the article that the investigators examining the stools were blinded to treatment, but no mention was made of whether the patients were aware of their treatment assignment. This was the only submitted study where those reading the stools were blinded and therefore is a valuable study. The success and tolerability of tinidazole seen in the children in this study is important data. The lack of a description of the randomization method is a deficiency of study design.

Supporting Studies considered pivotal by the FDA

- **Speelman 1985, Bangladesh (127)** Two randomized studies performed in expatriate children and adults. In both studies 2 stool specimens were examined weekly for 4 weeks and both enrolled symptomatic and asymptomatic subjects. In both of the studies approximately half of the enrolless were under age 10 and only 1 or 2 were over 40 years of age. Randomization was by picking an envelope with a T or M inside and was the same for both trials.

  The first compared tinidazole 2 g x 1 with metronidazole 2 g x1 or pediatric equivalents of 50mg/kg There 20 males and 13 females enrolled. Half of the enrollees were asymptomatic. Parasitologic success at 4 weeks was 94% (16/17) for tinidazole versus 56% or 9/16 for metronidazole.

  The second compared to 2g x1 or 50mg/kg x1 of tinidazole with metronidazole 2g qd for 3 days or 50mg/kg/day for 3 days. One third of the enrollees were asymtomatic. Parasitologic clearance was seen at 4 week followup in 15/15 of the tinidazole subjects compared to 14/15 of the metronidazole recipients.

  Both drugs were well tolerated by children and adults with minor side effects in both trials.

Medical Officer's Comment: *The results of these two trials point out the improvement in results for metronidazole with longer dosing and that a single dose of tinidazole is comparable with multi-day dosing of metronidazole and superior to single day dosing of metronidazole. The 4 week followup may still miss some late relapses but will pick up early relapses and therefore is a better endpoint than the 16 day follwup periods as seen in some other studies. The randomization method was described but the lack of blinding is a deficiency in study design. In both these studies a substantial portion of subjects were asymptomatic. The success rates of tinidazole did not seem to be affected by this inclusion.*

Gadzer, 1977 India (128): Randomized, comparative trial of 50 mg/kg gm single dose (to the nearest quarter of a tablet) of either tinidazole or metronidazole in

100 children. There were 65 males and 35 females. All complained of symptoms consistent with Giardiasis. All 100 had cysts detected in their stool. In the tinidazole arm 7 also had trophozoites detected and in the metronidazole arm 3 also had trpohozoites. Ascaris was also detected in 8 enrollees in each group and *E.histolytica* cysts were present in the stools of 3 members of the tinidazole group and 4 of the metronidazole group. The average age was 5.9 years for tindazole and 5.1 years for metronidazole. Actual mean drug dosage was 55.5 mg/kg for tinidazole and 52.0 m/kg for metronidazole. Results were categorized as cure, probable failure (persistent symptoms with negative stools), and failure (persistence of positive stools.) Tinidazole produced an 80% cure rate and a 20% failure rate. Metronidazole produced a 36% cure rate, 2% probable failure, and 62% failure. Stools were assessed by the formalin ether method at days 4,8,12,16. The number of stools obtained at each endpoint was not described.

The authors reported more rapid conversion to negative stools by day 4 for patients receiving tinidazole and to a more rapid improvement in those with diarrhea by day 8 for subjects receiving tinidazole. Please see the tables below.

Number of Patients with cysts in stool at successive followup visits

Day	Tinidazole Group		Metronidazole Group	
	Number	%	Number	%
0	50	100	50	100
4	42	84	45	90
8	16	32	35	70
12	10	20	30	60
16	10	20	31	62

From Gadzer Source #128

Number of patients with diarrhea at successive followup visits

Day	Tinidazole Group		Metronidazole Group	
	Number	%	Number	%
0	38	100	37	100
4	27	71	34	92
8	8	21	22	59
12	7	18	21	57
16	7	18	21	57

From Gadzer source #128

Mild gastrointestinal side effects were seen in 6 patients on tinidazole and in 2 on metronidazole. Hematology and chemistry laboratory values were obtained at the beginning and at the end of the study and no effects on these lab parameters were seen.

***Medical Officer's Comment**: There were only 16 days of followup so both early and late relapses may have been missed. Drug assignment was by "random order" and the lack of a more specific randomization plan is a deficiency. The strengths of this study are the evaluation of the days to conversion of stools to negative and the timing of the resolution of symptoms adds important data to t he other pivotal studies.. Biochemical and hematology lab values were obtained before and after drug administration providing useful safety information. Results were well categorized.*

- **Nigam, 1990 India(191).** Seventy five patients (50 male, 25 female) ranging in age from 10 to 61 with a mean age of 20 were randomized to receive a single dose of 50 mg/kg tinidazole (40 patients) or a single dose of 50 mg/kg metronidazole (35 patients) in an open label study. Enrollment criteria was the presence of cysts or trophozoites in the stool. Symptoms were not required for entry and 29 or 38.6% of subjects were asymtomatic. Parasitologic cure was achieved in 39 of 40 or 97.5% of patients receiving tinidazole and 19 of 35 or 54.3% receiving metronidazole by day 16. The number of stools required at each time point was not stated. Improvement in clinical symptoms was noted in 85% of tinidazole recipients versus 40% of metronidazole recipients. It is not made clear whether this was out of all enrollees or just those who were symptomatic upon entry.

  No effects were seen on blood and urine laboratory parameters obtained at entry and at last followup. Four tinidazole recipients complained of mild side effects (nausea, taste disturbances) and one of moderate side effect (vomiting). Two metronidazole recipients complained of mild gastrointestinal adverse effects.

***Medical Officer's Comment:** There were only 16 day followup so relapses may have been missed. In this study there must have been a moderately high rate of clearance asymptomatic cyst passers or else the overall results would have been affected. The lack of a description of the randomization method and a limited discussion of the improvement of symptoms are deficiencies in this study .*

- **Krishnamurthy 1978, India (190).** Open label randomized comparative study in 60 children aged 4 to 10with a mean age of 6 years. There were 34 males and 26 females enrolled. All were symptomatic at entry. Stool were assessed by formalin ether method but the number of stools evaluated at each time point was not described. Thirty received 50mg/kg tinidazole single dose and 30 received 50 mg/kg metronidazole as a single dose. Follow up was at 12 days. Parasitologic cure at 12 days was seen in 97% of the tinidazole group versus 50% of the metronidazole group. For patients excreting cysts only tinidazole cleared 10 out of 10 and metronidazole cleared 2 out of 8. For patients passing trophozoites only tinidazole cleared 11 out 12 and

metronidazole 11 out of 14. For patients excreting both cysts and trophozoites tinidazole cleared 8 out of 8 and tinidazole 5 out of 8.

More rapid symptom relief was experienced with tinidazole-at day 4, 70% of tinidazole patients were improved versus 23% of metronidazole patients. By day 12, 90% of tinidazole subjects were symptom free versus 63% of metronidazole subjects.

There was no data on side effects presented.

Medical Officer's Comment: *The randomization method was described as the first 30 patients receiving tinidazole followed by the next 30 patients receiving metronidazole. This is not a true randomization scheme. Followup was only 12 days. This was the shortest followup seen in any of the pivotal studies and so relapse would not be detected in this study. The strengths of the study were the examination of the differential clearing of cysts and trophozoites and the timing of the resolution of symptoms. The data presented indicate that the drugs are about equal in their ability to clear trophozoites .*

Additional Supportive Large Open Label Studies

The four trials listed and discussed briefly below were included as additionally supportive because they were either large, expanded the database in children, or compared shorter with longer regimens. Any of the other trials provided by the Applicant but not used as supportive either used a different dose, were not as well designed as the pivotal and supportive studies, and/or added no differing results to that already presented.

- **Suntornpoch 1981, Thailand (264)** Non randomized open label comparative study of 121 children given either a single dose of tinidazole 50mg/kg (48), a single dose of ornidazole 50mg/kg (40) or metronidazole 20mg/kg each day for 5 days (33). Response rates at 21 days were 94% tinidazole, 95% for ornidazole, and 97% for metronidazole. Side effects seen in 12.5% of tinidazole subjects, 27.5% of ornidazole subjects and 6% of metronidazole subjects.

