Trichomoniasis, Giardiasis, and Amebiasis**
SPONSOR:	**Presutti Laboratories, Inc.**
TYPE OF SUBMISSION:	**505(b)(2)**
OCPB DIVISION:	**DPE3**
REVIEWER:	**Gerlie De Los Reyes, Ph.D.**
TEAM LEADER:	**Philip M. Colangelo, Pharm.D., Ph.D.**

I. Executive Summary

A. Summary

Tinidazole has been marketed in countries other than the United States and Canada since the 1970's. In European countries, tinidazole (e.g., Fasigyn®) is approved for use in various antiprotozoal and antibacterial indications such as in the treatment of trichomoniasis [redacted] giardiasis, and amebiasis (intestinal and amebic liver abscess). In the United States, metronidazole is the only FDA-approved nitroimidazole; there appears to be an unmet medical need for infectious diseases like [redacted] trichomoniasis and giardiasis. The sponsor has submitted this 505(b)(2) NDA for the use of tinidazole (Tindamax®) tablets in the treatment of trichomoniasis (2 grams as single dose), [redacted] giardiasis (2 grams as single dose) [redacted], intestinal amebiasis (2 grams per day for 3 days), and amebic liver abscess (2 grams per day for 3-5 days) in adults. If approved, tinidazole will also be used by pediatric patients for the treatment of giardiasis (50 mg/kg/day single dose, not to exceed 2 grams), intestinal amebiasis (50 mg/kg/day for 3 days) and amebic liver abscess (50 mg/kg/day for 3-5 days). The dosage recommendations for adults and pediatrics were based on an evaluation of the clinical efficacy and safety database available for Fasigyn® (Tinidazole 500 mg) oral tablets.

The sponsor of tinidazole (Tindamax®) conducted a Bioavailability/Bioequivalence (BA/BE) study to establish a biolink between their proposed commercial tinidazole (Tindamax®) tablet and the European-approved tinidazole (Fasigyn®, Pfizer UK) tablet that has been tested in clinical efficacy and safety studies. Based on the findings of this BA/BE study, the sponsor's tinidazole tablet is bioequivalent to the reference tablet in terms of C_{max} and AUC. The study findings also showed that the administration of the to-be-marketed tablet with food and as a crushed tablet in artificial cherry syrup have no significant effect on the bioavailability of the drug from the tablet dosage form. In addition, the findings of an in vitro drug metabolism study conducted by the sponsor revealed that at test concentrations equivalent to up to 2-fold the C_{max} of tinidazole in healthy volunteers, tinidazole did not inhibit the enzyme activity of CYP3A4 and other CYP450 enzymes responsible for the metabolism of drugs.

B. Recommendation:

This 505(b)(2) submission for Tinidazole (Tindamax®) Tablets is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. The sponsor needs to address the labeling comments in Appendix 1.

C. Potential Phase IV study commitment: Pharmacokinetics in Hepatic Impairment

Because a considerable amount (≥ 40%) of the administered dose is eliminated as metabolites, the disposition of this drug may be --like metronidazole--significantly different between patients with normal hepatic function and those with liver impairment. However, a study investigating the pharmacokinetics of tinidazole in patients with hepatic impairment will not be recommended at this time on account of the limited duration of product use (single dose for most indications, 3 to 5 days for amebiasis), a projected accumulation ratio of approximately 2.0 on Day 5 in patients with 50% lower total clearance (assuming negligible hepatic function with no compensatory increase in renal elimination), as well as the good safety profile of the drug. At this time, the Division of Special Pathogens and Immunologic Drug Products (DSPIDP) is considering the approval of indications that require no longer than 5 days of therapy.

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II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Although tinidazole has been marketed in European countries for over 25 years, this drug has never been approved for US marketing prior to this NDA. The sponsor conducted a single-dose, randomized, open-label, unbalanced, 3-period, 4-treatment, 2-way crossover study to (1) compare the bioavailability of Tindamax® Tablet to a reference tinidazole tablet (Fasigyn®, Pfizer UK) under fasting conditions, (2) determine the bioavailability of tinidazole from the sponsor's tablet (Tindamax®) following a standard high-fat breakfast, (3) determine the relative bioavailability of tinidazole from a crushed tablet in a cherry syrup vehicle, and (4) to assess the safety and tolerability of the four single-dose tinidazole treatments. In addition, upon the Agency's request, the sponsor conducted an in vitro CYP450 metabolism study to evaluate the potential of tinidazole to inhibit the activities of CYP450 isoforms responsible for the metabolism of tinidazole, as well as other CYP450 enzymes mainly responsible for the metabolism of other drugs.

A. Bioequivalence/Bioavailability

Based on the sponsor's study findings (Table 1), the sponsor's tablet was bioequivalent to the reference tablet with respect to AUC and $C_{max,}$ after administration of a single oral 2g dose. The geometric mean ratios were 101.4%, 109.9%, 100.8%, and 101.5%, for ln(Cmax) for females, ln(Cmax) for males, ln[AUC(0-t)], and ln[AUC(0-inf)], respectively, and the 90% confidence intervals for each of these parameters were within the range of 80-125%. In addition, the arithmetic means of AUC and C_{max} were not significantly affected when the tinidazole test formulation was administered with a high-fat breakfast or when administered crushed in cherry syrup under fasted conditions compared to the test formulation administered under fasted conditions. All four single dose treatments of tinidazole appeared to be equally safe and well tolerated by subjects in this study.

Table 1. Summary of the Bioequivalence/Bioavailability Study Findings

Parameter (units)	Arithmetic Mean ± SD (minimum-maximum) Treatment A (n = 17)	Treatment B (n = 18)	Treatment C (n = 9)	Treatment D (n = 9)	90% CI Difference [a]	% Mean Ratio [a]
Cmax (µg/mL)	47.7165 ± 7.5412	45.5123 ± 7.9771	42.8247 ± 8.5493	46.3441 ± 9.2393	96.6 – 106.4(F)[b] 105.0 – 115.0(M)[b]	101.4 [b] 109.9 [b]
Tmax (hr)	1.60 ± 0.763	2.12 ± 1.09	3.00 ± 1.00	2.06 ± 0.390	62.9-101.4 [c]	82.2 [c]
AUC(0-t) (µg*hr/mL)	863.1 ± 127 8	861 2 ± 127 3	797.9 ± 108.5	889.6 ± 94.93	97.8 – 103.9	100.8
AUC(0-inf) (µg*hr/mL)	901 6 ± 126 5	893 7 ± 126.6	832.0 ± 104 6	923.7 ± 94.50	98.9 – 104.1	101.5
Kel (1/hr)	0.0529 ± 0 00588	0 0539 ± 0.00645	0.0582 ± 0 00773	0.0514 ± 0.00599	----	----
T1/2 (hr)	13.2 ± 1.41	13.0 ± 1.44	12.1 ± 1.66	13.6 ± 1.50	----	----

a = Ln-transformed parameters and LS means were used in obtaining confidence intervals and % mean ratios of Treatment A versus B

b = Statistical comparisons for Cmax were performed separately for males and females as TREATMENT*GENDER interaction was significant

c = Un-transformed parameters and LS means were used in obtaining confidence intervals and % mean ratios of Treatment A versus B

F = Females, M = Males
Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast

Treatment B = 4 x 500 mg Fasigyn Tablets Following a Minimum 10-hour Overnight Fast

Treatment C = 4 x 500 mg Tinidazole Tablets Following the Standard High Fat Breakfast

Treatment D = 4 x 500 mg Tinidazole Tablets Crushed in Cherry Syrup Following a Minimum 10-hour Overnight Fast

Source Data: Tables 14.2.5, 14.2.6, 14.2.7, 14.2.8, and 14.2.12

B. In Vitro Drug Metabolism

Tinidazole, as well as metronidazole, at concentrations from 0.03 to 300 µM did not inhibit any of the cytochrome P450 enzymes examined. The IC_{50} values were all >300 µM. Each of the model substrates, namely phenacetin, bupropion, diclofenac, bufuralol, p-nitrophenol, and testosterone for CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, respectively were tested near or approximately twice their apparent Km values. Tinidazole was tested alongside standard inhibitors to serve as positive controls.

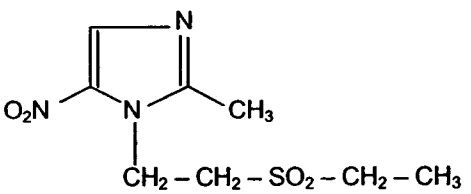
IV. Question-Based Review

A. General Attributes

1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Tinidazole USP ($C_8H_{13}N_3O_4S$; MW 247.28; Figure 1) is an almost white or pale yellow crystalline powder that is practically insoluble in aqueous solutions. Tinidazole was found to be stable when stored through 12 months under ICH conditions using stability-indicating methods. It discolors on intense prolonged exposure to light with no resulting chemically-detectable degradation.

