- **Misra, 1977 India (194)**: Comparative open label randomized trial comparing tinidazole 2.0 grams daily for 3 days to metronidazole 2.0 grams each day for 3 days. There were 60 adults enrolled in the study, 30 in each arm. There were 48 men and 12 women enrolled with an age range of 16 to 60 with an average of approximately 32. Entry and followup criteria included parasitologic examination of stool, sigmoidoscopy, and evaluation of gastrointestinal symptoms. It is not clear how many samples were obtained at each followup but a stool sample and sigmoidospy sample were obtained at entry and at 30 days. All patients underwent sigmoidoscopy at entry and at 30 days. Followup occurred at 5, 20 and 30 days. The test of cure was at 30 days. Ten patients in the tinidazole group and 11 in the metronidazole group were considered to have acute intestinal amebiasis (symptoms less than 15 days) and 20 patients in the tinidazole group and 19 in the metronidazole group were considered to have chronic intestinal amebiasis (symptoms for greater than 15 days).

Twenty-seven of the thirty patients who received tinidazole and 16 of the 30 who received metronidazole were considered cured. Cure was defined as the clearing of symptoms and the elimination of cyst and trophozoites from stool. Only mild side effects were reported in the tinidazole group and tinidazole was overall better tolerated than metronidazole. Two patients previously unsuccessfully treated with a 7 day course of metronidazole were cured with a course of tinidazole.

Eight patients (26.7%) on tinidazole had mild side effects and only 1/8 had minor than 1 side effect. Sixteen patients (53.5%) on metronidazole had side effects and 75% of these had more than 1 side effect. Twelve metronidazole recipients complained of side effects that were moderate in nature. The specific side effects were not listed but it was mentioned that almost all of them were gastrointestinal in nature, i.e. nausea, anorexia, vomiting, and abdominal discomfort.

Medical Officer's Comment: *The lack of blinding and the lack of a description of the randomization method are deficiencies in this study. The strengths are the requirement of sigmoidoscopy of all patients at entry and at followup and an evaluation of chronicity of symptoms. The validity of response is increased by the inclusion of sigmoidoscopy at entry and followup since this allowed for direct swab of the intestinal mucosa being examined for evidence of E.histolytica infection and for the examination of the condition of the mucosa itself.*

- **Bakshi, 1978 India (118)** Double blind, randomized multi-centered (3) controlled trial comparing 4 arms: tinidazole 2g a day for 3 days, metronidazole 2 grams a day for 3 days, tinidazole 600mg po BID for 5 days, and metronidazole 400mg po TID for 5 days.There were 292 men and 108 women in the 4 arms. In the 2.0 g arms there were 142 men and 58 women.

Table 7. Enrollment in Bakshi Trial

Drug	Dose	Number Enrolled	Number Excluded*	Number lost from trial**	Number completed
TNZ	0.6g bid x 5d	118	15	3	100
MTZ	0.4g tid x 5d	112	28	5	79
TNZ	2.0g od x 3d	140	1	5	134
MTZ	2.0g od x 3 d	140	10	7	123

**For extension of treatment beyond the stipulated period*

***For unclear reasons*

Adapted from Table 1 Bakshi, 1978 Source 118.

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

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.

Results were as presented in the above tables. Overall, the best results were achieved with tinidazole single daily dosing followed by tinidazole bid dosing for 5 days. The results reveal that tinidazole and metronidazole were both reasonable effective at clearing trophozoites but in those passing cysts single dose tinidazole was the most effective. However, the authors reported that since all patients were symptomatic all would likely have produced trophozoites if they had undergone purge.

Tinidazole produced less gastrointestinal side effects than metronidazole in any dosing regimen but tinidazole single dose x 3day produced slightly more gastrointestinal side effects than the lower multiple daily dose of tinidazole.

Medical Officer's Comment: *Dropouts were not adequately evaluated or accounted for: there were twenty dropouts for unclear reasons. Fifty-four patients were excluded from further analysis because their response on the last intended day of treatment was grossly unsatisfactory and therefore their treatment was extended. These cases should have been treated as failures. If they had been included as failures the results of success would have been the following: 87/115 (75.6%) for tinidazole 600mg po bid x 5 d, 67/107 (62.6%) for metronidazole 400 mg po tid for 5 days, 123/135 for tinidazole (91.1%) for tinidazole 2.0 g/d for 3d, and 66/133 (49.6%)for metronidazole 2.0g/d for 3days. The strengths of this study are the blinding and the size of enrollment. Its weaknesses are the dropping out of patients who required extension of therapy and the less stringent criteria for cure ("near elimination of symptoms") than that used in the other pivotal studies.("complete resolution of symptoms")*

Supporting Studies

There were four other studies considered supportive by the FDA that will be discussed briefly. There were 2 studies presented as supportive by the applicant that were not felt to be supportive by the Division and that will not be presented further here. One of these was also by Misra. This trial studied a dose of 600mg po BID of tinidazole for 5 days versus a metronidazole dose of 400mg po TID for 5 days. Efficacy was 76.6% for tinidazole and 73.3% for metronidazole. This trial will not be discussed in detail because the dose is different than the one being sought. The purpose and design of the randomized 4 armed double blind study by Chunge was to compare generic tinidazole and metronidazole with Fasigyn and Flagyl and therefore it will also not be reviewed further. The results of this study are discussed in the efficacy conclusions section. All the other open label studies utilizing the 2g/d for 3 days dosing confirmed the results of the pivotal studies.

- **Apte, 1978, Asia, (94):** Open label multi-center multi-country evaluation of tinidazole in the treatment of intestinal amebiasis, amebic liver abscess, giardiasis, and vaginal trichomoniasis. Ninety four physicians from 8 Asian countries participated. Of 1,682 case report forms received, 1517 fulfilled the criteria of the protocols and were accepted for inclusion in the analysis of results. Five hundred and two of these patients were treated for intestinal amebiasis.

Table 8. Enrollment by Country-Apte Trial

Country	Number of patients	Number of cures or partial cures (%)	Number with side effects (%)
Bangladesh	197	187(94.9%)	31(15.7%)
India	200	190(95%)	27(13.5%)
Indonesia	15	15(100%)	0
Korea	37	36(97.2%	5(13.5%)
Philippines	53	49(92.5%)	4(7.5%)
Total	**502**	**477(95%)**	**67(13.3%)**

***Medical Officer's Comment**: The report did not separate cures and partial cures. All of the pivotal studies only included cures in their success rates. WHO criteria define partial cure (which in some articles is referred to as partial failure) as the moderate relief of symptoms with negative stool parasitology. The results did not separate out children and adults.*

- **Salles 1999, Brazil (288)** Randomized open label multi-center study performed in children in Brazil. Children were identified by positive stool exam. Not all enrollees had abdominal symptoms, approximately 10% in each group did not have gastrointestinal symptoms. In addition, about 60% of each group also had Ascaris and 15-20% had infection with either Giardia, Necator, Strongyloides, etc. The doses studied were secnidazole 1ml/kg x1 versus tinidazole .5ml/kg daily for 2 days. It is not clearly stated in the study what the mg equivalent to 1ml of the suspension. Parasitological cure was achieved in 63% of tinidazole patients and 77% of secnidazole patients. Clinical improvement was seen in 93% of secnidazole patients and 91% of tinidazole patients. Both drugs were well tolerated.