- **Pengsaa 1999,Thailand (272)** Large randomized open label controlled trial in children comparing tinidazole 50 mg/kg in 51 children with albendazole 400m po gd for 3 days in 62 children. Parasitologic success in 96% of the tinidazole subjects and 50% of the albendazole subjects. Mostly mild side effects were reported in 38% of the tindazole recipients and 20.6% of the albendazole recipients ($p<0.05$)

- **Jokipii Finland 1987 (188)** Open label trial comparing single dose of 2g of tinidazole versus 150 mg po bid for 7 days of tinidazole. Nineteen adults received single dose and 26 received a week of therapy. Followup up was 8 weeks . Results revealed efficacy in the single dose tinidazole group of 92% and in the 7 day group was 74%.

- **Bouree 1982, France (124)** Open label non comparative single agent study in 400 subjects. Adults (310) received a 2 g single dose and children (90) received 50-70mg/kg single dose. Response was seen in 97% of adults and 89% of children. No side effects noted.

[redacted]

D. **Efficacy Conclusions**

Please see Table 1 below.

TABLE 1. Single Dose Tinidazole for Giardiasis

Study	Design	TNZ dose	TNZ Efficacy	MTZ dose	MTZ Efficacy	Follow up Period
Bakshi 1978	DB,R,C	50mg/kg	83/94 (88.3%)	50mg/kg	43/92 (46.7%)	16 days
Jokipii 1979	SB,R,C	2g	26/28 (92.9%)	2.4 g 2.4 g x 2 d	13/26 (50%) 24/31 (77.4%)	8 wks
Kryonseppa 1981	OL,R,C	2g	22/25 (88.0%)	2g x 2 d	19/25 (76.0%)	4 wks
Speelman #1 1985	OL,R,C	50 mg/kg	16/17 (94%)	60mg/kg	9/16 (56%)	4 wks
Speelman#2 1985	OL,R,C	50mg/kg	15/15 (100%)	50mg/kg x 3 d	14/15 (93%)	4 wks
Gadzer 1977	OL,R,C	2g	40/50 (80%)	2g	18/50 (36%)	16 days
Nigam 1991	OL,R,C	50mg/kg	39/40 (97.5%)	50 mg/kg	19/35 (54.3%)	16 days
Krishnamurthy 1978	OL,R,C	50mg/kg	29/30 (96.7%)	50mg/kg	15/30 (50%)	12 days
Jokipii 1982	SB,R,C	1.5g	45/50 (90%)	1.5 g*	45/50 (90%)	8 wks
Total Number of patients			349		370	

Comparator was Ornidazole
Adapted from data in NDAs 21,681

All of trials used the same definitions of success as defined by the WHO:
Cure: elimination of symptoms and clearance of stools of G. lamblia cysts and trophozoites;
Probable failure: persistence of symptoms despite negative stools; and
Failure: persistence of cysts or trophozoites in the stool. The standard of diagnosis for Giardiasis is to examine at least 2 if not 3 samples at entry and at all followup visits. Five of the studies did not mention how many samples were evaluated at each visit. One study requested 3 stools at each followup and 2 trials requested 2 studies at each followup. However, because of the variation and vagueness of the reported gastrointestinal symptoms in many of the trials, especially in the pediatric studies, the results presented are the parasitologic clearance rates.

The results show a parasitologic cure rate to a single dose of tinidazole of at least 1.5g to range from 80% to 100%. Single dose metronidazole produced parasitologic cure rates of 36% to 56%. However, parasitologic cure rates for metronidazole given for 2 to 3 days ranged from 76% to 93%. These results although not provided in such a way as to determine statistical significance suggest that single dose tinidazole performs better than single dose metronidazole. The difference in response for single dose tinidazole in comparison to multiday dosing of metronidazole is less pronounced, and close to comparable.

Followup longer than 30 days is provided in only two trials both by Jokipii from Finland. Since relapse may occur at later time points this is a deficiency in the data. However, the results in these 2 studies were consistent with the other studies of shorter duration implying that the relapse rate is relatively small. Other issues with trial design that deserve comment include blinding in only 3 trials-2 were single blind and the Bakshi trial though categorized by the Applicant as single blind clearly stated that the investigators evaluating the stools were blinded to treatment. All of the pivotal reports were randomized and comparative but the randomization methods were often not discussed or were simple alteration of therapy assignment..

Three of the trials (Bakshi, Gadzer, and Krishnamurthy) reported results on both the presence of cysts and trophozoites in the stool. Less than one third of the enrollees in these trials had trophozoites on entry. Krishnamurthy looked closely at clearance of cysts and/or trophozoites for tinidazole and metronidazole. Tinidazole cleared more infections in each group (cysts alone, trophozoites alone, and cysts and tropohzoites) but when cysts alone were present tindazole cleared all of 10 case versus 2/8 for metronidazole. In the 2 trials conducted by Speelman and the trial by Nigam approximately one third of the subjects were asymptomatic at entry with results ranging from 94% to 100%

Two of the trials Gadzer and Krishnamurthy compared the length of time required for symptomatic relief between tinidazole and metronidazole. Both reported a relative difference by day 4 in the reduction of diarrhea in the tinidazole patients compared to the metronidazole patients.

The remaining trials reported response rates for the 2g single dose of tinidazole between 86% and 100% providing further support for this dose in the treatment of Giardiasis as seen in Appendix II.

VII. Integrated Review of Safety

An integrated review of safety was performed by Dr. C Kraus.

VIII. Dosing, Regimen, and Administration Issues

The dose of tinidazole for the treatment of Giardiasis in adults is a single dose of 2 grams, and in children is a single dose of 50mg/kg. In children the tablets can be crushed and mixed with cherry syrup. The procedure for compounding is discussed at length in the clinical pharmacology review of this NDA.

IX. Use in Special Populations

A. Evaluation of Applicant's Gender Effects Analyses and Adequacy of Investigation

In the 8 pivotal and supportive studies 425 enrollees were male and 308 were female. Analyses of response by gender was not provided in any of the considered studies. No difference in response by gender was expected.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. AGE

Giardiasis is a primarily disease of both children and young adults. In the pivotal studies approximately half of the enrollees were under the age of 12 (384 out of 719). In the pediatric studies the age ranges were mostly from 3-11 with mean ages of 5 to 6 years of age. Separate analyses comparing response by age were not performed The response rates in the 4 of 8 pivotal studies which enrolled children were 88.3% to 100%, similar to the response rates in 4 adult pivotal studies which ranged from 80% to 97%. There were no more than 1 or 2 patients per study over the age of 60. Since this is primarily a disease of younger individuals a lack of data in the geriatric population is not very concerning but would be useful information to gather to expand the safety profile of this agent. This is especially pertinent in the United States where much Giardiasis is acquired overseas and a large proportion of the traveling population is over 65.

2. RACE or ETHNICITY

No racial or ethnic background was provided in any of the studies examined. However, certain inferences can be made by the country of origin of the study. Four were performed in India, 3 in Finland and one in expatriates in Bangladesh. There was a supportive study by Apte where trials were performed in several Southeast Asian countries providing efficacy and safety data in individuals of oriental background.

C. Evaluation of Pediatric Program

PLEASE SEE B.1 ABOVE UNDER THE DISCUSSION OF AGE

D. Comments on Data Available or Needed in Other Populations

There are 3 populations where further efficacy and safety data would add to an understanding of the risks and benefits of tinidazole therapy in the treatment of Giardiasis;
1-very young children from 6 months to 3 years;
2-geriatric population (especially travelers); and
3-individuals of black African descent.

X. Conclusions and Recommendations

A. Conclusions

1.Single dose tinidazole (2g/d in adults and 50mg/kg in children) is efficacious in the treatment of Giardiasis in chidren and adults with response rate ranging from 80 to 100%

2.Single dose tinidazole (2g/d or 50mmg/kg) is superior to single dose metronidazole (2g/d or 50mg/kg) in the treatment of Giardiasis

3. Single dose tinidazole (2g/d or 50 mg/kg) is probably comparable in efficacy to the usually recommended doses of metronidazole (by *The Medical Letter* not approved by the USFDA) in the treatment of Giardiasis although sufficient data to confirm this statement are limited.

4.There are not sufficient data to determine if there is any difference in relapse rate between tinidazole and metronidazole.