Figure 1. Chemical structure of tinidazole



Each Tindamax® film-coated tablet contains 250 mg or 500 mg tinidazole, as well as other ingredients listed in Tables 2A and 2B. The two tablet strengths are proportionally similar in terms of chemical composition. A 2g single oral dose of the drug is indicated for the treatment of trichomoniasis and giardiasis, whereas 2g/day for 3-5 days is indicated for the treatment of amebiasis. The antimicrobial action of the drug against anaerobic bacteria and protozoa is based on the generation of a free radical nitro compound which is believed to lead to DNA modification and inhibition of DNA synthesis.

Table 2A. Composition of the Uncoated Tablet

Component	250mg Tablet Quantity	500 mg Tablet Quantity
Tinidazole USP	250.0 mg	500.0 mg
Microcrystalline Cellulose NF		
Pregelatinized Corn Starch NF		
Croscarmellos Sodium NF		
Magnesium Stearate NF		
Purified Water USP*		
Total		

Table 2B. Composition of the Film-coated Tablet

Component	250mg Tablet Quantity	500 mg Tablet Quantity
Tinidazole Uncoated Tablets		
Purified Water USP*		
Total	362 mg	724 mg

*Purified Water is removed during processing.
**contains Polydextrose FCC, Titatnium Dioxide USP, Hypromellose 2910 USP, Triacetin USP, Polyethylene Glycol FD&C Red 40 Lake, and FD&C Yellow 6 Lake.

Using the USP Dissolution Method (Apparatus 1) and a validated HPLC assay, not less than % of tinidazole is expected to dissolve within minutes. The proposed dissolution acceptance criteria for both the 250mg and the 500mg strengths was acceptable. The proposed expiration dating period for the product is 2 years when stored under the USP controlled room temperature conditions. Lot C020234E (tablets of 500 mg strength) was used in the bioavailability and bioequivalence studies. This particular lot had a dissolution rate of % (range) in minutes.

The proposed commercial lot sizes are tablets for 250 mg, and tablets for 500 mg.

B. General Clinical Pharmacology

1. *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

In clinical studies, the most common clinical endpoints for trichomoniasis studies include (1) clinical cure and (2) microbiological (trichomonad) eradication in vaginal secretions, as well as (3) restoration of normal physiological conditions in the vagina (Milek and Nedelkova, 1974 --- Reference # 26 of the submission).

2. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to IV. F, Analytical Section; if no, describe the reasons)*

Yes, refer to IV.F Analytical Section.

3. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?*

Dose-response relationships:

Section 3.d provides a discussion of dose-response relationships.

Concentration-response relationships:

Concentration-therapeutic outcome relationship. Jokipii and Jokipii (1982---Ref# 121) attempted but failed to find a correlation between tinidazole absorption or elimination, and therapeutic efficacy in giardiasis patients, despite the effectiveness of the dose tested. At 1h, 24h, 2 and 3 days, individual concentrations were unrelated to outcome of therapy (success or failure). The mean serum half-life of tinidazole was similar between successful and failed patients (10.9 hours versus 12.1 hours, respectively).

Concentration-adverse events relationship. The mean tinidazole concentration at 1h in patients with dizziness was higher than in others (26.4 and 17.7 mcg/mL, respectively; $p<0.025$). There were no other associations of subjective side effects and drug concentrations or half-life (Jokipii and Jokipii,1982).

a) *based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

The pharmacokinetics of tinidazole after intravenous administration are linear at least over the dose range 400-1600mg (Wood et al., 1986—Reference 143 of the NDA submission). The oral administration of 2 grams as a suspension produced similar pharmacokinetic parameters (Chaikin et al., 1982 ---Reference 178). The half-life, Cmax and AUC of tinidazole (2 grams as oral tablet) obtained from plasma concentration data in the sponsor's bioavailability study were similar to the ones reported by Chaikin and co-workers (1982).

Table 4. Comparative pharmacokinetics (mean data) of tinidazole in humans after single dose

	Intravenous (Wood et al (1986---Ref 143)			Oral Suspension	Oral Tablet (Tindamax®)
Parameter	Nilsson-Ehle et al (1981) (n=4)	Wood et al (1986) (n=2)	Wood et al (1982) (n=6)	Chaikin et al (1982)--- Ref.178 (n=12)	Presutti Laboratories (n=17)
Dose (mg)	400	800	1600	2000	2000
Half-life (h)	12.9	11.6	13.3	12.3	13.2
Volume of distribution (mL/kg)	-	737	815	640	-
Clearance (mL/min/kg)	-	0.75	0.71	0.63	-
Urinary excretion (% dose)	18	20	25	21-33	-
Cmax (mcg/mL)				46.8	47.7
$AUC_{0-\infty}$ (mcg/mL*h)				838.1	902.0

b) *do PK parameters change with time following chronic dosing?*

Following a 2-gram single dose on the first day followed by 1 gram once daily dose for 4 successive days, tinidazole half-life, clearance, and the volume of distribution in healthy volunteers did not change with chronic dosing (Wood et al. 1982—Reference 139A).

Table 5. Pharmacokinetic parameters for tinidazole after administration of multiple intravenous or oral doses to healthy volunteers

	Day 1		Day 5	
	Males	Females	Males	Females
Intravenous				
Half-life (h)	13.5	11.6	14.7	11.9
Clearance (mL/min/kg)	0.58	0.63	0.53	0.64
Volume of distribution (L/kg)	0.67	0.64	0.67	0.65
AUC_{0-24} (mg.h/L)	196	265	301	347
Oral				
Half-life (h)	12.3	12.0	11.7	12.1
AUC_{0-24} (mg.h/L)	520	721	376	460

c) how long is the time to the onset and offset of the pharmacological response or clinical endpoint?

Trichomoniasis. Based on the findings of Milek and Nedelkova (1974), a single dose treatment with 2000 mg tinidazole was able to produce negative microscopic findings in patients with first attack, persistent, and relapsing forms of trichomonal vaginitis. In addition, efficacy rates in 9 blinded, randomized, controlled studies using 2g single dose tinidazole ranged from 80 to 100%, with only one study producing efficacy less than 90%. In 13 studies, 71% of tinidazole failures who were retreated 2g single dose were reported to experience symptom relief within 2 to 4 days after the second dose.

Giardiasis. Published trials encompassing over 1600 patients treated with a single 2g dose (50 mg/kg in children) showed efficacy rates of 80 to 100% at a few days to 3 months of follow-up. Majority of these papers reported cure rates of 88 to 94% at 2 to 8 weeks after therapy. In one study, following a single 1.5g oral dose of tinidazole, parasite eradication was achieved within 2 or 3 days; symptoms subsided usually within 5 days post-dose (Jokipii and Jokipii,1982 ---Ref. # 121). In another study, *G. lamblia* disappeared from the stool samples of all 26 patients by day 6 after receiving a single 2g oral dose of tinidazole (Jokipii and Jokipii, 1978 ---Ref.#188).

Intestinal amebiasis. Twenty-six (26) clinical reports comprising approximately 1,400 patients treated with tinidazole of 2g daily for 2 to 5 days showed that majority of the efficacy rates at 30 days after last dose was approximately 90%. In most of these reports, dosing of tinidazole was at 2g for 3 days. *Amebic liver abscess.* Findings of 18 clinical trials encompassing 470 patients treated with tinidazole (usually 2g from 1 to 5 days) suggest that the efficacy rate of tinidazole clusters at about 90% at 30 days after dosing.

d) are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Trichomoniasis. The recommended dose of tinidazole for the treatment of trichomoniasis appears to be consistent with observed *dose-response* relationships. Based on the results of a dose-finding

study by Milek and Nedelkova (1974), single doses of 1500 mg, 1600 mg, 1800 mg, and 2000 mg tinidazole are all successful in eradicating trichomonads, with response rates of 84.5%, 88%, 92.4%, and 94%, respectively. Thus, the optimal dose for single administration of tinidazole in the treatment of trichomoniasis is 2 grams.

Giardiasis. The findings of 19 published studies, encompassing over 1600 adults and children, established the efficacy of a single 2g tinidazole oral dose in the treatment of giardiasis. Additionally, 1 to 1.5g single dose produced 90% efficacy rate whereas the same dose range for 3 consecutive days produced a 100% efficacy rate (Welch et al., 1978—Ref.#115);a single 1.5g dose was reported to have a 90% cure rate (Jokipii and Jokipii, 1982). It appears from the combined findings of these studies that lower-than-2g doses when given for longer periods are also effective in treating giardiasis. However, the single dose regimen will probably result in better patient compliance . In addition, a single dose regimen may have better efficacy and toleration profiles than a week-long regimen of lower dose. Jokipii and Jokipii (1978—Ref.#188) reported a 74% and a 92% cure rate in patients who received 150mg BID x 7days and 2g single dose, respectively. Salih and Abdalla (1977---Ref. # 124) reported that giardiasis patients did not complain of any side-effects after a single 1g dose but some had nausea, headache, skin rash, and worsening of abdominal pain and diarrhea after receiving the 150mg BID, 7-day treatment course.