Medical Officer's Comment: *It is unclear from the report what the actual mg doses used were. The presence of other intestinal infections and the inclusion of asymptomatic patients strongly confounds the results.It is included primarily because it provided more data on the tolerance and efficacy of tinidazole in children.*

- **Scragg, 1977 ,South Africa (290)** Open label controlled trial in children comparing tinidazole 50 mg/kg single dose in 25 children with tinidazole 60mg/kg for 3 days gd also in 25 children. Parasitologic success was achieved in 96% of the children who received 3 days of tinidazole compared to 76% of the children receiving single dose. The regimens were also very well tolerated with no reports of significant side effects.

Medical Officer Comments: *These results are consistent with the experience in adults.*

- **Pehrson, Sweden, 1984 (286)** Small randomized open label trial comparing tinidazole 600mg po bid for 5 days in 14 patients with metronidazole 800mg po tid for 5 days in 16 patients. All patients were asymptomatic. No results were provided as to how many had only cysts or if any trophozoites were also seen. At one month none of the tinidazole patients were parasite free and 7/16 or 44% of the metronidazole patients were symptom free. One of the tinidazole patients developed a presumed amebic liver abscess during followup.

Medical Officer Comments: *Lower efficacy in asymptomatic cyst passers and poor activity against trophozoites about to encyst is typical for drugs of this class. This study also employed a lower dose for tinidazole and higher dose for metronidazole than many of the other published trials.*

Amebic Liver Abscess

Eighteen papers were presented as supportive of this indication. There were seven randomized comparative trials using the tinidazole dose of 2g/d for 2-5 days and all 7 of these were chosen as pivotal studies by the Applicant and the FDA. Two other trials were randomized, comparative trials that utilized a different tindazole dose. These 2 reports were considered supportive by the Applicant and by the Division. One open label noncomparative trial evaluated the use of tinidazole in children and since this was the only study in pediatric patients is also considered supportive.

Table 9. Type of Study-Amebic Liver Abscess

Type of Study	Number
Double Blind, Randomized, Comparative	2
Single Blind, Randomized, Comparative	2
Open Label, Randomized, Comparative	5
Open Label, Single Agent	9

All of the pivotal studies were performed in developing countries. Five of the 7 pivotal trials were performed before 1980, Mendis in 1984 and Simjee in 1985. Only Simjee required a positive amebic serology for entry and none of the trials utilized ultrasound as a diagnostic tool. Diagnosis in 6 of the trials was on clinical grounds listed in all of the trials as the same critieria: fever, enlarged tender liver, raised right hemidiapragm on routine or flouroscopic radiologic examination, typical anchovy like pus from liver aspiration (in 5/7 trials). A history of recent dysentery and the discovery of *E.histolytica* cysts or trophozoites in the stool and/or liver aspirate were considered supportive but not a requirement of entry. Patients who had received antiparasitic medications or who had secondary complications were excluded in all of the trials. Most of the patients were in-patients and were followed daily. The followup days listed in the study descriptions below are those days where specific study examinations were required. Test of cure for all of the pivotal studies was 30 days.

Pivotal Studies

- **Bakshi, India, 1978 (118)**-This report is actually a multicenter randomized single blind trial of tinidazole 2g/day for 2 days versus metronidazole 2g/day for 2 days. One hundred patients, 96 men and 3 women were enrolled in the study and 99 completed the study. The mean age was 38. The diagnosis was made on the basis of clinical grounds (presentation and radiologic examinations including flouroscopy) and aspiration of typical pus from the liver. No ultrasound data or serology data were provided. Follow-up was daily in the hospital for the first 10 days and then twice weekly until the test of cure visit at 30 days. The response was evaluated by the relief of symptoms and physical signs, restoration of diaphragmatic position and the return of white blood call count and ESR to normal. Results were recorded as either complete recovery by day 30, incomplete recovery by day 30, or failure. In

the tinidazole arm 48 out of 50 had a complete recovery versus 37 of 49 in the metronidazole group. One of the tinidazole patients had an incomplete recovery and one was a failure. Five of the metronidazole patients experienced an incomplete recovery and 7 were considered failures. In addition the speed of recovery was more rapid in the tinidazole group with 79% showing marked improvement in less than one week versus 49% of the metronidazole group.

Five tinidazole recipients complained of side effects: 3 reported nausea and 2 reported anorexia. Forty percent of metronidazole recipients reported side effects: 1/3 each nausea, anorexia and bitter taste. There were no drug induced adverse events on laboratory values detected for either drug.

Medical Officer's Comment: *This study has the largest enrollment of all the amebic liver abscess comparative trials presented. Another strength of this study is the well described criteria for diagnosis and cure. Because of these strengths and despite the randomization method not being stated this is the most important of the amebic liver abscess trials. Very few mild side effects (6%) seen in tinidazole arm.*

- **Simjee, South Africa, 1985 (302)** This was a randomized comparative double blind trial of tinidazole 2g/day for 5 days versus metronidazole 2g/day for 5days. Forty eight black residents of South Africa ranging in age from 11 to 60 with a mean age of 35 were enrolled. There was no enrollment by gender data provided. This was the only study where a positive serologic test was required as a diagnostic criteria. Consistent clinical findings and aspiration of pus from the liver were also required. Follow-up was at 5, 28 and 56 days. Cure was defined as resolution of symptoms and signs.

  Seventeen of 21 tinidazole patients were successfully treated with one course of drug. The 4 patients not cured were successfully retreated with tinidazole. In the metronidazole arm 25/27 were successfully treated with the first course of therapy and the 2 failures were successfully treated with a second course of metronidazole. The groups were also compared as to timing to resolution of certain symptoms and signs. The time to resolution of fever was 5.23 days in the tinidazole group versus 5.20 days in the metronidazole group; the time to resolution of liver tenderness was 7.94 days in the tinidazole group versus 7.96 days in the metronidazole group; and the time to disappearnce of right upper quadrant pain was 5.24 days in the tinidazole group and 4.24 days in the metronidazole group.

  Only 2 patients in either treatment group had adverse experiences none of which were serious or severe.

Medical Officer's Comments: *The clinicians and patients were unaware of the treatment assignment but the research assistant following the patients was aware of the treatment. Another strength of this study was the prolonged followup in comparison to the other amebic liver abscess trials. This is the only pivotal amebic liver abscess study where tinidazole performed worse than metronidazole. It was not noted whether any of the failures had an early response and then worsened. Consequently it is hard to know whether the longer followup was responsible for a lower response to tinidazole in this versus other studies. The response to tinidazole was still 80% and all the failures responded to a second course with tinidazole. The results are also noteworthy since this was the only trial to require a positive amebic serology for entry. Two weaknesses of the study were the lack of specific criteria listed for "cure" and the lack of a description of the randomization method.*

- **Islam, Bangladesh, 1978, (296).** This was a randomized comparative trial of tinidazole 2g/d for 3 days versus metronidazole 2g/day for 3 days. Thirty one patients were enrolled: 26 men and 5 women. The age range was 11 to 60 with an average age in the mid to late thirties. Diagnostic criteria were "unequivocal clinical, radiological, and laboratory features" of uncomplicated amebic liver abscess. Aspiration of the liver abscess was not required for inclusion but performed upon entry or during the trial if clinically necessary. No further description of inclusion criteria was provided.