5. [redacted]

B. Recommendations

1. Tinidazole 2g po once in adults and 50mg/kg once in children should be approved for the treatment of Giardiasis.

2. [redacted]

3. [redacted]

4. Additional data should be obtained on the use of tinidazole in children under the age of 3, in the geriatric population, and black African patients with Giardiasis.

Appendix I

Bibliography

Below is a listing of the studies referred to in this review. They are listed in alphabetical order. The number preceding each entry is the reference number from the Applicant's submission and are included for ease of location for any future review of the original application.

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Appendix II

This is a listing as provided by the Applicant of all of the Studies submitted for review In NDA 21,681.

11.2.3.1. Tinidazole Use in Giardiasis: Synopsis of all identified reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Andersson, 1972[186]	Sweden	tin - 150mg BID x 7 (n=24 patients, 10 healthy volunteers)	open-label (microscopic exam of 3 stools)	34 adults	few days, 1 and 2 months	24/24 (100%)	none reported in patients or controls
Pettersson, 1975[122]	Finland	tin - 2g single dose (n=53 adults) 1g single dose (n=9 children)	open-label (microscopic exam of 2 stools)	53 adults 9 children	1, 4-6 and 6-16 weeks	90% (overall)	15% (all minor)
Danzig, 1977[120]	South Africa	tin - 500mg - 1.5g (age-dependent)	open-label (exam of 2 stools)	38 children	8 and 22 days	35/38 (92%)	4/38 (10.5%)
Levi, 1977[125]	Brazil	tin - 150mg BID x 7 (n=30) mtzl - 125mg BID x 7 (age 1-5 yrs) 125mg TID x 7 (age 6-10 yrs) 250mg BID x 7 (age >10 yrs) (n=38) furazolidone - 8mg/kg/day TID x 7 (n=53) nimorazole - 125mg BID x 5 (age 1-5 yrs) 125mg TID x 5 (age 6-10 yrs) 250mg BID x 5 (age >10 yrs) (n=51) control - (n=23)	comparative (zinc sulfate flotation exam of 3 stools)	172 adults and children	7, 14, 21 days	tin: 96.7% mtzl: 86.9% furaz: 71.7% nim: 94.1% control: 34.8%	tin: 0% mtzl: 11.4% furaz: 18.2% nim: 14.3%

11.2.3.1. Tinidazole Use in Giardiasis: Synopsis of all identified reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Salih, 1977[123]	Sudan	tin - 150mg BID x 7 (n=21) 1g single dose (n=12)	open-label (microscopic exam of stool)	33 adults	1-2 weeks	7 day: 21/21 (100%) single dose: 11/12 (92%)	7 day dose: 5/21 single dose: 0
Gadzer, 1977[128]	India	tin - 50mg/kg single dose (n=50 children) mtzl - 50mg/kg single dose (n=50 children)	randomized, comparative (microscopic stool exams)	100 children	4, 8, 12, 16 days	tin: 40/50 (80%) mtzl: 18/50 (36%) p<0.01	tin: 6/50 (12%) mtzl: 2/50 (4%) no effect on blood chem. pts admitted for observation
El Masray, 1978[187]	Egypt	tin - 2g (n=55) placebo (n=20)	3 stool spec. (concentration) Comparative	55 51M,4F adults & children +20 controls	3-5 wk	tin: 53/55 (96%) placebo: 2/20 (10%)	no side effects noted
Welch, 1978[115]	Australia	mtzl - 200mg BID x 5 (n=20) tin - 1000-1500mg - single dose (n=21) tin - 1000-1500mg x 3/d (n=14) control - (n=1)	comparative (3 stool exams)	56 aboriginal children 6-9 yrs	7, 14, 21 days	mtzl: 16/20 (80%) tin - single dose: 19/21 (90%) tin - x 3/d: 14/14 (100%)	none noted with either drug
Bakshi, 1978[118]	India	tin - 50mg/kg - single dose (n=94 children) mtzl - 50mg/kg body wt - single dose (n=92 children)	single blind, randomized, multi-center (stool exam)	186 children	4, 8, 12, 16 days	tin: 88% mtzl: 47% p<0.01	tin: 8.5% mtzl: 2.2% (all mild) no abnormal urine or blood chem.

11.2.3.1. Tinidazole Use in Giardiasis: Synopsis of all identified reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Apte, 1978[94]	India	tin - 50mg/kg - single dose (n=74 children)	open-label, multi-center (stool exam)	74 children	15-90 days	88%	12.2%
Jokipii, 1978[188]	Finland	tin - 150mg BID x 7 (n=19) tin - 2g single dose (n=26)	open-label (3 stool exams, iodine F.E. conc.)	45 adults (14 M, 31 F)	daily for 7d, 2, 4, 8 weeks	tin, 7 days: 74% tin, single dose: 92%	38% of all patients
Farahmandian, 1978[189]	Iran	tin - 50mg/kg, 2g max (n=175) controls (no trmt.) (n=35)	open-label, 3 consec. stools (mer. iodine for. conc.)	175 children and adults + 35 controls	4 days	tin: 94.5% (156/165) control: 10% (3/30)	tin: 13% mild, GI
Krishnamurthy, 1978[190]	India	tin - 50mg/kg (n=30 children) mtz - 50mg/kg (n=30 children)	open-label, randomized, comparative	60 children	4, 8, 12 days	mtz: 50% (15/30) tin: 97% (29/30)	
Jokipii, 1979[126]	Finland	mtz - 2.4g single dose (n=26) 2.4g x 2/d (n=31) tin - 2g single dose (n=28)	single blind, alternate patient, comparative (microscopic stool exam)	85 adults	1, 2, 4 & 8 wks	mtz: 50% (13/26) mtz 2 doses: 74% (24/31) tin: 93% (26/28) vs mtz x 1d $p<0.001$ vs mtz x 2d p=NS	mtz 1 dose: 92% mtz 2 doses: 90% tin: 75% (all mild)

11.2.3.1. Tinidazole Use in Giardiasis: Synopsis of all identified reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Sabchareon, 1980[130]	Thailand	quinicrine - 100mg TID x 5 (n=20) mtz - 200mg TID x 7 (n=20) mtz - 2g single dose (n=21) tin - 2g single dose (n=21) ornid - 2g single dose (n=22) placebo - (n=20) Note: doses adjusted to body surface area	open-label, comparative (microscopic exam of stools daily)	124 children	30 days	quinicrine: 100% mtz, 7 days: 60% mtz, single dose: 52% tin: 86% ornid: 95% placebo = 0	numbers not reported
Kryonseppa, 1981[131]	Finland	mtz - 2g x 2/d (n=25) tin - 2g single dose (n=25)	comparative, randomized (stool exam)	50 adults	2, 4 wks	mtz: 76% tin: 88% p=NS	mtz: 7/25 (28%) tin: 5/25 (20%)
Bouree, 1982[124]	France	tin - 2g single dose (n=310 adults) 50-70 mg/kg, single dose (n=90 children)	open-label	310 adults 90 children		97% adults 89% children	none noted
Jokipii, 1982[121]	Finland	tin - 1.5g single dose (n=50 adults) ornid - 1.5g single dose (n=50 adults)	single-blind, randomized, comparative (microscopic stool exam)	100 adults	1, 2, 4, 8 wks	tin: 90% ornid: 90%	#'s orn. / tin lassitude 21 / 29 dizziness 35 / 10 bitter taste 3 / 17 nausea 2 / 5 other 5 / 9 none 7 / 7