Intestinal amoebiasis. Tinidazole given as a single daily dose was more effective in the treatment of intestinal amoebiasis than when given as divided doses (600 mg tinidazole twice daily). The success rates were 87% and 123% (compared to metronidazole) after 0.6g BID x 5 days and 2.0g OD x 3 days, respectively. Twenty percent (20%) of the patients on divided doses of tinidazole and 31.3% of patients on tinidazole given once daily complained of gastrointestinal side-effects (Bakshi et al.,1978 ---Ref. 119).

Amoebic liver abscess. The optimal dose and dosing regimen for amebic liver abscess is less clear based on the findings of clinical studies that evaluated tinidazole in the treatment of amebic liver abscess (The table below summarizes the efficacy information for the randomized, controlled trials). Majority of the 18 clinical trials conducted used 2g daily for 2 to 5 days*; cure rates ranged from 80 to 100%. However, in 1 double-blind, randomized, controlled study that treated patients with 1g BID for 1 day (Lasserre et al., 1983 ---Ref 298), the success rate was 94.3% in 35 patients during a follow-up period of 6 months. The investigators of this study suggested that a 1-day tinidazole treatment of amebic liver abscess may be sufficient because the parasite is located in the liver tissue that is in proximity to the usually hypervascularized abscess site, as well as the considerable amount of the drug undergoing hepatic metabolism. In another double-blind, randomized, controlled study (Hatchuel et al., 1975 ---Ref 295), 800 mg TID for 5 days produced 93% cure in 14 patients.

Tinidazole for Amebic Liver Abscess: Combined Efficacy Rate for 9 Randomized, Controlled Trials

Study author, year	# TNZ pts. evaluable	Design	# cured	% cured	TNZ Dose	Follow-up
Khokhani, 1977 (119)	10 adults	R,C	10	100%	2g/d x 2d	5, 10, 30 days
Mathur, 1977 (198)	11 adults	R,C	11	100%	2g/d x 2d	13 days
Islam, 1978 (296)	16 adults	R,C	15	93.8	2g x 3d	10,12, 20 days
Simjee,	21 adults	SB,R,C	17	80%	2g x 5d	5 days, 4, 8

1985 (119)						weeks
Bakshi, 1978 (118)	50 adults	R,C	48	96%	2g x 2d	30 days
Hatchuel, 1975 (295)	14 adults	DB,R, C	13	93%	800mg tid x 5d	20 days
Lasserre, 1983 (298)	35 adults	DB,R,C	33	94.3%	1g bid x 1d	6 months
Kundu, 1977 (297)	9 adults	R,C	8	88%	2g x 3d	5,10,30 days
Mendis, 1984 (299)	16 adults	DB,R,C	13	81.2%	2g x 3d	5,10,30 days
TOTAL	182 adults	---	168	92.3%	---	---

*It appears from the table above that 2g x 2 days is at least as efficacious as the 2g x 3 days regimen. However, based on the assessment of the medical officer assigned to review these published studies on the efficacy and safety of tinidazole use in amebiasis, the 2g x 3-5 days regimen for the treatment of amebic liver abscess was recommended. This is in consideration of medical issues including the temporal relationship between this disease and intestinal amebiasis (which usually precedes or occurs in conjunction with amebic liver abscess and requires at least 3 days of tinidazole therapy).

4. *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

Based on the findings of Mattie et al (1982), the pharmacokinetic parameters of tinidazole in patients with mixed aerobic-anaerobic infections are comparable to those calculated for healthy volunteers. In these patients, the volume of distribution (Vd), half-life, and percent oral absorption were 52.0 Liters, 13.08 hours, and 108%, respectively. Note: This reference was not part of the NDA submission: *Mattie H, Dijkmans C and van Gulpen C. 1982. The pharmacokinetics of metronidazole and tinidazole in patients with mixed aerobic-anaerobic infections, J Antimicrobial Chemo **10**, Suppl. A, 59-64.*

a) what are the basic PK parameters?

Table 6

Pharmacokinetic parameters of tinidazole after single 2 gram oral dose in healthy volunteers

$T_{1/2}$	12 -14 hours
Cmax	47.7 ± 7.5 mcg/mL
Tmax	1.6 ± 0.7 hours
AUC $_{0-\infty}$	901.6 ± 126.5 mcg*h/mL
Vd	50 Liters
Plasma protein binding	12%
F_{urine}	20-25% as unchanged drug
F_{feces}	12%

b) is this a high extraction ratio or a low extraction ratio drug?

Based on the hepatic clearance (CL_H) predicted from *in vitro* data gathered by Li et al (2003), tinidazole could be classified as a low extraction drug (<30% liver blood flow; < 6mL/min/kg).

c) does mass balance study suggest renal or hepatic as the major route of elimination?

It appears that hepatic metabolism (≥40% of the dose) has a greater role in the elimination of the parent tinidazole compound than does renal excretion (20-25% of the dose). However, tinidazole metabolites are excreted mainly into the urine. The major urinary metabolite of tinidazole is not active but the toxicity profile is unknown.

Following 800 mg IV infusion of ^{14}C-tinidazole, 63% of the dose was excreted in the urine during 5 days; 12% of the dose was excreted in the feces. (Wood et al., 1986—Reference 143). Although tinidazole was the major ^{14}C-component (about 38% urinary ^{14}C), ethyl 2-(5-hydroxy-2-methyl-4-nitro-1-imidazolyl) ethyl sulphone was the major metabolite (about 30% urinary ^{14}C). 2-Hydroxylmethyltinidazole was a minor metabolite (about 9% of urinary ^{14}C), and its corresponding glucuronide was apparently absent because of the similarity in metabolite profiles before and after enzymic hydrolysis. Unknown polar metabolites were present, which accounted in total for no more than about 10% urinary ^{14}C. In addition, 12% ^{14}C was found in the feces; 34% of the radioactivity was attributed to the major urinary metabolite.

A recent publication by Li et al (2003) suggests that about 70% of the *in vitro* metabolism of tinidazole is mediated by CYP3A4. However, the extent by which the liver metabolizes this drug in the body is still unclear. Several lines of literature evidence suggest that tinidazole undergoes biliary excretion followed by enterohepatic circulation, namely: (1) the secretion of the drug into the bile, (2) the plateaus and double peaks in the serum concentration curves, and (3) the greater-than-100% bioavailability of tinidazole after oral administration (Vinge et al., 1983 --- Ref. # 269; Kager et al., 1981---Ref. #355; von Konow and Nord, 1982 --- Ref. # 343 in the submission).

C. Intrinsic Factors

1. *What intrinsic factors (age, gender, race, weight, height, disease, genetic [redacted] pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?*

2. *Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

a) elderly

The pharmacokinetics of tinidazole in the elderly have not been investigated. Elderly patients may have reduced renal and/or hepatic function. However, since there are no dosage reduction recommendations for patients with renal and hepatic impairment at this time, tinidazole (at the usual recommended dosage) has to be given cautiously to elderly patients.

b) pediatric patients

The recommended pediatric dosage in the labeling of tinidazole (Fasigyn®) varies depending on the country where the label originated. However, the most common dosage recommendation is 50-75 mg/kg as a single dose (for trichomoniasis and giardiasis) or 50-60 mg/kg once daily for 3 to 5 consecutive days (for amoebiasis). Table 7 summarizes international labeling information currently available for tinidazole.

Table 7
Pediatric Dosage Regimen of Tinidazole

Country	Recommended Dosage in Children
Australia	N/A. Cited the limited information on the use and safety of tinidazole in children
Belgium	For children: -50 to 75 mg/kg body weight (single dose-trichomoniasis and giardiasis); -50 to 60 mg for amoebiasis for 3 or 5 consecutive days; -no dosage recommendation for children in the treatment of anaerobic infections, since no clinical data are available
France	Limited to the treatment of giardiasis: -50 to 70 mg/kg as a single dose (not to exceed 2 g)
Germany	For trichomoniasis and giardiasis (single dose but 1 repeat dose may be needed in individual cases): Children > 12 years: same as adult dose Children > 6 years: ½ the adult dose For amoebiasis: same as for trichomoniasis and giardiasis but for 3 to 5 successive days
India	Depending on indication, the daily dose varies between 50 and 75 mg/kg up to a maximum of 2 g , as a single dose or up to 6 consecutive days
Japan	N/A. The label noted that the safety of tinidazole in young children has not been established.
Netherlands	For trichomoniasis and giardiasis: 50-75 mg/kg as a single dose For amoebiasis: 50-60 mg/kg once daily for 3 to 5 consecutive days
South Africa	For trichomoniasis and giardiasis: 50-75 mg/kg as a single dose (may need to be repeated) For amoebiasis: 60 mg/kg once daily for 3 to 5 consecutive days
Spain	Limited to Amoebiasis: 50-60 mg/kg for 3 to 5 consecutive days
Sweden	N/A
Switzerland	Same as in the labeling for Netherlands
UK	Same as in the labeling for Netherlands

Safety. Based on the medical officer's assessment of the findings from 6 studies, tinidazole at a 50 mg/kg daily dose is safe for pediatric use [Scragg (Ref. #290); Ahmed (Ref. #284); Gadzer (Ref. #128; Bacshi (Ref. #118); Suntornpoch (Ref. #264) and Krishnamurthy (Ref. #190) in the treatment of amoebiasis and giardiasis. In addition, Scragg and coworkers reported cure rates of 76% and 96% in children (4 months to 11 years old) with acute amebic dysentery treated for 3 days with single daily doses of 50 mg/kg and 60 mg/kg, respectively. The drug was well tolerated and completely free from any toxic effects at both dose levels.