  Treatment was to be continued if clinically necessary. The average tinidazole treatment period was 4 days (range 3 to 6 days) and for metronidazole was 7 days (range 4 to 10 days.). Additional aspirations were to be performed if clinically necessary. Five of 16 tinidazole patients required aspiration (1 once, 2 twice and 2 three times) and seven of 15 metronidazole patients required aspiration (2 once, 3 twice, and 2 three times.) Followup at was performed 10, 12, and 30 days. Complete response (defined as clearance of all symptoms and signs) at day 30 was noted in 15 of 16 tinidazole patients (93.8%) and 12 of 15 metronidazole patients (80%).

  Two tinidazole patients complained of anorexia and 2 of metallic taste. Six patients in the metronidazole group complained of anorexia nad 4 of headache. All side effects were mild.

Medical Officer Comment: *The weaknesses of this study are the lack of blinding, the lack of a description of response measurement at a specific predetermined length of therapy, and the randomization method. The strengths are the comparison of the 2 groups on 3 measures: response, length of therapy and necessity of additional aspirations. In all 3 areas tinidazole performed better (though the response rates were not markedly different) than metronidazole.*

- **Mathur, India 1977 (198).** This was a randomized comparative study of tinidazole 2g/day for 2 days versus metronidazole 2 g/day for 2 days. Twenty-three male patients were enrolled. The age range was 11 to 60 with a mean age of 37. The diagnosis was made by consistent clinical picture with confirmation by aspiration of typical pus from the liver abscess. Response was categorized as excellent (marked clinical response by 7 days with complete resolution by 30 days), good (marked clinical response after 7 days with complete resolution by 30 days), fair (some residual symptoms at 30 days) or poor (minimal to no response of symptoms by 30 days.). One patient in the tinidazole was removed on day 2 for rapid deterioration. This patient died shortly thereafter. The paper reports the results in the tinidazole arm as 11/11 with excellent or good response (7 excellent, 4 good) but should be 11/12 or 91.7% because of the one patient removed. In the metronidazole arm excellent or good response was seen in 10 of 11 (6 excellent and 4 good) or 91% of subjects. There were no side effects reported in the tinidazole arm.

Medical Officer Comment: *The weaknesses of this study were the lack of a description of the randomization method or the provision of information about blinding. The response measurement criteria were well delineated but as noted above the response rate in the tinidazole arm needed to be adjusted to include the patient removed on day 2 as a failure. This was a trial comparing 2 days of 2g daily of tinidazole with 2g daily of metronidzole. The 2 g/day for 2 d regimen produced similar results to the 3 day regimen used in some of the other pivotal studies.However, the sample size is very small..*

- **Khokhani, India, 1977 (119).** This was a randomized comparative trial of tinidazole 2g/d for 2 days with metronidazole 2g/ day for 2 days. Diagnostic criteria were clinical features consistent with the diagnosis and confirmed by the aspiration of typical pus from the abscess. Nineteen patients were enrolled. Followup was at 5, 10, 30 days. Clinical and radiological improvement were the criteria for efficacy. All symptoms and signs were resolved by day 30 to be labelled a "cure." Ten out of ten tinidazole patients were cured compared to 5/ 9 metronidazole patients (55.5%.) Only 1 aspiration was required in 8 out of 10 tinidazole patients, the remaining 2 required 2 aspirations. Six out of 9 metronidazole patients required 2 or more aspirations. There were no side effects reported on tinidazole.

Medical Officer Comment: *The weaknesses of the study design were the lack of information about the type of randomization method or blinding. In addition to a comparison of cure rates the number of aspirations required as adjunctive to drug therapy was presented. This provided another measurement of response by which to compare the 2 regimens..*

- **Kundu India 1977 (297)**-This was a randomized comparative trial of tinidazole 2g/d for 3 days versus metronidazole 2g/d for 3 days. Diagnostic criteria were consistent clinical and radiological features and anchovy-like pus from the aspirate. Eighteen patients with a mean age of 41 were enrolled, 9 in each arm, 17 men and 1 women, and were examined at 5, 10, and 30 days. Response was categorized as excellent,

good, fair, or poor as described above in Mathur. One patient in each arm died. The remaining 8 tinidazole patients had excellent or good responses. Three of the remaining 8 metronidazole patients had excellent or good responses for an efficacy rate of 33%. The size of the abscesses was determined by the amount of pus removed at the entry aspiration and the sizes were similar in the 2 groups. In the discussion portion of the study it was mentioned that tinidazole was very effective for small and medium size abscesses but not for large ones. However, no data correlating abscess size to response is provided in the article.

There was one side effect reported in the tinidazole group (anorexia). There were 7 reported side effects in 4 metronidazole recipients (2 complaints of anorexia, 2 of nausea, and 1 each of giddiness, headache, and sleeplessness.)

Medical Officer Comment: *A random allocation chart was used but no discussion of blinding was provided. The lack of response data by sizeof abscess at enrollment is an omission especially in light of the conclusions of response based on size make in the article's discussion section. The categorization of response used both in this study and in Mathur provided a clear and simple way of comparing response .*

- **Mendis, Sri Lanka, 1984 (299).** This was a randomized double blind comparative trial of tinidazole 2 g/d for 3 days versus metronidazole 400 mg po tid for 5 days. Thirty-four patients were enrolled by randomization to a table of random numbers. The enrollment by gender was not provided. The age range was 21 to 60 with a mean age of 39. The diagnosis was made based on clinical and radiological features consistent with amebic abscess. Stools and liver aspirate were examined parasitologically but positive results not required for entry. Aspiration was not required at entry. Followup was at 5, 10 and 30 days. Response was categorized as rapid response (liver tenderness, hepatomegaly, and fever clearing within 5 days), intermediate (same symptoms responded within 6 to 8 days), and slow (symptoms taking longer than 8 days to clear.) Results were reported as tinidazole having 81.2% efficacy (13/16) and metronidazole 33.3% efficacy (6/18). However, these results represent the rapid responses only. If the rapid and intermediate results are combined the results are 100% efficacy for tinidazole and 14/18 or 77.8% for metronidazole. Time to symptom clearance was also studied. The average time to defervescence was 2.5 days for tinidazole and 5.2 days for metronidazole. The average time to the liver becoming nonpalpable was 5.6 days for tinidazole and 7.4 days for metronidazole.