11.2.3.1. Tinidazole Use in Giardiasis: Synopsis of all identified reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Speelman, 1985[127]	Bangladesh	Trial #1: mtz - 60mg/kg (n=16) tin - 50mg/kg single dose (max 2g) (n=17) Trial #2: mtz - 50mg/kg (max 2g/d) (n=15) tin - 50mg/kg single dose (max 2g) (n=15) (children given syrup)	single-blind, randomized, comparative (4 micro-scopic stool exam FE conc.) (expatriates)	#1 - 33 12 adults & 21 children #2 - 30 13 adults & 17 children	4 wks	#1 - mtz: 56% tin: 94% p<0.02 #2 - mtz: 93% tin: 100%	#'s mtz / tin met.taste 4 / 0 nausea 3 / 1 vomiting 1 / 1 headache 2 / 1 dizziness 3 / 1 anorexia 1 / 2 none 8 / 5 problems administering syrup 0 / 5
Bassily, 1987[114]	Egypt	mtz - 500mg/d x 10 days (n=20) tin - 2g single dose (n=30) ornid - 1g single dose (n=30)	comparative (3 stool exams)	80 adults	3 wks	mtz: 95% tin: 90% ornid: 97%	no side effects reported
Nigam, 1991[191]	India	tin - 50mg/kg (n=40) mtz - 50mg/kg (n=35)	randomized, comparative (3 stool exams FE conc.)	75 children & adults avg. age=20	4, 8, 12, 16 days	tin: 97% mtz: 54% p<0.01 symptom improv. w/tin within 2-4d	tin: 12.5% mtz: 5.7% 1 pt on tin required domperidone for vomiting No change in blood/urine
Suntornpoch, 1981 [264]	Thailand	tinidazole - 50mg/kg (n=48) ornid - 50mg/kg (n=40) mtz - 20mg/kg x 5 days (n=33)	comparative open label	121 children	7, 14, 21 days	tin: 94% ornid: 95% mtz: 97%	tin: 6/48 (12.5%) ornid: 11/40 (27.5%) mtz: 2/33 (6%)

11.2.3.1. Tinidazole Use in Giardiasis: Synopsis of all identified reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Pengsaa, 1999 [272]	Thailand	tinidazole - 50mg/kg (n=51) albendazole - 400mgQD x 3 days (n=62)	randomized, controlled	113 children	1 - 2 weeks	tin: 49/51 (96%) albend: 31/62 (50%) p<0.001	tin: 24/63 (38%) albend: 14/68 (20.6%) (p<0.05)

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

/s/

Maureen Tierney
5/17/04 02:12:18 PM
MEDICAL OFFICER
Giardiasis NDA 21,681 and NDA 21,792

Leonard Sacks
5/17/04 02:27:07 PM
MEDICAL OFFICER

Renata Albrecht
5/17/04 05:26:09 PM
MEDICAL OFFICER

Edward Cox
5/17/04 07:08:51 PM
MEDICAL OFFICER

Medical Officer's Review
Of
NDA 21, 682
Tinidazole

Amebiasis Indication

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Tinidazole should be approved for the treatment of intestinal amebiasis and amebic liver abscess in adults and children over 3 years of age. The extensive literature database and postmarketing experience worldwide have shown that tinidazole is safe and effective in the treatment of these conditions.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no specific recommendations for Phase 4 studies. Further information on the safety and efficacy in pediatric patients under the age of 3 and in all children treated with the 5 day course for amebic liver abscess may be pursued as required by other regulations.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

There was no active clinical research program. Support for this indication was derived from the medical literature and the approval of this agent in many countries around the world. The 26 published articles on the use of tinidazole in the treatment of intestinal amebiasis studied 2200 patients 1400 of whom were treated with tinidazole. The 18 trials in the literature examining tinidazole's effectiveness in amebic liver abscess evaluated over 700 patients with approximately 500 patients receiving tinidazole.

B. Efficacy

Intestinal Amebiasis

There were 26 published clinical reports on the use of tinidazole in the treatment of intestinal amebiasis submitted. These trials included approximately 2200 patients and about 1400 were treated with tinidazole. Nine of the trials were randomized and eight of these were metronidazole comparative. Four of these trials utilized the proposed tinidazole dose of 2 grams once daily for 3 days and therefore these four studies were chosen as the pivotal studies. One of these studies was categorized as single blind, the rest were not blinded. The one blinded study noted that the investigators reading the stools were not aware of the treatment of the patients but it is not mentioned if the patients were aware of their treatment status. Therefore this may actually be a double blind study. These studies enrolled 376 adults with a mean age in the low thirties, 255 men and 121 women. The results of these pivotal studies are included in the table below.

TABLE 1: PIVOTAL STUDIES INTESTINAL AMEBIASIS

Study	TNZ Efficacy 2g/d x 3d	MTZ Efficacy 2g/d x 3d	Study Design	Measure of Cure	Sigmoid-oscopy	Follow-up Period
Swami* (197)	25/29 86.2%	8/27 29.6%	OL,R,C	Complete resolution of symptoms; Stools -	"Wherever possible"	4,20,30 days
Singh (196)	25/27 92.6%	17/29 58.6%	OL,R,C	Complete resolution of symptoms; Stools -	"Wherever possible"	4,20,30 days
Misra (194)	27/30 90%	16/30 53.3%	OL,R,C	Complete resolution of symptoms; stools-	All patients	5,20,30 days
Bakshi (118)	123/134 91.7%	66/123 53.6%	DB,R,C	Near complete resolution of symptoms; Stools -	Not mentioned	4,20,30 days
Total	220	209				

Adapted from Tables on p11-90 and 11-95 of submission of NDA 21,682

***Efficacy results differ from Applicant's table-see text for explanation**

The first 3 trials in the table above utilized the same definitions of success and failure: cure was defined as elimination of cysts and trophozoites from the stool and sigmoidoscopy samples and clearance of symptoms; probable failure was

defined as negative stool parasitological exams but with some persistence of symptoms; and failure was defined as persistence of cysts or trophozoites in the stool. These 3 trials also utilized sigmoidoscopy in many of their enrollees with followup sigmoidoscopy in all those with abnormal screening examinations. Misra required sigmoidoscopy of all entrants. In the trial by Bakshi cure was defined as negative stool examination with near elimination of symptoms. No sigmoidoscopy evaluations were done in the Bakshi trial but its size and the blinding of its investigators to treatment made it an important trial to evaluate.

All of the trials utilized the same followup periods of 4 or 5 days, 20 days and 30 days post therapy. A cure was achieved if stools and sigmoiosdcopy specimens were negative 30 days and the patient was free (or in the case of Bakshi nearly free) of abdominal symptoms. All patients were symptomatic upon entry with similar symptom lists in all the studies (diarrhea, bloody diarrhea, abdominal pain, tender abdomen on exam, distention, vomiting, etc). Only 2 of these studies presented data on the severity of symptoms in the different groups upon entry. Only the trial by Misra provided information on the numbers of acute (less than 15 days) and chronic (15 days or longer) upon entry in each group (about 1/3 in each group were acute and 2/3 chronic) but did not provide data on results with reference to the chronicity of the infection. Swami, however, did provide data on the response relative to disease severity. See below.

Table 2. Disease Severity and Response-Swami Study

	Tinidazole # Cured	Metronidazole # Cured
Dysentery	19/20	13/22
Non-dysentery	9/9	2/5

In the pivotal trials of intestinal amebiasis 2g qd x 3 d of tinidazole versus 2g qd x 3d of metronidazole, tinidazole was shown to have cure rates ranging from 86.2% to 92.6% in comparison to 29.6% to 58.6% in the metronidazole arms. In the Swami study where a cure rate of 29.6% was achieved in the metronidazole arm additional days of therapy produced a cure rate of 15/27 or 55.5%. The Bakshi trial had 2 additional arms looking at tinidazole 600mg po bid x 5 days and metronidazole 400 mg po tid for 5 days and the reported cure rates were 87% for tinidazole 5 days and 67% for metronidazole 5 days.

Two of the studies, Swami and Bakshi, looked at the percentages of cysts and trophozoites in the tinidazole and metronidazole groups at entry . In the Swami study only 4 out of 30 in each group had trophozoites in the stool. Results were not reported with regards to the form of *E.histolytica* in the stool. The Bahkshi trial looked at the differential rates of clearing of cysts and trophozoites in its 4 arms. Please see below.

Table 3. *E. histolytica* Cysts and Trophozoites In Stool and Success Rates (Bakshi Trial)

Drug	Dose	Number evaluated	Success in those passing cysts	Success in those passing trophozoites	Success in all patients
TNZ	0.6g bid x 5d	100	52/64 (81.2%)	35/36 (97.2%)	87%
MTZ	0.4g tid x 5d	79	53/63 (84.2%)	14/16 (87.5%)	67%
TNZ	2.0g od x 3d	134	85/91 (93.4%)	38/43 (88.3%)	91.7%
MTZ	2.0g od x 3d	123	44/93 (47.3%)	22/30 (73.3%)	53.6%

Adapted from Tables III,IV,andV Bakshi 1978 Source 118.