Efficacy. Based on the medical officer's assessment, there is sufficient efficacy data supporting the use of the 50mg/kg single dose for the treatment of giardiasis in children and the 50 mg/kg/d for 3 days in intestinal amebiasis. However, there is limited data on the 50mg/kg/day for 3 to 5 days for amebic liver abscess.

In the study conducted by Gazder and coworkers (1977) to evaluate the efficacy and safety of tinidazole in the treatment of giardiasis in children (mean age 5.9 years old), a 50 mg/kg single dose (rounded up to the nearest quarter of the 500-mg tablet) was administered. Based on this, the reviewer thinks that the accuracy and efficiency of pediatric dosing in studies like this could be improved further if dosing is rounded up to the nearest half of a 250 mg tablet or if an oral suspension was available.

c) gender

Based on the findings of the bioavailability study conducted by the sponsor of Tindamax®, males have a slightly (~10%) higher Cmax than females. The peak exposure (Cmax) to tinidazole from the sponsor's formulation was slightly (~10%) higher in males than in females following a 2g single dose of tinidazole (Tindamax™) tablets; the extent (AUC) of absorption was not influenced by gender. This slight gender difference in Cmax is probably a consequence of a gender difference in the gastric emptying rate as evidenced by a shorter Tmax for the male subjects compared to the female counterparts. However, this slight difference is not expected to be of clinical relevance and thus no dosage adjustment based on gender is necessary. In addition, in several published studies, females had consistently (35-45%) higher Cmax than their male counterparts, a finding that was attributed to the lower body weights of the female subjects (Populaire et al., 1980---Ref. 176; Carmine et al, 1982 ---Ref. 16; Wood et al., 1982 ---Ref. 139A; Chaikin et al., 1982 ---Ref. 178).

In the sponsor's study, there was no gender-dependent difference in the half-life of tinidazole, in agreement with the findings of Populaire et al. (1980).

A dedicated study to compare the pharmacokinetics of tinidazole in male and female subjects had been previously conducted (Chaikin et al.,1982---Ref #178). There were no apparent gender-mediated differences in weight-normalized pharmacokinetic parameters, i.e., the mean oral plasma clearances, apparent volumes of distribution, and elimination half-lives were not statistically significantly different between genders. The 1.3-fold higher mean tinidazole AUC and Cmax in females than males was attributed to a smaller mean body weight of females, and consequently, a higher administered dose per body weight basis.

d) race

All except one subject in the bioavailability/bioequivalence study were Caucasians. None of the publications in the submission pertained to the influence of race on the pharmacokinetics of tinidazole. Thus, it would not be possible to assess the influence of this intrinsic factor on the pharmacokinetics of tinidazole.

e) renal impairment

The pharmacokinetics of tinidazole after single dose IV and oral administration in patients with severe chronic renal failure have been investigated (Robson et al., 1984---Ref # 156). The pharmacokinetic parameters in patients with creatinine clearance <22 mL/min not on dialysis were not statistically significantly different from those with normal renal function. Thus, adjustment of dosage would not appear necessary in patients with severe renal impairment. In patients undergoing hemodialysis, tinidazole clearance during hemodialysis was 71 mL/min. There was no accumulation of the major metabolite (hydroxymethyl tinidazole) in normal subjects and in patients undergoing HD. If tinidazole treatment starts a dialysis day, it is recommended that an additional tinidazole dose be administered either as a full dose (Robson et al., 1984) or a half-dose (Flouvat et al., 1983---Ref #219), after a hemodialysis session.

In a paper published by Lamp and coworkers (1999), it was suggested that a dosage adjustment may be needed in patients with decreased renal function receiving multiple doses. This is in accord with the Australian labeling, which states that the drug should be administered with caution in patients with impaired renal function if receiving more than a single dose. However,

based on tinidazole (Fasigyn®, Simplotan®, Tricolam®) labelings for Germany, India, Sweden, Switzerland, Belgium, UK, Netherlands and France, dosage adjustment is not required for patients with renal insufficiency (creatinine clearance <22 mL/min) because there appears to be no statistically significant modification in the pharmacokinetic parameters in these patients, following a single dose of tinidazole.

During hemodialysis, elimination of tinidazole is rapid; the half life of elimination is reduced to 4.9 hours. A 6-hour hemodialysis session removes about 43% of the circulating tinidazole and the metabolites (Flouvat et al., 1983). Thus, it would seem advantageous to administer an additional half-dose of tinidazole after the end of hemodialysis, if the tinidazole treatment starts a dialysis day.

There are no studies evaluating the pharmacokinetics of tinidazole in severely renally impaired patients undergoing continuous ambulatory peritoneal dialysis (CAPD).

f) hepatic impairment

The pharmacokinetics of tinidazole in patients with hepatic impairment have not been studied. Since a significant amount of the tinidazole dose is known to be eliminated as metabolites, it is necessary to exercise caution in the selection of appropriate dosage in these patients, especially when receiving the drug for longer periods of time (>5 days).

f.1) What is the projected accumulation ratio (R') of tinidazole after 5 days administration of 2 grams daily in patients with severe hepatic impairment?

From the PK findings of a study that administered tinidazole as a 2-gram loading dose, followed by 1-gram maintenance dose for 4 days in healthy volunteers, the projected accumulation ratio (R) of tinidazole on Day 5 is 1.36 (Wood et al., 1982---Ref 139A). Given a dosing interval (τ) of 24 hours, the half-life of tinidazole in healthy subjects in this study is 12.5 hours. Since about 50% of the administered tinidazole dose is metabolized, and assuming 0% hepatic function with no compensatory renal elimination of tinidazole in patients with severe hepatic impairment, the projected half-life in these patients is about 25 hours. Thus, the projected accumulation ratio (R') of tinidazole on Day 5 in these patients with severe hepatic impairment is approximately 2.0. This value (R') is 51% higher than the estimated accumulation ratio (R) in patients with normal hepatic function.

Trichomoniasis or giardiasis patients will generally require a single 2g oral dose of tinidazole. Amebiasis patients may require 2g daily for up to 5 days of therapy. A review of the adverse event profile of tinidazole from 28 clinical studies covering all 3 indications suggests no significant difference between single dosing and multiple dosing regimens of tinidazole (11% versus 13.8% total incidence, respectively).

g) what pregnancy and lactation use information is there in the application?

Tinidazole crosses the placental barrier and reaches breastmilk. After a 500 mg IV infusion in 21 females who underwent a first trimester legal abortion, fetal tissue and placental tissue tinidazole concentrations reached 58%, and 37% of the respective serum values (Karhunen et al., 1984---Ref # 151 of the submission). The levels attained in breastmilk are comparable to that achieved in the serum at 12, 24, and 48 hours. At 72 hours, drug level was higher in milk than in serum; at 92 hours, only traces of tinidazole were detectable in milk samples and none in serum (Mannisto et

al., 1983; Mannisto et al., 1984). After 7 days' treatment with tinidazole, the milk/serum ratio may reach as high as 1.62 (Welling and Monro, 1971---Ref. 21).

According to the *Australian label* of tinidazole (Fasigyn®), the drug may continue to appear in breastmilk for more than 72 hours after administration. Thus, women should not breastfeed until at least three days after having discontinued taking the drug (same recommendation as in Evaldson et al., 1985 ---Ref # 150).

According to the Belgian label: Tinidazole is contraindicated during the first trimester of pregnancy. During the second and third trimesters of pregnancy, it may be used when the benefits of the use outweigh the risks for both the mother and the fetus. Tinidazole is also contraindicated during lactation. In the absence of a suitable alternative therapy, tinidazole may be used but lactation should be discontinued.