  The adverse events seen are presented in the table below:

Table 10. Adverse Events Mendis Trial

Adverse event	Tinidazole	Metronidazole
Nausea	2	6
Vomiting	1	3
Metallic taste	1	2
Dizziness	4	2
Headache	6	4

Medical Officer Comment: *The strengths of this study was the use of blinding, the measurement of time to response, and the use of a table of random numbers. One weakness was the lack of requiring more specific entry criteria such as either liver aspirate or serology. Gastrointestinal side effects were seen more commonly with metronidazole and dizziness and headache more commonly with tinidazole.*

Supportive Studies

Three additional studies were considered to be supportive. Two of these were randomized double blind trials that were not considered pivotal because they used different doses of tinidazole. The trial by Hatchuel looked at using 800mg po tid of tinidazole for 5 days in comparison to the same dose of metronidazole and the trial by Laserre evaluated tinidazole 1 gram po bid for one day versus ornidazole in the same dose. Since none of the pivotal studies enrolled children, the one open label study by Scragg which did evaluate the use of tinidazole for the treatment of amebic liver abscess in pediatric patients was considered additionally supportive by the Division. The rest of the open label studies enrolled anywhere from 10-80 patients and reported efficacies from 90-100% for tinidazole 2g for 3 days. These reports were therefore supportive of the recommended dose of 2g po qd for 3 days.

- **Hatchuel, South Africa, 1975, (295)** This was a double blind randomized trial where diagnostic entry and cure were based on clinical assessment. All 15 patients who received metronidazole 800mg po TID for 5 days were cured and 13 of the 14 patient who received tinidazole in the same dose were cured. The passage of cysts in the stool was examined at various time points and it was noted that 3 of the tinidazole patients and 4 of the metronidazole patients were still passing cysts after 7 days.

Medical Officer's Comment: *The higher dose and longer therapy with metronidazole appears to have higher success. The persistent passage of cysts suggests that luminal agents may be required if cyst passage persists after treatment with either tinidazole or metronidazole. There was a "pre-arranged randomization scheme."*

- **Lasserre, Thailand, 1983, (298)**. This was a double blind randomized trial assessing tinidazole 1 g po bid for 1 day with ornidazole in the same dose.

Eighty patients were enrolled but eight were found to have another diagnosis. Seventy-two were continued, 35 received tinidazole and 37 ornidazole. Diagnostic criteria were appropriate clinical features and anchovy like pus from the liver aspirate. Clinical success was achieved in 94.3% of tinidazole patients and 94.6% of ornidazole patients.

Medical Officer's Comment: *No definition of success provided. No randomization method was mentioned.*

- **Scragg, South Africa, 1977, (301):** This was an open label study evaluating the use of tinidazole in a dose of 50-60mg/kg/day for 3 days (15 children) or 5 days (10 children). The average dose was 55mg/kg/day. The majority of the children were malnourished to some degree. The followup period was 6 months. Twenty-three of twenty five patients ((92%) were cured. Two 11 month old children with secondary bronchopneumonia required surgical intervention. One was then given emetine and metronidazole and was eventually cured and one died.

Medical Officer Comment: *Tinidazole was tolerated well by the pediatric patients in this study. The mean age in this study was 15 months with a range of 6 months to 6 years. In general amebic liver abscess is more common in adults than children. The experience in this study might suggest that very young children may be more susceptible to the development of this complication due to immature immune systems.*

D. Efficacy Conclusions

Please see Table 1 below.

TABLE 1: PIVOTAL STUDIES INTESTINAL AMEBIASIS (Repeated)

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 (Repeated)

	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 tinidaozle 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 in *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)Repeated

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 (as seen in Appendix II) 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.

TABLE 4. PIVOTAL STUDIES AMEBIC LIVER ABSCESS (Repeated)

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% as seen in Appendix II.

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.

VII. Integrated Review of Safety

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

VIII. Dosing, Regimen, and Administration Issues

Intestinal Amebiasis: Adults 2g/d for 3d
Children greater than 3 years 50mg/kg/d (not to exceed 2 g) for 3d

Amebic Liver Abscess: Adults 2g/d for 3 to 5 d
Children greater than 3 years of age 50mg/kg/d not to exceed 2 g) for 3 to 5 d

Absorption of tinidazole may be improved when taken with food but administration with food is not necessary. Tablets may be crushed in cherry syrup for administration to children. A procedure for compounding is provided in the pharmacology/pharmacokinetics review.

IX. Use in Special Populations

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

Intestinal Amebiasis

In the pivotal trials 525 men and 171 women were enrolled. No analyses of efficacy or safety by gender were performed.

Amebic Liver Abscess.

The 7 pivotal trials enrolled 272 patients, the gender of which is known for 190 subjects. Ten were female and 180 were male. Most of this discrepancy is probably secondary to the increased incidence of amebic liver abscess in men. No analyses of efficacy or safety by gender were performed.

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

Age

Intestinal Amebiasis-The age range in the 4 pivotal trials was 16 to 60 with mean ages from 29 to 33.

Amebic Liver Abscess-The age range in the 7 pivotal trials was 11 to 60 with mean ages from 35 to 41.

No analyses of efficacy response or safety by age were performed.

Race or Ethnicity
Intestinal Amebiasis-all trials performed in India, no more specific racial breakdown provided. Several supportive studies performed in a number of southeast asian countries.
Amebic Liver Abscess-No racial or ethnic background information provided except in the Simjee trial from South Africa where all of the enrollees were black. The pediatric study by Scragg was also performed in South Africa but the race of the enrollees was not mentioned. All of the other pivotal trials were conducted in India or Bangladesh. No analyses of response or safety by race or ethnic background were done but response were not noted to vary based on country of origin.

C. Evaluation of Pediatric Program

Intestinal Amebiasis

There were no randomized, blinded trials in children but the trials by Scragg and Apte treated over 550 children in South Africa and Southeast Asia with good success rates that were similar to the response rates seen in adults. The safety experience of the 3 day regimen is adequate.

Amebic Liver Abscess

This complication of amebic liver abscess is seen less commonly in children than adults and therefore enrolling large numbers of children in amebic liver abscess trials is difficult. There was only 1 trial evaluating the use of tinidazole in children. The age range in this trial was 6 months to 6 years with a median age of 15 months. Only 10 children in this study received the 5 day regimen. Consequently more data on the safety of this dose in children is necessary. Further data on the use of tinidazole in children under 3 years of age is also recommended.

D. Comments on Data Available or Needed in Other Populations

More data on the safety of the 5 day dose of 50mg/kg/day in children for 5 days for the treatment of amebic liver abscess is necessary. More data should be obtained for the use of tinidazole for the treatment of both intestinal amebiasis and amebic liver abscess in children between 6 months and 3 years and in individuals over the age of 60.

X. Conclusions and Recommendations

A. Conclusions

1. Tinidazole is effiective in the treatment of intestinal amebiasis in adults and children.
2.

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. Recommendations

1. Tinidazole should be approved for the treatment of intestinal amebiasis at the dose of 2g/day for 3 days in adults and 50mg/kg/d for 3 days in children over the age of 3.

2. Tinidazole should be approved for the treatment of amebic liver abscess at the dose of 2g/d for 3 to 5 days in adults and 50mg/kg/d for 3 to 5 days in children over 3. Aspiration of the liver abscess may be required in addition to tinidazole therpay in the treatment of amebic liver abscess.

3. More data on the safety and efficacy of the 5 day regimen for the treatment of amebic liver abscess in children should be obtained.

4. Additional data on the treatment of intestinal amebiasis and amebic liver abscess in individuals under 3 years of age and over age 60 should be obtained.

5. Further data on the use of tinidazole in the treatment of amebic liver abscess should be obtained using ultrasound and serology as the diagnostic measures.

Appendix I

Biblography

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 in any future review of the original application.