The pivotal studies did not include children but two of the studies chosen as supportive were studies in pediatric patients. In the studies reported by Apte and Salles parasitologic cure rates were seen in 95% and 96% respectively. Parasitologic cure rates were used because of less reliable symptom histories in this age group.

All of the remaining studies utilizing a 2g/d x 3 days of tinidazole reported response rates over 90% except for the report by Chunge. This was a 4 armed study to decide the relative efficacies of generic and brand name forms of metronidazole and tinidazole. This study was performed at 3 hospitals in Kenya where patients with "luminal amebiasis" were enrolled. Enrollment criteria required symptoms but many of the symptoms were vague and diarrhea was not required. The best parasitologic cure rate was 51% for Fasigyn (a brand name product by Pfizer of tinidazole.) The discrepancy in results with the other studies most likely arises from the inclusion of those without true intestinal amebiasis.

One of the nonpivotal studies by Pehrson performed in Sweden enrolled only asymptomatic patients. No data was provided on the whether trophozoites were seen in addition to cysts in the stool. One month after receving tinidazole 600mg po bid for 5 days 14/14 still were passing cysts. At the same followup 9 of 16 subjects who had received metronidazole 800mg po tid for 5 days were still excreting cysts.

Amebic Liver Abscess

There were eighteen trials in the literature identified by the Applicant evaluating the use of tinidazole in the treatment of amebic liver abscess. Nine of these were randomized comparative studies. The seven randomized studies utilizing the 2g/d for 2d, 3d, or up to 5 days were selected as the pivotal studies. Two of these trials were blinded. Simjee was single blind and Mendis was double blind. The 7 pivotal trials enrolled 272 patients. Enrollment by gender was available for only 190 patients of whom 10 were female and the rest male. Ages of enrollees ranged from 11 to 60 with mean ages for the studies ranging from 35 to 41. There were

no racial enrollment characteristics mentioned except for the Simjee trial performed in South Africa where all enrollees were black. All the other trials were performed in India or Bagladesh. No pivotal trials enrolled children but one of the supportive studies, Scragg, enrolled 25 children in South Africa all described as African children ranging in age from 5 months to 6 years with a median age of 15 months.

The results of the pivotal trials are included in the table below.

TABLE 4. PIVOTAL STUDIES AMEBIC LIVER ABSCESS

Study	TNZ Dose	TNZ Efficacy	MTZ Dose	MTZ Efficacy	Diagnosis Anchovy Pus Required	Response Measurement
Kundu (297)	2g/d x 3d	8/9 (88%)	2g/d x 3d	3/9 (33%)	Yes	Excellent, good, fair, poor-excellent or good considered cure
Islam (296)	2g/d x 3d	15/16 (94%)	2g/d x 3d	12/15 (80%)	No	Not clearly stated
Kokhani (119)	2g/d x 2d	10/10 (100%)	2g/d x 2d	5/9 (56%)	Yes	Clinical and radiological improvement
Mather (198)	2g/d x 2d	11/12* (91.7%)	2g/d x 2d	10/11 (91%)	Yes	Same as Kundu
Bakshi (118)	2g/d x 2d	48/50 (96%)	2g/d x 2d	37/49 (76%)	Yes	Complete versus incomplete
Simjee (302)	2g/d x 5d	17/21 (80%)	2g/d x 5d	25/27 (93%)	Yes (also serology)	Not clearly stated
Mendis (299)**	**2g/d x 3d**	**16/16 (100%)**	**400mg tid x5d**	**14/18 (77.8%)**	**No**	**Rapid, intermediate, slow**
Total		**134**		**138**		

*Denominator different from presented in Applicant's review-the Division felt one subject removed incorrectly. Adapted from Table on p.11-105 of NDA 21,682

**Results differ from Applicant-see text for explanation

Amebic liver abscess is a much less common illness than intestinal amebiasis and therefore the number of enrollees in the 7 pivotal trials is limited to only 272. Since most of these trials were performed over 20 years ago the diagnostic criteria did not include ultrasound in any of the studies and serology was only obtained in the study by Simjee. The other 6 studies utilized clinical and radiographic criteria such as fever, enlarged tender liver, raised right hemidiaphragm, fluoroscopy, etc. to determine diagnosis and clinical improvement. All the trials except Islam and Mendis required aspiration of typical anchovy like pus to confirm the diagnosis.

Final follow-up for all the studies was at 30 days. A variety of response measurement patterns were reported such as rapid, intermediate or slow; complete versus incomplete; or excellent, good, fair or poor. However, all of these have in common that all symptoms and clinical signs must indicate cure by 30 days to be considered a success. The ranges of success for tinidazole 2g/d for 2d, 3d or 5d was 80 to 100% and that for metronidazole was 33 to 91%. Metronidazole was given as 2g/d for 2,3 or 5 days in 6 of the studies but in Mendis was 400mg po tid for 5 days.

All of the trials utilized aspiration of the liver abscess for diagnosis or therapeutic intervention or both. Two of the trials by Khokani and Islam evaluated the number of times aspiration was required in the different arms. In Islam a similar number of aspirations were required in the tinidazole and metronidazole groups. However, in Khokani only 2 out of 10 tinidazole patients required more than 1 aspiration whereas 6 out 9 metronidazole patients required multiple aspirations. Kundu and Simjee looked at the sizes of abscess based on the volume of the initial aspirations which was similar across groups. No data on response according to size was provided; however, in the Kundu discussion section it is stated that tinidazole did well in the treatment of small to medium abscesses but not as well with large abscesses. No statement about size and response to metronidazole is made. Mendis reports that the average time to symptom clearance was 5.6 days in the tinidazole group in comparison to 7.4 days for tinidazole.

All of the remaining studies reported response rates for the 2g/d x 3d dose of tinidazole of greater than 90%.

The study by Scragg provided information on the use of tinidazole in the treatment of amebic liver abscess in children. Ten children received 5 days of tinidazole therapy and 15 received 3 days of tinidazole therapy. Two patients failed therapy. Both were 11 month old infants who developed secondary pneumonia-one died and the other was successfully treated with surgery and other therapy. All the other children were treated and tolerated the therapy well.

The data provided might support a dose of 2g/day for 2 to 5 days as well as 3 to 5 days. The rationale for supporting the 3 to 5 day regimens as proposed by the Applicant are twofold. One is the occasional concomitant occurrence of intestinal amebiasis and liver abscess and the other is to be consistent with most of the approvals worldwide.

Approval is requested for children 3 years of age. However, the one supportive study in amebic liver abscess in children by Scragg described above had a mean age of 15 months. This study suggests that amebic liver abscess may occur more frequently as a complication of intestinal amebiasis in the very young. Consequently further study of the safety of the 5 day regimen in these very young patients would be valuable.

C. **Safety:**

Please refer to the safety review by Dr. Carl Kraus

D. **Dosing**

Intestinal amebiasis: 2g/d for 3 days in adults
50mg/kg/d for 3 days in children over 3 years of age

Amebic liver abscess: 2g/d for 3-5 days in adults
50mg/kg/d for 3-5 days in children

E. **Special Populations**

Intestinal Amebiasis

The age range of the enrollees in the 4 pivotal trials was 16 to 60 with the mean ages in these trials varying from 29 to 33. In these trials 376 patients were enrolled at the 2g doses for 3 days for tinidazole and metronidazole, 255 men and 121 women. In the Bakshi trial an additional 150 men and 50 women were administered lower doses and longer durations of therapy of either agent. There were no racial breakdowns provided as all the trials were performed in India. Scragg and Apte provided data on the use of tindazole in approximately 550 children from India, Bangladesh, Korea, the Philippines and Indonesia.

Amebic Liver Abscess

The 7 pivotal trials enrolled 272 patients. Enrollment by gender was available for only 190 patients of whom 10 were female and the rest male. Ages of enrollees ranged from 11 to 60 with mean ages for the studies ranging from 35 to 41. There were no racial enrollment characteristics mentioned except for the Simjee trial performed in South Africa where all enrollees were black. All the other trials were performed in India or Bangladesh. No pivotal trials enrolled children but one of the supportive studies, Scragg, enrolled 25 children in South Africa all described as African children ranging in age from 5 months to 6 years with a median age of 15 months.