D. Extrinsic Factors

1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?*

There are no literature reports regarding drug interactions that result in alteration of the pharmacokinetics of tinidazole. Alcohol use is contraindicated with tinidazole because of the potential to experience disulfiram-like effects when these two agents are taken together. Based on the findings of the study conducted by the sponsor, the oral bioavailability of tinidazole is not significantly influenced when co-administered with a high-fat meal.

2. *Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.*

No factors were identified and so there are no dosage adjustments for any of these factors at this time.

3. Drug-Drug Interactions

a) is there an in vitro basis to suspect in vivo drug-drug interactions?

The findings of the in vitro metabolism study conducted by the sponsor showed that tinidazole --- like metronidazole---at concentrations of up to 2-fold its C_{max} in healthy volunteers did not inhibit the CYP450 enzymes mainly responsible for the metabolism of drugs.

Although there is no information (i.e., literature or experimental) to directly address in vivo drug interaction studies with tinidazole, the proposed labeling for tinidazole is based upon the drug interaction information from the approved labeling for metronidazole.

b) is the drug a substrate of CYP enzymes?

Based on *in vitro* metabolism literature information submitted by the sponsor, tinidazole is metabolized by CYP3A4 to a major extent (77%) and by CYP2B6 to a minor extent (12%).

c) is the drug an inhibitor and/or an inducer of CYP enzymes?

According to the literature, tinidazole is metabolized in vitro mainly by CYP3A4, as well as to a minor extent by CYP2B6. The sponsor investigated the potential of tinidazole to inhibit the metabolic activities of CYP3A4, CYP1A2, CYP2B6, CYP2C9, and CYP2D6, using metronidazole as comparator. Tinidazole, as well as metronidazole, did not have an inhibitory effect on the enzymes at substrate concentrations of up to 2-fold the tinidazole Cmax measured in healthy volunteers. Based on these in vitro findings, tinidazole is not expected to have a high-risk potential for inhibiting the metabolism of other drugs in vivo. However, there is a growing list of case reports and clinical studies suggesting potential drug interactions between metronidazole and other CYP3A4 substrates, even if in vivo drug interaction studies involving CYP3A4 probe substrates (e.g., midazolam, erythromycin) prove otherwise.

The potential of tinidazole to induce metabolism of other drugs has not been evaluated.

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Information not available.

e) are there other metabolic/transporter pathways that may be important?

Information not available.

f) *does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?*

No.

g) what other co-medications are likely to be administered to the target patient population?

Because anaerobic infections are often mixed with facultative bacteria, combination of tinidazole with antibiotics may be prescribed. Based on the in vitro evidence, tinidazole may enhance the antimicrobial effects of doxycycline and other antibiotics. This interaction, if it indeed occurs at the in vivo level, is not a safety concern and may be beneficial in antimicrobial combination chemotherapy. The effect of concomitantly administered antibiotics on the pharmacokinetics and pharmacodynamics of tinidazole is unclear.

h) *are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

There is a case report suggesting that oxytetracycline may antagonize the therapeutic effects of metronidazole (Szanto, 1971 ---not a part of the NDA submission). A 66-year-old female was treated with oxytetracycline (250 mg four times a day) for bronchitis, as well as metronidazole for trichomonas vaginitis (250 mg four times a day for one week). There was no improvement 10 days later in the trichomonas infection. Oxytetracycline was discontinued and the metronidazole was repeated, resulting in complete bacteriologic clearance and subsidence of the vaginal discharge.

i) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

A possible mechanism for the pharmacodynamic interaction between oxytetracycline and metronidazole in vivo involves the eradication of gastrointestinal flora responsible for deconjugation of biliary-excreted metronidazole conjugated metabolites. This may result in a decrease in enterohepatic recirculation of metronidazole, and consequently, a reduction in the therapeutic effect of metronidazole. Tinidazole, like, metronidazole undergoes biliary excretion and enterohepatic recycling.

j) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None.

E. General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Low Solubility, High Permeability (BCS II).

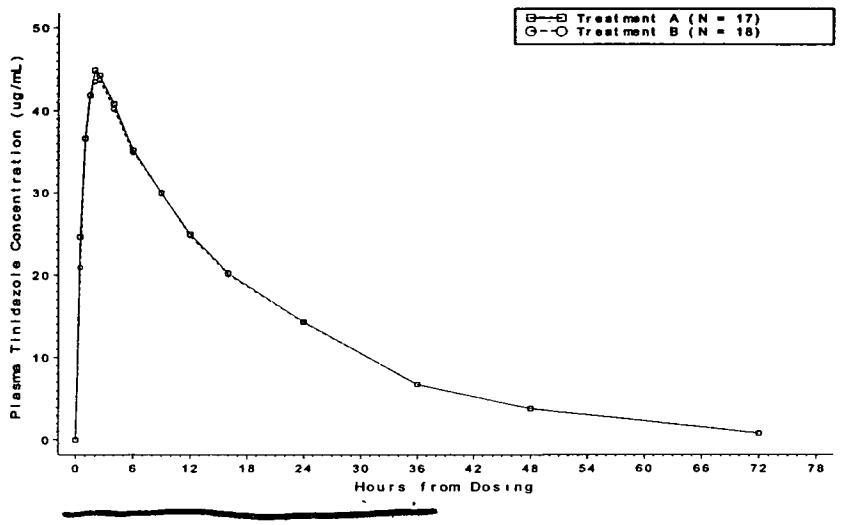
Tinidazole is practically insoluble in aqueous solutions. It is soluble in [redacted] sparingly soluble in methanol. After oral administration, it is completely absorbed (with an absolute bioavailability of ≥100%).

Using the USP Dissolution Apparatus 1, with water as the dissolution medium, not less than [redacted]% of the drug dissolves in the medium within [redacted] minutes.

2. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial (reference) formulation in terms of comparative exposure?

Figure 2 provides the time course of mean plasma tinidazole concentrations for Treatments A (Tindamax™) and B (Fasigyn®, UK). There was no significant difference in tinidazole exposure from the two formulations.

Figure 2
Mean Plasma Tinidazole Concentrations for Treatments A and B (linear scale)



Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast

Treatment B = 4 x 500 mg Fasigyn Tablets Following a Minimum 10-hour Overnight Fast

Note Refer to Table 1 for a comparison of Tinidazole pharmacokinetic parameters following Treatment A and Treatment B.

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Table 1. Summary of the Bioequivalence/Bioavailability Study Findings

Parameter (units)	Arithmetic Mean ± SD (minimum-maximum)				90% CI Difference [a]	% Mean Ratio [a]
	Treatment A (n = 17)	Treatment B (n = 18)	Treatment C (n = 9)	Treatment D (n = 9)		
Cmax (µg/mL)	47.7165 ± 7.5412	45.5123 ± 7.9771	42.8247 ± 8.5493	46.3441 ± 9.2393	96.6 – 106.4(F)[b] 105.0 – 115.0(M)[b]	101.4 [b] 109.9 [b]
Tmax (hr)	1 60 ± 0.763	2.12 ± 1.09	3 00 ± 1.00	2.06 ± 0.390	62.9-101.4 [c]	82.2 [c]
AUC(0-t) (µg*hr/mL)	863 1 ± 127.8	861.2 ± 127.3	797 9 ± 108.5	889.6 ± 94 93	97.8 – 103.9	100.8
AUC(0-inf) (µg*hr/mL)	901 6 ± 126.5	893 7 ± 126 6	832.0 ± 104 6	923.7 ± 94 50	98 9 – 104.1	101 5
Kel (1/hr)	0.0529 ± 0.00588	0.0539 ± 0 00645	0.0582 ± 0 00773	0 0514 ± 0 00599	----	----
T1/2 (hr)	13 2 ± 1 41	13.0 ± 1.44	12.1 ± 1.66	13.6 ± 1.50	----	----

a = Ln-transformed parameters and LS means were used in obtaining confidence intervals and % mean ratios of Treatment A versus B

b = Statistical comparisons for Cmax were performed separately for males and females as TREATMENT*GENDER interaction was significant

c = Un-transformed parameters and LS means were used in obtaining confidence intervals and % mean ratios of Treatment A versus B

F = Females, M = Males

Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast

Treatment B = 4 x 500 mg Fasigyn Tablets Following a Minimum 10-hour Overnight Fast

Treatment C = 4 x 500 mg Tinidazole Tablets Following the Standard High Fat Breakfast

Treatment D = 4 x 500 mg Tinidazole Tablets Crushed in Cherry Syrup Following a Minimum 10-hour Overnight Fast