Intestinal Amebiasis

284) Ahmed T, Ali F, Sarwar SG. Clinical evaluation of tinidazole in amoebiasis in children. Archives of Disease in Childhood 1976; 51: 388-389.

94) Apte, V.V., Packard, R.S., Tinidazole in the treatmant of trichomoniasis, giardiasis and amoebiasis: Report of a multicentre study. Drugs 15 (Suppl 1):1978, 43-48. 118)

118)Bakshi, J.S., Ghiara, J.M., Nanivadekar, A.S., How does tinidazole compare with metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. Drugs 15 (Suppl).1978, 33-42.

114) Bassily, S., Farid, Z., El-Masry, N.A., Mikhail, E.M., Treatment of intestinal *E. histolytica* and *G. lamblia* with metronidazole, tinidazole and orinidazole: A comparative study. J Trop Med Hyg 90:1987, 9-12.

326) Chunge CN, Estambale BBA, Pamba HO, et. al. Comparison of four nitroimidazole compounds for treatment of symptomatic amoebiasis in Kenya. East Afr Med J 1989; 66(11): 724-727.

15)DeEsearte,1974 in 15) Sawyer P. R., Brogden R. N., Pinder R. M., Speight T, Avery G. S. Tinidazole: A review of its antiprotozoal activity and therapeutic efficacy. Drugs 11:1976, 423-440 116)

116)Garcia, E.G., Treatment of symptomatic intestinal amoebiasis with tinidazole. Drugs 15 (Suppl 1):1978, 16-18.

285) Islam N, Hasan M. Tinidazole treatment of intestinal amebiasis. Curr Ther Res 1975; 17(2): 161-165. 112) Joshi, H.D., Shah, B.M., A comparative study of tinidazole and metronidazole in the treatment of amoebiasis. The Indian Practioner 28:1975, 295.

15)Lewis, 1974 from15) Sawyer P. R., Brogden R. N., Pinder R. M., Speight T, Avery G. S. Tinidazole: A review of its antiprotozoal activity and therapeutic efficacy. Drugs 11:1976, 423-440 116)

195) Mabadeje AFB, Oredugba O. Single dose tinidazole in the treatment of amebic dysentery. Cur Ther Res 1977; 21: 685-688.

193)Misra NP, Laiq SM Comparative trial of tinidazole and metronidazole in intestinal amebiasis. Cur Therap Res 1974; 16: 1255-1263194)

194) Misra NP, Gupta RC. A comparison of short course single daily dosage therapy of tinidazole with metronidazole in intestinal amebiasis. J Int Med 1977; 5: 434-437.

15)Nava, 1973 from from15) Sawyer P. R., Brogden R. N., Pinder R. M., Speight T, Avery G. S. Tinidazole: A review of its antiprotozoal activity and therapeutic efficacy. Drugs 11:1976, 423-440 116)

15) Orozco, 1974 from 15) Sawyer as above

286) Pehrson P, Bengtsson E. Treatment of non-invasive amoebiasis – a comparison between tinidazole and metronidazole Annals of Trop Med Parasitol 1984; 78(5): 505-508.

113) Prahash, C , Bansal, B.C , Bansal, M R., A comparative study of tinidazole and metronidazole in symptomatic intestinal amoebiasis. J Assoc Physicians in India 22:1974, 527.

287) Prakash C, Bansal C, Bansal M. Tinidazole in symptomatic intestinal amoebiasis. Trop Med Hyg 1974; 77: 165-167.

288) Salles JM, Bechara C, Tavares AM, et. al. Comparative study of the efficacy and tolerability of secnidazole suspension (single dose) and tinidazole suspension (two days dosage) in the treatment of amebiasis in children. Braz J Inf Dis 1999; 3(2): 80-88.

290) Scragg JN, EM Proctor. Tinidazole treatment of acute amebic dysentery in children. Am J Trop Med Hygiene 1977; 26(4): 824-825.

196) Singh G, Kumar S. Short course of single daily dosage treatment with tinidazole and metronidazole in intestinal amebiasis: a comparative study. Cur Med Res Opinion 1977; 5: 157-160.

197) Swami B, Lavakusulu D, Devi CS. Tinidazole and metronidazole in the treatment of intestinal amebiasis. Cur Med. Res Opinion 1977; 5:152-156.

150 Torres from 15) Sawyer P. R., Brogden R. N., Pinder R. M., Speight T, Avery G. S. Tinidazole: A review of its antiprotozoal activity and therapeutic efficacy. Drugs 11:1976, 423-440 116)

115) Welch, J.S., Rowsell, B.J., Freeman, C., Treatment of intestinal amoebiasis and giardiasis: Efficacy of metronidazole and tinidazole compared. Med J Aust 1:1978, 469-471.

291) Zuberi SJ, Ibrahim M. Tinidazole in amoebiasis. Practitioner 1973; 211: 93-95.

Amebic Liver Abscess

292) Abiose PA, Olupitan SB, Yousuf M. Tinidazole in the treatment of amoebic liver abscess. Curr Ther Res 1976; 20(1): 32-35.

94) Apte, V.V., Packard, R.S., Tinidazole in the treatmant of trichomoniasis, giardiasis and amoebiasis: Report of a multicentre study. Drugs 15 (Suppl 1):1978, 43-48.

118) Bakshi, J.S., Ghiara, J.M., Nanivadekar, A S., How does tinidazole compare with metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. Drugs 15 (Suppl):1978, 33-42.

293) Cervantes LF, Kuri H, Castillo A, Guzman C. Treatment of amebic hepatic abscess with tinidazole. Rev Gastroenterol Mex 1975; 40(4): 185-193.

15) DeEsearte from 15) Sawyer P. R., Brogden R. N., Pinder R. M., Speight T, Avery G. S. Tinidazole: A review of its antiprotozoal activity and therapeutic efficacy. Drugs 11:1976, 423-440.

294) de Esesarte G. The effect of Tinidazole in amoebic proctasigmoiditis. J Int Med Res 1974; 2: 355-358.

295) Hatchuel W. Tinidazole for the treatment of amoebic liver abscess. SA Med J 1975; 25: 1879-1881.

296) Islam N, Hasan M. Tinidazole and metronidazole in hepatic amoebiasis. J Trop Med Hygiene 1978; 20-22.

119) Khokhani, R.C., Garud, A.D., Deodhar, K.P., Sureka, S.B., Kulkarni, M. Damle, V.B., Comparative study of tinidazole and metronidazole in amoebic liver abscess. Curr

297) Kundu SC, Bhattacherjee TD, Dasgupta DP, et. al. Comparative evaluation of tinidazole and metronidazole in the treatment of amoebic liver abscess. J Ind Med Assoc 1977; 69(6): 127-129.

298) Lassere R, Jaroonvesama N, Kurathong S, Soh CT. Single day treatment of amebic liver abscess. Am J Trop Med Hyg 1983; 32: 723-726.

198) Mathur SN, Itigi A, Krishnaveni, Rai V. Tinidazole and metronidazole in the treatment of amebic liver abscess. J Int Med Res 1977; 5: 429-433.