Clinical Review

I. Introduction and Background

A. **Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups**

a. Identifying Information:

Applicant: Presutti Laboratories
1607 N Douglas Ave.
Arlington Heights, Ill. 60004

Date of Submission: July 15, 2003
CDER Stamp Date: July 17, 2003
Date Received by MO: July
Date Review Completed:

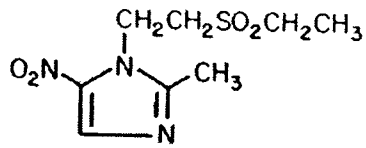
Generic Name: Tinidazole

Laboratory code: CP 12,574

Proposed Trade Name: Tindamax™

Chemical Name: 1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole

Chemical structure:



Molecular Formula and Weight: $C_8H_{13}N_3O_4S$. 247.28

Pharmacologic Category: 2-methyl-5-nitroimidazole

Dosage Form: 250 and 500 mg Tablets

Route of Administration: Oral

Related Drugs: Metronidazole, Ornidazole, Secnidazole

B. Proposed Indications and Dosages:

Intestinal Amebiasis: 2 grams daily for 3 days for adults
50 mg/kg(max 2g) daily for 3 days for children

Amebic Liver Abscess: 2 grams daily for 3 to 5 days for adults
50 mg/kg (max 2g) daily for 3 to 5 days for children

B. Summary and State of Armamentarium for Indication(s)

There are three different clinical presentations of amebiasis: intestinal, and extraintestinal. The treatment for the 3 different clinical syndromes differs.

Tissue invasive disease can be categorized as intestinal and extraintestinal. Most of the extraintestinal amebiasis is hepatic. The drugs of choice according to *The Medical Letter* for mild to moderate intestinal amebiasis are metronidazole and tinidazole. The recommended metronidazole dose is 500-750 mg po TID for 7 to 10 days. The recommended tinidazole dose is 2 grams divided tid po for 3 days. For severe intestinal or hepatic amebiasis *The Medical Letter* recommends metronidazole 750 mg po tid for 7 to 10 days or tinidazole 800 mp po tid for 5 days. Hepatic amebic abscesses may also require surgical drainage.

C. Important Milestones in Product Development

Please refer to Dr. Alivisatos' review of NDA 21,618 of tinidazole for trichomoniasis for a more extensive discussion of the history of the product development of tinidazole in the United States.

The applicant initially submitted a PRE-IND requesting comments regarding their plan to submit an IND followed by an NDA for the use of tinidazole for the treatment of trichomoniasis and giardiasis. The original pre-IND submission consisted of a briefing document that contained 200 references as well as copies of selected articles regarding the clinical use of tinidazole for trichomoniasis and giardiasis as well as the toxicology and pharmacokinetics of the compound.

IND 62,292 was submitted on April 4, 2001 (CDER stamp date April 6, 2001). The submission consisted of an outline for a bioequivalence study as well as literature based summaries of clinical trials used for trichomoniasis and giardiasis.

On June 19, 2003 the sponsor requested orphan drug designation for tinidazole in the treatment of amebiasis. This request was granted by the Office of Orphan Products Development of the USFDA on August 20, 2003

D. Other Relevant Information

Tinidazole is approved for use in the UK, Australia, Austria, Belgium, Costa Rica, El Salvador, Finland, France, Germany, Guatemala, Honduras, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, South Africa, Spain, Sweden, and Switzerland. In the UK it is approved for the following indications: urogenital trichomoniasis; giardiasis; intestinal amoebiasis; amoebic liver abscess; non-specific vaginitis; prevention of postoperative infections; treatment of anaerobic infections; acute ulcerative gingivitis; and for the eradication of *Helicobacter pylori* associated duodenal ulcers. The maximum approved total dose is 12 grams in liver abscess or intraabdominal infection and the maximum approved total duration of treatment is 6 days.

The approved dosage regimens for intestinal amebiasis are 2g/d (and 50-60mg/kg/d for children) for 2-3 days in UK, South Africa, Belgium, Netherlands, Spain, Switzerland, and Australia. In several of the countries approval also extends therapy for additional days should that clinically be warranted and in Spain adults may also be treated with 500 mg po bid for 5-10 days. In Sweden approval is only granted for adults at 2g/d for 3 days. In Germany the adult dose is 2g/d for 3 days but the pediatric dose is 1g/d for 3 days. In France the approved dose is 1.5g/d for 4 to 5 days for adults only.

The approved dosage regimens for amebic liver abscess are 1.5-2g/dfor 3 days (may be continued for up to 5 to 6 days) and 50-60mg/kg/d for 5 days in children in UK, South Africa, Belgium, Netherlands, Spain (can also use 500mg po bid in adults), France (only in adults) and Switzerland. In Germany, Sweden, and Australia the adult approved dose is 2g/d for 3 days with allowance for up to 5-6 days. In Germany the pediatric dose is 1g/d for 5 days and in Australia it is 50mg/kg/d for 5 days.

E. Important Issues with Pharmacologically Related Agents

Tinidazole is a nitroimidazole, closely related to metronidazole. It is the applicant's position that given the extensive worldwide use of tinidazole for the requested indications, the repetition of preclinical and clinical trials in the US would be of no added value. Proposed product labeling includes all relevant potential safety and adverse event information included in the metronidazole label. A brief review of metronidazole and safety issues associated with its use is presented below:

Review of Metronidazole: Mayo Clin Proc, August 1999, Vol 74; page 82: Metronidazole is a synthetic drug that enters cells by passive diffusion and is activated by a reductive process. This produces short-lived metabolites that damage bacterial DNA and lead to cell death. This occurs

regardless of the growth phase of the organism and thus there is activity against non-dividing organisms. This process requires a low oxidation-reduction potential and explains why metronidazole is active against anaerobes and less against aerobes. Oral absorption is almost 100% and is not affected by food whereas vaginal absorption is very poor. The drug is metabolized by the liver into several compounds and ultimately metronidazole and it metabolites are excreted primarily in the urine. In general it is well tolerated. The most serious AEs involve the CNS although they are rare unless large doses are used or treatment is prolonged. Metronidazole can cause seizures, encephalopathy, cerebellar dysfunction and peripheral neuropathy. The latter is usually reversible after discontinuation of treatment although resolution may require a prolonged period. The other CNS effects usually resolve with treatment discontinuation.

Metronidazole usage has been associated with C. difficile colitis as well as with pancreatitis. More common GI AEs include nausea, diarrhea, a metallic taste, stomatitis, and a dry mouth. Reversible neutropenia, dark urine, burning of the vagina or the urethra and C albicans overgrowth can occur. ETOH consumption while taking the drug can lead to a disulfiram-like reaction.

Metronidazole can inhibit the metabolism of warfarin and will prolong the prothrombin time in patients on coumarin-type anticoagulants.

Concerns exist that metronidazole may promote the development of cancers in humans and mutagenicity has been demonstrated in the Ames salmonella mutant system. There is tumorigenic activity in mice and rats and the long term effects of high-dose prolonged therapy have not been studies in humans.

There are also concerns that metronidazole may be teratogenic although there appears to be little evidence of this in animal models and no increases in stillbirths or teratogenicity have been seen in pregnant women taking the drug. Use of metronidazole is contraindicated during the first trimester of pregnancy and during breastfeeding.

The pharmacokinetics of tinidazole in patients with severe renal impairment (CrCL < 22 mL/min) are not significantly different from the pharmacokinetics seen in healthy subjects. Therefore, no dose adjustments are necessary in patients with severe renal impairment. However during hemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from approximately 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. Thus, if tinidazole is administered on a day when dialysis is performed, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the hemodialysis. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis (CAPD) has not been investigated.
There is no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies. In the absence of data on tinidazole, usually recommended doses should be administered cautiously in such patients receiving tinidazole.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Pharmacology/Toxicology:
The MO defers to the pharmacology reviewer for comment. A brief synopsis is provided below:

Single-dose toxicity studies:

Tinidazole is reported to have an oral LD50 of > 3600 mg/kg in mice and > 2000 mg/kg in rats. The applicant also references intraperitoneal and subcutaneous acute dose toxicity studies in these species.

Repeat-dose toxicity studies:

In rats tinidazole dosed up to 300 mg/kg/day for 30 days produced no clinical signs of toxicity or findings at necropsy. LD was established at 1000 mg/kg. No changes were seen in the hematology and chemistry profiles of the rats but hepatomegaly with hyperplasia and softening of the testes with inhibition of spermatogenesis were noted. At 500 mg/kg, cecal enlargement was seen. Similar findings were found in rats treated with metronidazole at doses > 125 mg/kg.