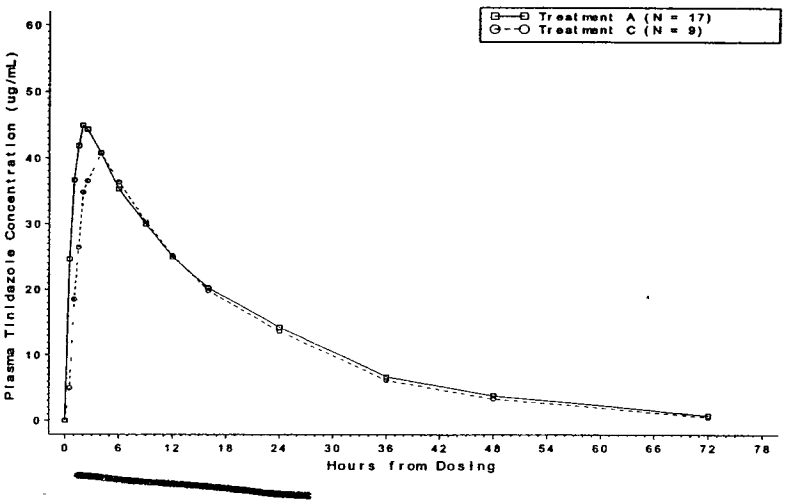
Source Data: Tables 14.2.5, 14.2.6, 14.2.7, 14.2.8, and 14.2.12

B.1. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The co-administration of a high fat meal did not affect tinidazole AUC but slightly reduced the Cmax by about 15% and prolonged the Tmax from 1.6 h to 3.0 h, suggesting that food had a greater effect on the rate than on the extent of tinidazole absorption (Figure 3). The high-fat meal most probably decreased the gastric emptying rate of the subjects. This food-induced decrease in peak concentration and exposure (AUC) of tinidazole is not likely going to result in a clinically significant reduction in the oral bioavailability of Tindamax™.

Figure 3 provides the time course of mean plasma tinidazole concentrations for Treatments A(Tindamax™/Fasted) and C(Tindamax™/Fed).

Figure 3
Mean Plasma Tinidazole Concentrations versus Time for Treatments A and C (linear scale)



Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast

Treatment C = 4 x 500 mg Tinidazole Tablets Following the Standard High Fat Breakfast

Note Refer to Table 1 for a comparison of tinidazole pharmacokinetic parameters following Treatment A and Treatment C.

The results of the statistical analysis to compare the pharmacokinetic parameters of Treatment C versus Treatment A are presented in Table 8.

Table 8
Statistical Comparisons of Plasma Tinidazole Pharmacokinetic Parameters: Treatment C Versus Treatment A

	Treatment ---- Means -----				
Parameter	C	A	Pct Difference	90% CI Difference	% Mean Ratio
Tmax	2.980	1.069	178.78	207.0-350.5	278.8
ln(Cmax)	3.719	3.876	-4.03	80.9- 90.4	85.5
ln[AUC(0-t)]	6.657	6.671	-0.20	94.7-102.8	98.7
ln[AUC(0-inf)]	6.701	6.724	-0.34	94.3-101.3	97.7

Treatment C = 4 x 500 mg Tinidazole Tablets Following the Standard High Fat Breakfast: test
Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast: reference

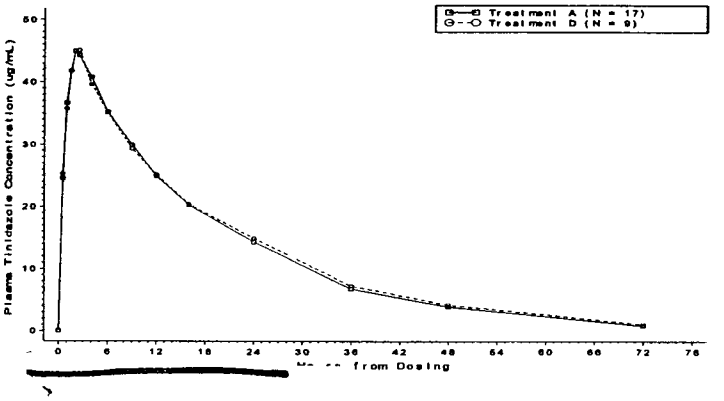
Values for Treatments C and A are the least-squares means (LSMEANS) from the ANOVA

Pct Difference = difference between treatments (C - A) expressed as a percentage of Treatment A

Mean Ratio = 100*exp(test-reference) for ln-transformed parameters
Mean Ratio = 100*test/reference for untransformed parameters

B.2. Does the drug from a suspension of the crushed tablet in cherry syrup have a bioavailability (BA) comparable to the BA of the drug from the intact oral tablet?

Figure 4
Mean Plasma Tinidazole Concentrations versus Time for Treatments A and D (linear scale)



Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast

Treatment D = 4 x 500 mg Tinidazole Tablets Crushed in Cherry Syrup Following a Minimum 10-hour Overnight Fast

Note: Refer to Table 1 for a comparison of tinidazole pharmacokinetic parameters following Treatment A and Treatment D

The suspension of the crushed tinidazole tablet in artificial cherry syrup did not significantly affect the oral bioavailability of tinidazole compared to when administered as a whole tablet. Figure 4 provides the time course of mean plasma tinidazole concentrations for Treatments A (Tindamax™/whole tablet) and D (Tindamax™/cherry syrup suspension).

The results of the statistical analysis to compare the pharmacokinetic parameters of Treatment D versus Treatment A are presented in Table 9 .

Table 9
Statistical Comparisons of Plasma Tinidazole Pharmacokinetic Parameters: Treatment D Versus Treatment A

		Treatment Means		Pct	90% CI	% Mean
Parameter	Gender	D	A	Difference	Difference	Ratio
Tmax	Female	1.836	2.356	-22.08	63.1- 92.8	77.9
	Male	2.323	1.707	36.12	113.2-159.0	136.1
ln(Cmax)	Female	3.927	3.926	0.03	94.5-106.0	100.1
	Male	3.683	3.759	-2.00	87.0- 98.9	92.8
ln[AUC(0-t)]		6.787	6.823	-0.53	92.6-100.4	96.4
ln[AUC(0-inf)]		6.825	6.861	-0.53	92.5-100.6	96.4

Treatment D = 4 x 500 mg Tinidazole Tablets Crushed in Cherry Syrup Following a Minimum 10-hour Overnight Fast: test
Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast: reference

Values for Treatments D and A are the least-squares means (LSMEANS) from the ANOVA

Pct Difference = difference between treatments (D - A) expressed as a percentage of Treatment A

Mean Ratio = 100*exp(test-reference) for ln-transformed parameters
Mean Ratio = 100*test/reference for untransformed parameters

C. *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

Table 10. Specifications and analytical methods

Test and Method	Specification
Identification-HPLC	
Assay - HPLC	
Unknown related substances - HPLC	
Total related substances - HPLC	
Dissolution – USP, App 1, water - HPLC	
Content uniformity – USP<905> - HPLC	USP requirements

The dissolution of the sponsor's 500 mg tablet (Lot C020234E) used in the bioequivalence/bioavailability study was within specifications. Following oral dosing, the sponsor's tablet was bioequivalent to the reference tablet commercially available worldwide. Additionally, the pharmacokinetic parameters of tinidazole from the sponsor's tablet were found to be comparable to those in the literature. Thus, it appears that the dissolution specifications for the drug in the to-be-marketed tablet are sufficient to ensure the *in vivo* performance of the product.

lots of the 500mg tablet and lots of the 250mg tablet were subjected to dissolution testing. The table below summarizes the percent dissolution means and ranges (in parentheses).

Dissolution data for the 500mg and 250mg strengths of Tindamax® oral tablets

Tablet Strength	500mg				250mg		
Lot Number	RD010907A	C020233	**C020234***	C020235	D020255	D020256	D020257
Dissolution (%)							
Drug Substance Lot							

*lot used in the bioequivalence and bioavailability studies

F. Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

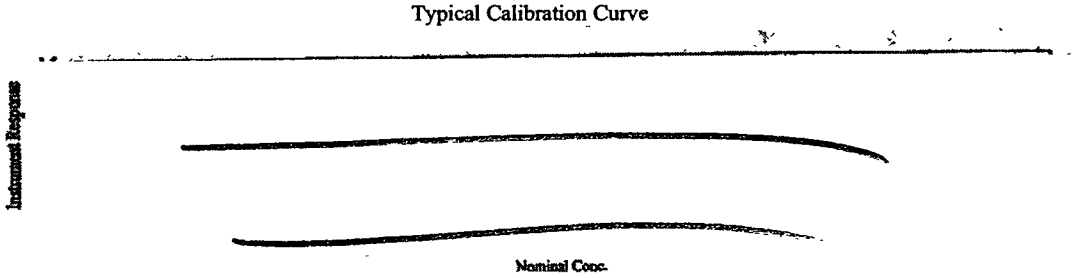
For the sponsor-generated studies, i.e., the BA/BE studies, the study samples were assayed

2. *What bioanalytical methods are used to assess concentrations?*

a) what is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curve ranged from . Sample plasma concentrations ranged from BLQ (Below the limit of quantitation) to .

Figure 5.
Typical Calibration Curve



b) *what are the lower and upper limits of quantification (LLOQ/ ULOQ)?*

The lower and upper limits of quantification were set at respectively.