299) Mendis S, Dharmasena BD, Jayatissa SK. Comparison of tinidazole with metronidazole in the treatment of hepatic amoebiasis: a controlled double blind study. Ceylon Med J 1984; 29: 97-100.

15)Nava, 1974 from 15) Sawyer P. R., Brogden R. N., Pinder R. M., Speight T, Avery G. S. Tinidazole: A review of its antiprotozoal activity and therapeutic efficacy. Drugs 11:1976, 423-440.

300) Quaderi MA, Rahman S, Rahman A, Islam N. Amoebic liver abscess and clinical experiences with tinidazole in Bangladesh. J Trop Med Hyg 1978; 81: 16-19

301) Scragg JN, Prcotor EM. Tinidazole in the treatment of amoebic liver abscess in children. Arch Dis Child 1977; 52: 408-410.

302) Simjee AE, Gathiram V, Jackson T, Khan B. A comparative trial of metronidazole vs. tinidazole in the treatment of amoebic liver abscess. S Afr Med J 1985; 68: 923-924.

303) Vanijanonta S, Bunnag D, Looareesuwan S, Harinasuta T. Low dose tinidazole in the treatment of amoebic liver abscess. Southeast Asian J Trop Med Pub Health 1985; 16(2): 253-256.

Appendix II

Listing of all the clinical trials submitted by the Applicant for NDA 21,682.

Blank

Page

11.3.3.5. Tinidazole Use in Intestinal Amebiasis – All Identified Reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Nava, 1973*		tin: 2g QD x 2d	open-label	22	30 days	21/22 (95%)	
Prakash, 1974b [113]	India	tin: 600mg BID x 5d (n=25) mtz· 400mg TID x 5d (n=25)	comparative, open-label	50	6, 20, 30 days	tin: 15/25 (60%) 19/25 (76%) w/ 10d tx mtz: 10/25 (40%)	tnz: 4% (1) mtz: 8% (2)
DeEsesarte, b1974*	N/A	tin: 2g or 2.1g QD x 3d	open-label	100	N/A	90/100 (90%)	N/A
Lewis, 1974*	Ghana	tin: 2g QD x 3d (n=14) 800 mg TID x 3d (n=15)	open-label	29	15, 30 days	14/15 (93%) – at 30 days (all pts w/follow-up)	N/A
Orozco, 1974*	Columbia	tin: 2g QD x 2d	open-label	30	30 days	30/30 (100%)	N/A
Misra, 1974 [193]	India	tin - 600mg BID x 5d mtz - 400mg TID x 5d (n=30 each)	single-blind, randomized, comparative	60	30 days	tin - 23/30 (76.6%) mtz - 22/30 (73.3%) trmt extended to 10d in 4 tin pts, 5 mtz pts	tin - 2/30 (6.6%) mtz - 9/30 (30%)
Torres, 1975*	N/A	tin: 2g QD x 2d	open-label	40	N/A	32/40 (80%)	N/A
Islam, 1975 [285]	Bangladesh	tin: 2g QD x 3d (n=49) 2g QD x 6d (n=1)	open-label	50	6, 11, 30 days	48/49 (98%) (parasite cure) 1/1 (100%) 44/50 (88%) clinical	anorexia – 5 nausea – 2 met. taste – 3 gen. malaise – 10

* taken from Sawyer [15], papers not obtained

11.3.3.5. Tinidazole Use in Intestinal Amebiasis – All Identified Reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Misra, 1977 [194]	India	tin - 2g QD x 3d mtz - 2g QD x 3d (n=30 each)	randomized, comparative	60	5, 20, 30 days	tin - 27/30 (90%)* mtz - 16/30 (53.3%) 2 pts refractory to mtz cured on tin *(p<0.01)	tin - 8/30 (26.7%)* all mild mtz - 16/30 (53.3%) most moderate *p<0.01 for # & intensity
Mabadeje, 1977 [195]	Nigeria	2g tinidazole (single dose)	open-label	43	3, 7, 14, 28 days	37/43 (86%) remaining 6 cured with 2nd dose	5/43 (11.6%) salivation (5) nausea (1)
Singh, 1977 [196]	India	tin - 2g QD x 3d mtz - 2g QD x 3d (n=30 each)	randomized, comparative	60	5, 20, 30 days	tin - 25/27 (92.6%)* mtz - 17/29 (58.6%) *(p<0.01)	tin - 14/27 (51.9%) mild mtz - 22/29 (75.9%) mild to moderate
Welch, 1978 [115]	Australia	tin - 1-1.5g single dose (n=7) tin - 1-1.5g x 3d (n=21) mtz - 200mg bid x 5d (n=7) control (n=12)	comparative, open label	43 children	7, 14, 21 days	tin - 6/7 (85%) tin - 18/21 (85%) mtz - 3/7 (43%) control – 0/12	none
Scragg, 1977 [290]	S. Africa	tin - 50mg/kg single dose (n=25) tin - 60mg/kg x 3d (n=25)	open label	50 children	6, 14, 21, 28 days	50mg/kg x 1d (76%) 19/25 60mg/kg x 3d (96%) 24/25	well tolerated, no side effects
Swami, 1977 [197]	India	tin - 2g QD x 3d mtz - 2g QD x 3d (n=30 each)	randomized, comparative	60	4, 20, 30 days	tin - 28/29 (96.5%)* mtz - 15/27 (55.5%) *(p<0.01)	tin - 15/29 (51.7%) 2/15 moderate mtz - 10/27 (37%) 8/10 moderate

11.3.3.5. Tinidazole Use in Intestinal Amebiasis – All Identified Reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Garcia, 1978 [116]	Phillippines	tin - 2g QD x 2d (n=17 adults) 50/mg/kg x 3d (n=4 children)	open-label	21	4, 15, 22 days	adults: 16/17 (94%) children: 4/4 (100%)	12/21 (57%)
Apte and Packard, 1978 [94]	Asia	tinidazole: 2g QD x 3d (n=443 adults) 2g QD x 2d (n=15 adults) 50mg/kg QD x 3d (n=44 children)	open-label, multi-center	502	15-90 days	477/502 (95%)	67/502 (13.3%)
Scragg, 1976 [289]	S. Africa	tin - 60mg/kg x 3 days (n=30)	open-label	30 children	7, 14, 21, 28 days	28/30 (93%)	none
Prakash, 1974 [287]	India	tin - 600mg bid x 5 days (n=50)	open-label	50	6, 20, 30 days	96% (parasitology) 82%-41/50 (combined para & clin)	3/50 (6%): 2 nausea 1 bitter taste
Zuberi, 1973 [291]	Pakistan	tin - 150mg tid x 5 days (n=5) 300mg tid x 5 days (n=13) 600mg bid x 5 days (n=12)	open-label	30	6, 30 days	26/29 (87% clinical cure) 29/30 (96% parasit. cure)	1 pt. (pruritis)
Bassily, 1987 [114]	Egypt	tin: 1.5g x 10d (n-18) mtz: 1.5g x 10d (n-17) ornid: 1g x 10d (n-18)	open-label, comparative	53	3 weeks	tin: 67% mtz: 88%* ornid: 94%* *(p=.04 comp. to tin)	tin - 16.8% of pts mtz - 29.5% ornid - 8.3% p=NS
Ahmed, 1976 [284]	Bangladesh	50mg/kg/d x 3d	open-label	40 children	6, 11, 30 days	Clin: 39/40 (97%) Parasit: 40/40 (100%)	6/40 (15%)