A 15 day study of oral tinidazole 150 mg with oxyphenonium bromide 1 mg is also referenced. There were no behavioral, neurological, somatic, or laboratory changes.

Dogs treated orally with daily doses of 450 and 100 mg/kg respectively of tinidazole and metronidazole for 30 days revealed no toxicity. At the highest dose 2 of 8 dogs had a dose dependent increase in alkaline phosphatase associated with liver alterations (not specified).

Monkeys receiving oral doses of up to 300 mg/kg/day for 30 days had no clinical findings or signs at necropsy.

The applicant also referenced 6 month studies of doses up to 600 mg/kg/day orally in rats and up to 1 year studies in dogs. In the dogs, muscle rigidity and tremors were seen at dose of 75 mg/kg/day and above.

Genetic Toxicology:

The applicant referenced multiple segment I, II, and III studies. Specifically for segment I (mating and fertility), at doses of 150 mg or 300 mg/kg/day for 20 days in the rat, there were no effects at the 150 mg/kg dose and a small decrease in mating and fertility at the higher dose. As noted above in a chronic 4 week study in rats at doses ranging from 125 – 4000 mg/kg PO in rats there was a decrease in spermatogenesis at doses ≥ 1000 mg/kg. These changes resolved after the drug was stopped and were similar to changes induced by metronidazole at doses of ≥ 500 mg/kg. Additionally in a 26 week rat study of doses ranging between 60 – 600 mg/kg/day PO a decrease in spermatogenesis was seen.

In a 4 week dog study of oral tinidazole compared to oral metronidazole (doses not specified), no effects were seen on testicular histology.

Finally the applicant referenced a 5 day mouse study of 200 mg/kg IP of tinidazole versus 400 mg/kg of metronidazole and noted no effect on sperm number or morphology or on testicular weight.

For segment II (embryo-fetal development) the applicant referenced multiple studies in mice, rats, and rabbits. In the mouse at doses of 125 – 250 mg/kg/day PO, there were no fetal or maternal abnormalities on days 7 – 12. Similarly at doses of 100 or 300 mg/kg PO/day in the rat, no effect was seen in fetuses at days 6 – 15. However at doses of 600 mg/kg, there was fetal mortality without abnormalities after 7 – 14 days and at 2000 mg/kg doses there was also maternal mortality.

In rabbits at doses up to 300 mg/kg there were no fetal abnormalities but there was fetal mortality.

For segment III (perinatal development) the applicant referenced 1 study in rats of 150 or 300 mg/kg PO that revealed no effect on fetal viability or growth and development on days 1 – 20.

Special Toxicity Studies:

The applicant referenced multiple carcinogenicity and mutagenicity studies. Tinidazole is mutagenic in vitro as demonstrated in a variety of anaerobic bacteria as well as in the standard Ames assay. This mutagenic potential is directly related to the cytotoxic and antiprotozoal and/or antibacterial activity of the compound in that it appears only under anaerobic conditions and is mediated via nitro group activation.

The applicant also referenced a 2 year carcinogenicity study in rats where tinidazole (dose not specified) was compared to ornidazole and where no carcinogenicity was shown for either compound. Similar studies in hamsters revealed similar results.

Carcinogenicity studies in mice and rats with metronidazole revealed lung tumors and lymphomas. The clinical relevance of these studies is unclear given that acute nature of the dosing of both metronidazole and tinidazole (proposed indications) as compared to the prolonged durations of treatment in the animals wherein age-related phenomena could not be ruled out.

Microbiology:

The MO defers to the microbiology reviewer.

The sponsor presented MIC data that was provided in four of the studies reviewed for this NDA. These data are listed in the table below. It is important to note that the methods used here are not standardized.

Table 5.In vitro Comparison of Tinidazole versus Metronidazole against *Entamoeba histolytica*

Study	# isolates	Tinidazole MIC (ug/ml)	Metronidazole MIC (ug/ml)	Relative Potency TNZ vs. MTZ
Siega (173)	N/A	6.25	6.25	1
Prakash (175)	14	0.312-2.5	0.16-1.25	0.5
Mahajan (313)**	6	0.625-1.25	0.312-0.625	0.5
Howes (33)*	?	40	40	1

**done with liver marmite serum *done with Lockes medium
From p.10-14 from NDA 21,682

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics and Pharmacodynamics

Tinidazole is similar to metronidazole and both are completely absorbed after oral administration. Peak concentrations occur in 0.5 to 3 hours for metronidazole as compared to 2-6 hours for tinidazole. Both agents are absorbed after vaginal administration (metronidazole > tinidazole) and after rectal administration with a bioavailability of 44 – 100%. Both agents are distributed into all tissues and body fluids with a volume of distribution equivalent to that of body water and with plasma protein binding of 12% (tinidazole). CSF penetration also occurs. Both agents appear in the breast milk and placenta and cross over to the fetus.

Tinidazole is metabolized prior to excretion. Tinidazole is the main compound in the plasma accompanied by a small amount of a 2-hydroxymethyl metabolite that has antimicrobial activity. Other metabolites include a 5-hydroxy, 4-nitro metabolite and an unidentified compound. After IV administration, 37 – 44% is excreted in the urine over 34 hours. This percentage includes 32% unchanged drug. 5 days post administration, 63% is excreted in the urine and the remainder is eliminated by the fecal route. Plasma half-life is 12 – 13 hours.

In subjects with renal dysfunction, there is a slight to moderate increase in plasma half-life but pharmacokinetics are not significantly altered. Current German labeling suggests no dosage adjustments in such patients.

Information is lacking regarding the pharmacokinetics of tinidazole in subjects with liver disease. In subjects with such dysfunction receiving metronidazole, a reduction in metabolic elimination has been reported with extended half-lives. Dose reductions are recommended in such subjects treated with metronidazole and as per the applicant, in the absence of tinidazole data, similar recommendations would be reasonable in subjects receiving tinidazole.

IV. Description of Clinical Data and Sources

A. Overall Data

Intestinal Amebiasis

The applicant has identified 26 published clinical reports on the use of tinidazole in the treatment of intestinal amebiasis. These trials included approximately 2200 patients and about 1400 were treated with tinidazole. Nine of the trials were randomized and eight of these were metronidazole comparative. Four of these trials utilized the proposed tinidazole dose of 2 grams once daily for 3 days. These four studies were considered the pivotal studies. One of these studies was single blind, the rest were not blinded. Three of the randomized trials compared split dosing of tinidazole 600 mg po bid for 5 days with metronidazole in a variety of split dose regimens. One of the split dose trials was single blinded. One open label study was included as a supportive study since it enrolled 502 adults and children. There was one additional double blind randomized comparative study that evaluated the generic forms of metronidazole and tinidazole with Fasigyn and Flagyl. This study did not appear to well differentiate luminal disease from tissue invasive disease and therefore was not included in the pivotal or supportive studies. Another one of the randomized studying utilizing split dose also enrolled patients who were asymptomatic cyst passers and therefore the results for both tinidazole and metronidazole were poor. Lastly, one of the randomized studies compared single dose secnidazole versus 2 days of tinidazole in children.

Amebic Liver Abscess

Eighteen trials were identified by the Applicant in the literature evaluating the use of tinidazole in the treatment of amebic liver abscess. Nine studies were randomized trials comparing tinidazole with metronidazole. Seven of these trials used the tinidazole dose of 2g/day for 2-5 days. Two of these trials were blinded. Simjee (312) was single blind and Mendis (299) was double blind. Two trials used different tinidazole doses: 800mg po tid for 5 days {Hatchuel (295)} and 1g po bid for 1 day {Laserre(298).}Both of these trials were double blind. These nine trials evaluated the efficacy of tinidazole in which 324 patients received tinidazole. Twenty-five of these were children. Two of the comparative trials had open label introductory trials enrolling an additional 24 patients.

Postmarketing Experience

Tinidazole is approved for use in the UK, Australia, Austria, Belgium, Costa Rica, El Salvador, Finland, France, Germany, Guatemala, Honduras, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, South Africa, Spain, Sweden, and Switzerland. In the UK it is approved for the following indications: urogenital trichomoniasis; giardiasis; intestinal amoebiasis; amoebic liver abscess; non-specific vaginitis; prevention of postoperative infections; treatment of anaerobic infections; acute ulcerative gingivitis; and for the eradication of *Helicobacter pylori* associated duodenal ulcers. The maximum approved total dose is 12 grams.