Table 11. Limits of Quantitation
Tinidazole
Concentration in µg/mL

Limit	LLOQ	ULOQ
Nominal Concentration	[redacted]	
Average Concentration	[redacted]	
Standard Deviation	0.0231	1.39
Precision (%)	2.1%	1.4%
Accuracy (%)	108.7%	98.8%
N	6	6

c) what is the accuracy, precision and selectivity at these limits?

Accuracy and Precision. Intra-assay and inter-assay accuracy were determined by comparing the mean measured concentrations of the quality control sample with their nominal concentrations. Intra-assay and inter-assay precision were determined from the relative standard deviations of the quality control samples. On at least [redacted] occasions [redacted] replicates of each QC sample pool were assayed. [redacted] The data for accuracy and precision are presented in Tables 12 and 13. The quality control sample data meets the intra-assay and inter-assay accuracy and precision criteria.

Table 12 Intra-Assay Quality Control Sample Statistics
Tinidazole
Concentration in µg/mL

Nominal Concentration	[redacted]								
Average Concentration									
Standard Deviation	1.14	0.536	0.0602	1.81	0.758	0.262	0.947	0.581	0.0478
Precision (%)	1.5%	1.1%	2.1%	2.5%	1.5%	8.8%	1.2%	0.8%	1.7%
Accuracy (%)	97.3%	97.1%	93.8%	99.4%	99.7%	98.9%	98.6%	98.4%	92.2%
N	6	6	6	6	6	6	6	6	6

Table 13. Inter-Assay Quality Control Samples Statistics
Tinidazole
Concentration in µg/mL

Nominal Concentration	[redacted]		
Average Concentration			
Standard Deviation	2.49	0.826	0.197
Precision (%)	3.1%	1.7%	6.7%
Accuracy (%)	100.5%	98.2%	98.4%
N	30	30	30

[redacted]

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

12 page(s) of revised draft labeling has been redacted from this portion of the review.

Appendix 2
Clinical Pharmacology and Biopharmaceutics Individual Study Review

A. A Randomized, Open-Label, Four-Treatment, Three-Period, Single-Dose Study to Compare the Bioavailability of a Test Tinidazole Tablet Formulation to a Tinidazole Tablet Formulation Marketed Abroad and to Assess the Effect of Food and Crushing of the Test Tablet in Healthy Subjects

Objectives: The primary objective of the study was to compare the bioavailability of the sponsor's 500 mg test tablet formulation of tinidazole to a 500 mg tinidazole reference tablet formulation (Fasigyn®, Pfizer UK) following a single 2000 mg dose (4 x 500 mg tablets), administered in the fasted state.

The secondary objectives of this study were as follows:
- To determine the effect of a standard high fat breakfast on the bioavailability of the sponsor's 500 mg tinidazole tablet when given as a 2000 mg dose
- To determine the relative bioavailability of the sponsor's 500 mg tinidazole tablet when crushed and administered in cherry syrup following an overnight fast
- To assess the safety and tolerability of the four-single-dose treatments of tinidazole

Study Design: This was a single-dose, randomized, open-label, unbalanced, 3-period, 4-treatment, 2-way crossover study.

Number of Subjects (planned and analyzed): A total of 18 subjects were enrolled in the study, and all of them successfully completed the study. All 18 subjects were considered for safety evaluation and included for pharmacokinetic analysis. The data for 1 subject were not included in the summary statistics and statistical analysis for Treatment A due to vomiting.

Test Product, Dose, Duration, Mode of Administration, and Batch Number: The test product was Tinidazole 500mg tablets, manufactured by Presutti Laboratories, Inc., Lot No. C020234E, manufactured on 19 Mar 2002. Subjects randomized for Treatment A received a single oral dose of four 500 mg tablets taken with 240 mL of water following a minimum 10-hour overnight fast. Subjects randomized to Treatment C received a single oral dose of four 500 mg tinidazole tablets taken with 240 mL of water 30 minutes after a high-fat breakfast.

Subjects randomized to Treatment D received a single oral dose of four 500 mg tinidazole tablets crushed and suspended in cherry syrup for a final volume of 30 mL following a minimum 10-hour overnight fast. After administration of the study drug, the oral dosing syringe was rinsed with 30 mL of water twice. Subjects drank both rinses and an additional 180 mL water. Cherry syrup was manufactured by Humco™ (Lot no. 343336; expiration date: Nov 2004).

Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The reference product was Fasigyn™ 500 mg tablets, manufactured by Pfizer Limited, England (Lot no. 0081003, expiration date September 2003. Subjects randomized to Treatment B received a single oral dose of four 500 mg Fasigyn™ tablets taken with 240 mL water following a minimum 10-hour overnight fast.

Criteria for Evaluation:

Pharmacokinetics: Tinidazole plasma pharmacokinetic parameters AUC (0-t), AUC(0-inf), and Cmax were evaluated. There were 15 blood draws per subject per treatment including time 0 through 72 hours post dose.

Safety: Safety was assessed with physical examination, electrocardiogram (ECG), clinical laboratory (hematology, serum chemistry, and urinalysis during screening and at 72 hours post dosing in period 3), vital signs and adverse event monitoring conducted throughout the study. The study subjects were confined to the clinic during each study period throughout 36 hour post dose and returned for events as scheduled through 72 hours.

Statistical Methods:

Pharmacokinetics: Pharmacokinetic parameters and plasma concentrations of tinidazole were listed and summarized. The summary statistics include coefficient of variation (CV%), arithmetic mean, standard deviation (SD),standard error of the mean (SEM), minimum (min), maximum (max), and sample size (N). The mean and individual plasma concentration-time curves of tinidazole were presented on both linear and semi-logarithmic scales.

For the comparison of Treatment A and B, Treatment C and A, Treatment D and A, a parametric (normal theory) general linear model was applied to the logarithmic transformation of AUC(0-inf), AUC(0-t), and Cmax. The analysis of variance (ANOVA) model included the following factors: sequence, subject within sequence, period, gender, formulation, and treatment*gender with weight as the covariate. Treatment*gender, gender, and weight were removed from the ANOVA model if they were not statistically significant (P>0.10). If treatment*gender was significant, then the analysis was conducted separately for males and females. The 2-one-sided hypotheses were tested at the 5% level for AUC(0-t), AUC(0-inf), and Cmax by constructing 90% confidence intervals for the ratio of the test and reference means.

Bioequivalence of Treatment A to Treatment B with respect to the ln-transformed AUC(0-t), AUC(0-inf), and Cmax was concluded if the 90% confidence interval of the ratio of the product means for each parameter fell within the range of 80% to 125%. The 90% confidence interval was obtained from the antilog of the lower and upper bounds of the 90% confidence interval for the difference in the least-squares means of the ln-transformed data.

Pharmacokinetic Results: The arithmetic means of the pharmacokinetic parameters of plasma tinidazole for Treatments A,B,C, and D and the final statistical comparisons of these parameters following Treatment A versus Treatment B, Treatment C versus Treatment A, Treatment D versus Treatment A are presented below.

Parameter (units)	Arithmetic Mean ± SD (minimum-maximum)				90% CI Difference [a]	% Mean Ratio [a]
	Treatment A (n = 17)	Treatment B (n = 18)	Treatment C (n = 9)	Treatment D (n = 9)		
Cmax (µg/mL)	47.7165 ± 7.5412	45.5123 ± 7.9771	42.8247 ± 8.5493	46.3441 ± 9.2393	96.6 – 106.4(F)[b] 105.0 – 115.0(M)[b]	101.4 [b] 109.9 [b]
Tmax (hr)	1.60 ± 0.763	2.12 ± 1.09	3.00 ± 1.00	2.06 ± 0.390	62.9-101.4 [c]	82.2 [c]
AUC(0-t) (µg*hr/mL)	863.1 ± 127.8	861.2 ± 127 3	797.9 ± 108.5	889.6 ± 94.93	97.8 – 103.9	100.8
AUC(0-inf) (µg*hr/mL)	901.6 ± 126.5	893.7 ± 126 6	832.0 ± 104.6	923.7 ± 94 50	98 9 – 104 1	101 5
Kel (1/hr)	0 0529 ± 0 00588	0 0539 ± 0 00645	0.0582 ± 0 00773	0 0514 ± 0 00599	----	----
T1/2 (hr)	13.2 ± 1.41	13 0 ± 1.44	12.1 ± 1.66	13.6 ± 1 50	----	----

a = Ln-transformed parameters and LS means were used in obtaining confidence intervals and % mean ratios of Treatment A versus B

b = Statistical comparisons for Cmax were performed separately for males and females as TREATMENT*GENDER interaction was significant

c = Un-transformed parameters and LS means were used in obtaining confidence intervals and % mean ratios of Treatment A versus B