11.3.3.5. Tinidazole Use in Intestinal Amebiasis – All Identified Reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Salles, 1999 [288]	Brazil	tin: 0.5ml/kg suspension x 2d sec: 1ml/kg suspension x 1d	randomized, open-label multi-center	303	7, 14, 21 days	Clin: 91% tin 93% sec Para: 63% tin 77% sec	tin – 15 (10.2%) sec – 12 (7.7%)
Pehrson, 1984 [286]	Sweden	tin: 600mg bid x 5d (n=14) mtz: 800mg tid x 5d (n=16)	randomized, open-label, comparative	30	30 days	tin: 0% mtz: 44%	not discussed
Joshi, 1975 [112]	India	2 studies: 1. tin-600mg bid x 5d (n=60) *therapy extended to 10d if needed	open-label	60	5, 10, 20, 30 days	44/48 (91.7%) (8 pts. required 10 days of therapy)	none
		2. tin-600mg bid x 5d (n=30) mtz-800 or 400mg bid x 5d (n=30) *therapy extended to 10d if needed	randomized, comparative	60	5, 10, 20, 30 days	tnz: 29/30 (96.7%) (4 pts. needed 10d of tx) mtz: 24/30 (80%) (10 pts. needed 10d of tx) *p<0.05	6/30 tin - 20% 7/30 mtz - 23% (nausea, malaise, vertigo)
Bakshi, 1978 [118]	India	1. tin: 2gx3d (n=134) 2. tin: 600mg bid x 5d (n=100) 3. mtz: 2gx3d (n=123) 4. mtx: 400mg tid x 5d (n=79)	single-blind, randomized, comparative	436	5, 20, 30 days	1. tin: 91.7%* 2. tin: 87% 3. 53.6% 4. 84.8% (p<0.01 vs. 2gx3d mtz)	1. 31% (42/134)* 2. 20% (20/100) 3. 54% (67/123) 4. 16% (13/79) (*p<0.01 vs. 2gx3d mtz)
Chunge, 1989 [326]	Kenya	1. Fasigyn 2gx3d (n = 59) 2. generic TNZ 2gx3d (n=64) 3. Flagyl 400mgTIDx5d (n=49) 4. generic MTZ 400mgTIDx5d (n=53)	double-blind randomized, comparative	225	3, 6 days	clinical: 100% in all groups parasitologic: 1. 51%* 2. 23% 3. 49% 4. 34% *p<0.01 vs.	not mentioned

11.3.3.5. Tinidazole Use in Intestinal Amebiasis – All Identified Reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
						generic TNZ	

Tinidazole Use in Amebic Liver Abscess All Identified Reports							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Hatchuel, 1975 [295]	S. Africa	2 trials: (#1) tin 800mg TID x 5d (n=10) (#2) tin 800mg TID x 5d (n=14) mtz 800mg TID x 5d (n=15)	open label (#1) double-blind (#2) comparative, randomized	#1 - 10 pts #2 - 29 pts	20 days	#1: 9/10 tin (90%) #2: 13/14 tin (93%) 15/15 mtz (100%) 3 pts on tin and 4 on mtz continued to pass cysts after d7	not reported
Khokhani, 1977 [119]	India	tin: 2g x 2d (n=10) mtz: 2g x 2d (n=9)	randomized, comparative	19	5, 10, 30 days	tin: 10/10 (100%) mtz: 5/9 (55.5%) p=0.05	tin: 0 mtz: 1/10 (10%) anorexia, nausea, vomiting
Mathur, 1977 [198]	India	2 trials (#1) tin 2g x 2-3/d (n=14) (#2) tin 2g x 2d mtz 2g x 2d (n=11 in each group)	(#1) open-label (#2) comparative, randomized	#1 - 14 pts #2 - 22 pts	13 days	#1: 14/14 tin (100%) #2: tin: 11/11 (100%) mtz: 10/11 (91%)	tin: 0 mtz: 2/11 (18%)
Quaderi, 1978 [300]	Bangladesh	tin - 2g QD x 2d (n=16) 2g QD x 3d (n=19) + retreatment of failures	open-label	35 (age 18-30)	7, 14, 30 days, 2 mo	2g x 2d: 9/16 (56%) 2g x 3d: 19/19 (100%) retreatment 2g x 3d: 6/7 (84%)	bitter taste 31% constipation 25%
Islam, 1978 [296]	Bangladesh	Initial dose: tin - 2g QD x 3d (n=16) mtz - 2g QD x 3d (n=15) dosing extended if no sign of improvement at day 3	randomized, comparative	31	10, 12, 20 days	tin: 15/16 (93.8%) mtz: 12/15 (80%) p<0.05	tin: 5 events mtz: 14 events
Simjee, 1985 [302]	S. Africa	tin - 2g QD x 5d (n=21) mtz - 2g QD x 5d (n=27)	randomized, comparative,	48 avg age =	5 day, 4 & 8 weeks	tin: 17/21 (80%) mtz: 25/27 (92.5%)	tin: 2/21 (9.5%)

			single-blind	35			mtz: 2/27 (7.4%)
Bakshi, 1978 [118]	India	tin - 2g QD x 2d (n=50) mtz - 2g QD x 2d (n=49)	randomized, comparative	99	5, 10, 30 days	tin: 48/50 (96%)* mtz: 37/49 (75.5%) *p<0.05	GI: tin: 6%* mtz: 40% *(p<0.05)
Apte & Packard, 1978 [94]	Asia	tin - 2g QD x 3d	open-label	82	15-90 days	77/82 (93.9%)	13/82 (8.8%)
DeEsesarte, 1974 *	Mexico	tin - 50mg/kg/d x 5d (children)	open-label	10	N/A	9/10 (90%)	N/A
Nava, 1974 *		tin - 2g QD x 3d	open-label	50	N/A	45/50 (90%)	N/A
Lasserre, 1983 [298]	Thailand/ Korea	tin - 1g BID x 1d (n=35) ornidazole - 1g BID x 1d (n=37)	double blind, randomized, comparative	72	6 mo	tin: 94.3% ornid: 94.6%	not mentioned
Cervantes, 1975 [293]	Mexico	tin - 2g QD x 3d	open label	30	10 and 20 days	93% (28/30)	not mentioned
Vanijanonta, 1985 [303]	Thailand	tin - 1.2g – 1.5g single or divided dose	open label	36	up to 6 months	100%	not mentioned
Scragg, 1977 [301]	S. Africa	tin - 50mg/kg x 3 (n=15) or 5d (n=10)	open label	25 children	up to 6 months	23/25 (92%)	11 month old with broncho-pneumonia died