D. Literature Review

The Medical Letter, April 2002; Drugs for Parasitic Infections:

- Amebiasis: drugs of choice include metronidazole 500-750 mg po TID for 5 days
- Giardiasis : alternatives include quinacrine 100 mg po TID x 5 days , tinidazole 2 grams once, furazolidone 100 mg po qid for 7 to 10 days and paromomycin 25-35mg/kg/d in 3 doses for 7 days. Pediatric Dosing is available for all of the above.

This NDA is a review of all the published clinical trials of the use of tinidazole in the treatment of intestinal and hepatic amebiasis.

V. Clinical Review Methods

A. How the Review was Conducted

The MO independently reviewed all publications submitted in support of the NDA and summarized them. Trials were determined to be pivotal if they were well designed, utilized the dose recommended, with adequate enrollment and defined entry criteria and response measurements. Trials were determined to be supportive if they did not meet al the characteristics of a pivotal trial but by provided useful information because of the size of their enrollment, blinded study design, demonstrated efficacy with smaller doses of tinidazole or use in an important population (especially children.)
Only efficacy was assessed in the review.

B. Overview of Materials Consulted in Review

Seventeen volumes were submitted in support of the amebiasis indications.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

As above, all publications that constituted this submission appeared to adhere to ethical standards although this could not be independently confirmed. Ongoing compassionate use trials are being conducted ethically.

E. Evaluation of Financial Disclosure

Original data did not constitute part of this submission. Thus, investigator integrity could not be assessed.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

1. Tinidazole is efficacious in the treatment of intestinal amebiasis in children and adults at the dose requested.
2. [redacted]

3. Tinidazole is effective in the treatment of amebic liver abscess in children and adults when used in conjunction with abscess aspiration when clinically necessary.
4. Tinidazole was well tolerated by the children and adults with intestinal amebiasis and amebic liver abscess.

B. General Approach to Review of the Efficacy of the Drug

The MO independently reviewed all publications submitted in support of the NDA and summarized and analyzed them. If the MO felt the conclusions made by the study were in error the corrected rates of response were used in the overall analysis of the pivotal and supportive studies. This was not a meta-analysis so the rates of response were not combined. The ranges of the response rates were examined and the various studies were evaluated on the strength of their conclusions based on the quality of study design. Only efficacy was assessed. Please see the safety review by Dr. Carl Kraus.

C. Detailed Review of Trials by Indication

Intestinal Amebiasis:

There were 26 published clinical reports on the use of tinidazole in the treatment of intestinal amebiasis submitted. These trials included approximately 2200 patients and about 1400 were treated with tinidazole. Nine of the trials were randomized and eight of these were metronidazole comparative. Four of these trials utilized the proposed tinidazole dose of 2 grams once daily for 3 days and therefore these four studies were chosen as the pivotal studies. One of these studies was categorized as single blind, the rest were not blinded. The one blinded study noted that the investigators reading the stools were not aware of the treatment of the patients but it is not mentioned if the patients were aware of their treatment status. Therefore this may actually be a double blind study. These 4 studies enrolled 376 adults with a mean age in the low thirties, 255 men and 121 women.

Table 6. Types of Studies-Intestinal Amebiasis

Type of Study (Single Dose of 1.5 g or greater or pediatric equivalent)	Number of Studies
Double Blind Randomized Controlled	1
Single Blind Randomized Controlled	2
Open Label Randomized Controlled	6
Open Label Comparative or Placebo Controlled (no description of randomization)	3
Open Label single agent	14

Pivotal Studies

- **Swami, 1977, India (197)** Comparative open label, randomized trial of tinidazole 2 gm daily for 3 days versus 2. gm of metronidazole daily for 3 days. Sixty patients were randomized, thirty to each arm. There were 41 men and 19 women with a mean age of approximately 30. Twenty-nine patients who received tinidazole completed the protocol and 27 who received metronidazole completed the study. Three patients were lost to followup and one was determined to have an amebic liver abscess. Symptoms included diarrhea, bloody diarrhea, abdominal pain , fever, etc. All had symptomatic, parasitologically confirmed amebiasis by the presence of cysts or trophozoites in the stool. Only one patient had trophozoites detected upon entry, all the other patients had cysts only detected. Patients were followed up at 4, 20, and 30 days. The number of stools evaluated at each time point is not mentioned. Sigmoidosocopy was performed at enrollment and followup "wherever possible." If sigmoidoscopy was abnormal upon entry it was repeated at 30 days.

Cure was defined as the resolution of symptoms and the absence of trophozoites or cysts in the stool at day 30. This was achieved in 28 of 29 patients in the tinidazole arm and 15 of 27 in the metronidazole arm. Patients were categorized upon entry as to whether they had a more severe dysentery like presentation (bloody stools and fever) or a non-dysentery like presentation (non bloody diarrhea without fever.) Please see below. The response to therapy in patients with this different clinical presentations are presented below. The number of patients with a non dysentery presentation who received metronidazole is too small to make any conclusions. However, the difference in response to therapy in patients with dysentery suggests a superior response to tinidazole.

Table 2 (Repeated) Disease Severity and Response-Swami (197)

	Tinidazole # Cured	Metronidazole # Cured
Dysentery	19/20	13/22
Non-dysentery	9/9	2/5

Three of the 28 cured tinidazole patients required some additional days of therapy beyond 3 days because of positive stools on day 3. Eight of the metronidazole patients required additional therapy for the same reason. Consequently 25 of 29 tinidazole patients were cured after 3 days of therapy versus 7 of 27 metronidazole patients. Probable failure (or "partial cure") which is defined as negative stools with partial resolution of symptoms was achieved in one tinidazole patient and in 5 metronidazole patients. Seven metronidazole patients were treatment failures. Please see below.

Table 6. Number of Additional Days of Therapy Required-Swami (197)

Number of Total Days of Therapy	Number of Tinidazole patients	Number of Metronidazole patients
4	2	-
5	1	4
6	-	2
7	-	1
8	-	1

No serious side effects were observed.

***Medical Officer's Comment:**. It is more appropriate to report success rate as those cured after 3 days of therapy since the study was designed to compare 3 days of tinidazole therapy to 3 days of metronidazole therapy. These rates would then be 86.2% (25/29) in for the tinidazole arm and 26.6% (8/30) for the metronidazole arm. The lack of blinding and the lack of a description of the randomization method are deficiencies in the study design. The strengths were the use of the WHO standards used for cure, partial cure, and failure and the use of sigmoidoscopy whenever possible.*

Singh, 1977, India (196): Comparative open label randomized trial of tinidazole 2 gm daily for 3 days versus metronidazole 2 gms daily for 3 days. Sixty subjects were enrolled and 56 completed the study; four were dropped due to noncompliance. Three of these were in the tinidazole group and one in the metronidazole group. There were 24 men and 32 women with a age range of 16 to 55 with a mean age of 29.5. Entry criteria specified a positive stool parastitologic examination by direct smear or formalin ether, sigmoidoscopy "wherever possible" and gastrointestinal symptoms. Cure was defined as elimination of symptoms and clearance of cysts and trophozoites in stool in followup examinations performed at 5, 20 and 30 days. The test of cure was at 30 days. In the tinidazole arm 25 of 27 or 92.6% were cured and in the metronidazole arm 17 of 29 or 58.6% were cured. Parasitologic success was achieved in 100% of the tinidazole subjects and 86% of the metronidazole subjects. Of note there were 6 patients in the tinidazole group with concomitant Giardia all of whom were cleared of both infections. There were also 6 patients in the metronidazole group with concomitant giardiasis, 4 of these 6 were cleared of both infections.

No severe side effects were noted. There were no changes noted in hematology and chemistry laboratory values obtained at entry and at 30 days.

***Medical Officer's Comment:** The lack of blinding and the lack of a description of the randomization method are deficiencies in the study design. The strengths are the use of the WHO standards used for cure, the use of sigmoidoscopy and the evaluation of lab values for safety. The reasons given for the 4 dropouts were noncompliance but no further details were provided. Three of these were in the tinidazole group and only one in the metronidazole group.*