F = Females, M = Males
Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast

Treatment B = 4 x 500 mg Fasigyn Tablets Following a Minimum 10-hour Overnight Fast

Treatment C = 4 x 500 mg Tinidazole Tablets Following the Standard High Fat Breakfast

Treatment D = 4 x 500 mg Tinidazole Tablets Crushed in Cherry Syrup Following a Minimum 10-hour Overnight Fast

Source Data: Tables 14.2.5, 14.2.6, 14.2.7, 14.2.8, and 14.2.12

Table 8. Statistical Comparisons of Plasma Tinidazole Pharmacokinetic Parameters: Treatment C Versus Treatment A

Parameter	Treatment Means C	Means A	Pct Difference	90% CI Difference	% Mean Ratio
Tmax	2.980	1.069	178.78	207.0-350.5	278.8
ln(Cmax)	3.719	3.876	-4.03	80.9- 90.4	85.5
ln[AUC(0-t)]	6.657	6.671	-0.20	94.7-102.8	98.7
ln[AUC(0-inf)]	6.701	6.724	-0.34	94.3-101.3	97.7

Treatment C = 4 x 500 mg Tinidazole Tablets Following the Standard High Fat Breakfast: test
Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast: reference

Values for Treatments C and A are the least-squares means (LSMEANS) from the ANOVA
Pct Difference = difference between treatments (C - A) expressed as a percentage of Treatment A

Mean Ratio = 100*exp(test-reference) for ln-transformed parameters
Mean Ratio = 100*test/reference for untransformed parameters

Table 9. Statistical Comparisons of Plasma Tinidazole Pharmacokinetic Parameters: Treatment D Versus Treatment A

Parameter	Gender	Treatment Means D	Means A	Pct Difference	90% CI Difference	% Mean Ratio
Tmax	Female	1.836	2.356	-22.08	63.1- 92.8	77.9
	Male	2.323	1.707	36.12	113.2-159.0	136.1
ln(Cmax)	Female	3.927	3.926	0.03	94.5-106.0	100.1
	Male	3.683	3.759	-2.00	87.0- 98.9	92.8
ln[AUC(0-t)]		6.787	6.823	-0.53	92.6-100.4	96.4
ln[AUC(0-inf)]		6.825	6.861	-0.53	92.5-100.6	96.4

Treatment D = 4 x 500 mg Tinidazole Tablets Crushed in Cherry Syrup Following a Minimum 10-hour Overnight Fast: test
Treatment A = 4 x 500 mg Tinidazole Tablets Following a Minimum 10-hour Overnight Fast: reference

Values for Treatments D and A are the least-squares means (LSMEANS) from the ANOVA

Pct Difference = difference between treatments (D - A) expressed as a percentage of Treatment A

Mean Ratio = 100*exp(test-reference) for ln-transformed parameters
Mean Ratio = 100*test/reference for untransformed parameters

Safety Results: Of the 18 subjects dosed with study treatments, 15 subjects (83%) experienced at least 1 treatment-emergent AE. A lesser percentage of subjects reported AEs following the fasted and fed test treatments than the reference treatment. A greater percentage of subjects experienced AEs (primarily Dysgeusia upon ingestion) following the crushed test tablet in cherry syrup. Dysgeusia (verbatim terms included metallic, bitter, and bad taste) was the most frequent AE reported (following all treatments) with all episodes considered by the Investigator to be study-drug related. The majority of the AEs experienced during this trial were mild in severity and were considered by the Investigator to be study-drug related. All AEs considered study-drug related resolved in less than 48 hours and most resolved in less than 24 hours. No serious adverse events occurred and no subjects discontinued the study due to AEs.
No treatment-related trends were noted in regards to the clinical laboratory, vital sign, ECG, and physical examination findings.

Conclusion: Pharmacokinetic and statistical analyses of the data resulting from the administration of a single oral dose of 4 x 500 mg tinidazole test formulation (Presutti Laboratories) and 4 x 500 mg Fasigyn (Pfizer, UK) under fasted conditions indicated that the mean ratios (based on LS means) were 101.4%, 109.9%, 100.8%, and 101.5%, for ln(Cmax) for females, ln(Cmax) for males, ln[AUC(0-t)], and ln[AUC(0-inf)], respectively, and the 90% confidence intervals (based on LS means) for each of the parameters ln(Cmax), ln[AUC(0-t)], and ln[AUC(0-inf)] were within the range of 80–125%. Therefore, the tinidazole test formulation (Presutti Laboratories) satisfied the established bioequivalence criteria when compared to the reference formulation Fasigyn™ (Pfizer, UK). Based on arithmetic means, peak exposure (Cmax) and extent of exposure [AUC(0-t) and AUC(0-inf)] were not affected when tinidazole test formulation was administered with a high-fat breakfast or administered crushed in cherry syrup under fasted conditions when compared to the test formulation administered under fasted conditions.

A single 2000 mg dose (4 x 500 mg tablets) of tinidazole (Presutti Laboratories) administered in a fed state or fasted state (either whole tablet or crushed in cherry syrup) appeared to be equally safe and well tolerated by the healthy subjects in this study compared to a single 2000 mg dose (4 x 500 mg tablets) of Fasigyn™.

B. In Vitro Drug Metabolism Study

Objective: To determine whether tinidazole and metronidazole inhibit human cytochrome P450 catalytic activity in vitro.

Study Design: This inhibition study determined the degree of inhibition of CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 for several concentrations (0, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300 µM) of the tinidazole and metronidazole. A single concentration of each model substrate (near or approximately twice the apparent Km) was tested in duplicate, using a known inhibitor as positive control. Metabolism of the model substrates was quantified by measuring the amount of a metabolite formed. The metabolite was assayed by HPLC [redacted] Negative controls or blanks were used to control for bias.

Enzyme Inhibition Method:

[redacted]

Enzymes, Substrates, Positive Controls:

Enzyme	Substrate	Positive Control	% Inhibition by Positive Control*
CYP1A2	[redacted]	[redacted]	88.0, 96.0
CYP2B6			89.0, 97.5
CYP2C9			88.0, 87.5
CYP2D6			86.5, 89.5
CYP2E1			71.0, 70.0
CYP3A4			68.5, 72.5

* The first and the second % inhibition values are means for tinidazole and metronidazole, respectively.

Results:

Enzyme	Tinidazole IC_{50}	Metronidazole IC_{50}
CYP1A2	> 300 µM	> 300 µM
CYP2B6	> 300 µM	> 300 µM
CYP2C9	> 300 µM	> 300 µM
CYP2D6	> 300 µM	> 300 µM
CYP2E1	> 300 µM	> 300 µM
CYP3A4	> 300 µM	> 300 µM

Conclusion:

Tinidazole and metronidazole at concentrations up to 300 µM did not inhibit any of the cytochrome P450 enzymes examined. All IC_{50} values were determined to be > 300 µM.

__1__ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Appendix 3
Cover Sheet and OCPB Filing/Review Form (2-3 pages)

I. Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-618, 21-681, 21-682	**Brand Name**	Tindamax™
OCPB Division (I, II, III)	DPE III	**Generic Name**	Tinidazole
Medical Division	ODE IV	**Drug Class**	Antiprotozoal, antibacterial
OCPB Reviewer	Gerlie De Los Reyes, Ph.D.	**Indication(s)**	Trichomoniasis [redacted] Giardiasis, Amebiasis (intestinal and amebic liver abscess)
OCPB Team Leader	Philip Colangelo, Pharm. D., Ph.D.	**Dosage Form**	Tablet (250 mg, 500 mg)
		Dosing Regimen	For Trichomoniasis and Giardiasis· 2g single dose; For Amebiasis 2 g per day for 3 to 5 days
Date of Submission	16 July 2003	**Route of Administration**	oral
Estimated Due Date of OCPB Review	15 January 2004	**Sponsor**	Presutti Laboratories, Inc.
PDUFA Due Date	17 May 2004	**Priority Classification**	10-month standard review
Division Due Date	17 April 2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
II. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
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:	x	1		CYP inhibition
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference.	x	1		**Of crushed tablet in cherry syrup versus the to-be-marketed tablet**
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1 (single-dose)		using Fasigyn (Pfizer, UK) as reference drug
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	47			Note: 505(b)(2)
Total Number of Studies	4			

Filability and QBR comments

	"X" if yes	
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above	**• About [redacted] of the administered oral dose is metabolized. However, there is no information regarding the pharmacokinetics of tinidazole in hepatically-impaired patients. • The drug interactions section of the labeling of this drug will include those found in the metronidazole labeling.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

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

/s/

Gerlie De Los Reyes
5/17/04 07:22:24 PM
BIOPHARMACEUTICS

Edward Cox
5/17/04 07:35:43 PM
MEDICAL OFFICER
for Phil Colangelo (I discussed with Phil Colangelo and he concurs with the review. I am signing on his behalf)