* from Sawyer [15], paper not obtained

Abiose, 1976 [292]	Nigeria	tin - 2g/d x 3 days	open label	20	90 days	18/20 (90%)	4/20 (20%) 2 - nausea 1 - taste 1 - pruritis
De Esesarte, 1974 [294]	Mexico	(amebic proctitis) tin - 2g/d x 2 days	open label	36	30 days	32/36 (91%)	2/36 (5%) - nausea
Kundu, 1974 [297]	India	tin - 2g/d x 3 days (n=9) mtz - 2g/d x 3 days (n=9)	randomized, comparative	18	5, 10, 30 days	tin: 8/9 (88%)* mtz: 3/9 (33%) *p<0.05	tin: 1/9 (11%) mtz: 4/9 (44%)
Mendis, 1984 [299]	Sri Lanka	tin - 2g/d x 3 days (n=16) mtz – 400mg tid x 5d (n=18)	randomized, double blind, comparative	34	5, 10, 30 days	tin: 13/16 (81%)* mtz: 6/18 (33%) *p<0.01	tin / mtz nausea 2 / 6 vomiting 1 / 3 met taste 1 / 2 dizziness 4 / 2 headache 6 / 4

Blank

Page

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 02:20:34 PM
MEDICAL OFFICER

Leonard Sacks
5/17/04 02:28:56 PM
MEDICAL OFFICER

Renata Albrecht
5/17/04 05:26:35 PM
MEDICAL OFFICER

Edward Cox
5/17/04 07:13:31 PM
MEDICAL OFFICER

Medical Officer's Review
of
NDA 21, 618
Tinidazole

Trichomoniasis

Table of Contents

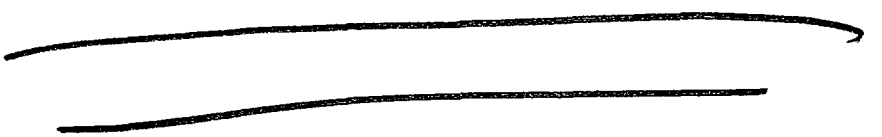
Clinical Review for NDA 21-618

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The MO determined that although the overall quality of the nine studies submitted in support of the single 2 gm dose treatment regimen for vaginal trichomoniasis was poor, the overall uniformity of the efficacy rates in these studies as well as in an additional 25 submitted as supportive indicated that a 2 gm single dose of tinidazole is efficacious in the treatment of trichomoniasis in women and should be approved.



II. Summary of Clinical Findings

A. Efficacy

Five published clinical trials were submitted by the applicant for use as pivotal studies [Gabriel (3), Hillstrom (9), Lyng (14), O'Prasertsawat (4), and Chaisilwattana (43)] in support of the 2 gram single dose treatment of the trichomoniasis indication. These trials were characterized as randomized, blinded, controlled trials of tinidazole (2 g single dose) versus various comparator agents including metronidazole (2), ornidazole (2), and placebo (1). Enrollment and efficacy criteria included culture results in four studies and wet mount analysis in one. Five hundred eighty-six females and 201 males were enrolled and 336 female tinidazole recipients were considered evaluable by the authors of the studies.

Clinical and microbiologic efficacy of the 2 g single tinidazole dose was assessed at various timepoints post-treatment (one week to one month) and ranged between 92% and 100%. In two trials, [Gabriel (3), O'Prasertsawat (4)] where single dose tinidazole was compared to single dose metronidazole, comparable efficacy was shown between treatment arms [tinidazole 40/42 (95.2%), metronidazole 39/40 (97.5%) and tinidazole 65/65 (100%), metronidazole 66/67 (98.5%) in each trial respectively]. Similar efficacy was shown when single dose tinidazole was compared to 1.5 g single dose ornidazole, [Hillstrom (9): tinidazole 43/45 (95.6%), f/u: 37/40 (92:5%), ornidazole 45/45 (100%), f/u: 41/42 (97.6%) and Chaisilwattana (43): tinidazole day 4: 52/52 (100%), day 14: 98.1%, metronidazole Days 4 and 14: 98.1%].

In a double-blind, placebo-controlled trial by Lyng (14) all female patients were treated in an open-label fashion and all male partners in a double-blind randomized fashion with either 2g tinidazole or placebo. Relapse rates for women with treated partners were lower than for women whose partners were treated with placebo. Efficacy in the Lyng study at 1 month after 1st intercourse (avg. 60 days after dosing) for patients with untreated partners was 72.6% vs. 91.8% for patients with treated partners.

The quality of the studies was assessed according to the JAHAD scoring system [Assessing the quality of reports of randomized clinical trials: Is blinding necessary?, Jahad AR et al, Controlled Clinical Trials 17:1-12 (1996)]. Quality scores for these studies were as follows: Gabriel: 1, Hillstrom: 3, O'Prasertsawat: 4, Lyng: 0, Chaisilwattana: 2. Issues that led to the issuance of low scores included the absence of information regarding withdrawals or dropouts and inappropriate randomization or blinding.

Four additional studies were considered supportive by the applicant of the 2 gm single dose regimen in women. Two were double-blind, placebo-controlled studies (Rees (32), and Mati (31), that enrolled 29 and 31 tinidazole patients respectively. Ten of twenty-nine and 16/31 tinidazole recipients were considered evaluable with efficacy of 80% vs. 0% placebo and 100% vs. 26.7% placebo when assessed by wet mount only at approximately 1 week post-treatment. The quality scores of these studies were 3 and 2 respectively.

Finally, the applicant provided 2 publications of open comparative trials of the 2 gm single dose regimen in women. In one [Chandhuri (35)], the 2 gram single dose of tinidazole was compared to carnidazole. Seventy-seven subjects were enrolled of whom 38 tinidazole recipients were included in the efficacy analysis. 94.7% as documented by wet mount at 2 weeks were considered cured. The quality score of this study was 3. In a similar study by Aimaku (34), the comparator utilized was metronidazole. Fifty-seven subjects were enrolled of whom 27 tinidazole recipients were considered evaluable. 96% as determined by culture results at 15 days were considered cured. The quality score of this study was 2.

In summary, as per the applicant, there were 425 female subjects (from 9 trials) treated for vaginal trichomoniasis with the single 2 gm tinidazole dosing regimen. Although all 9 trials were submitted as randomized comparative studies the MO found issue with the methods of randomization and blinding as well as with the little information provided in all of the studies regarding withdrawals, dropouts, and details of the statistical analyses. Follow-up periods ranged from a minimum of 7 days to 1 month post-treatment and in only 5 of the 9 trials was efficacy determined by the gold standard method of culture. As per the applicant total efficacy was 409/425 (96.2%). If only those trials where culture was utilized are considered, efficacy was 298/309 (96.4%). Final determination of efficacy was based on the trials listed in the following table and excluded the data from the Lyng trial. The MO determined that although the overall quality of the studies submitted in support of the single 2 gm dose treatment regimen for vaginal trichomoniasis was poor, the overall uniformity of the efficacy rates in these studies as well as in an additional 25 submitted as supportive indicated that a 2 gm single dose of tinidazole is efficacious in the treatment of trichomoniasis in women and should be approved.

Tinidazole 2g Single Dose for Trichomoniasis
Efficacy Rate for 4 Pivotal and 4 Supporting Randomized, Blinded, Controlled Trials

Study. year	# TNZ pts	Design	Comparator	% Cured	Method of Assessment	Follow-up Period
O'Prasertsawat 1992	65	DB, R, C	metronidazole	100% TNZ 98.5% MTZ	Culture	6 – 16 d
Chaisilwattana 1980	52	DB, R, C	ornidazole	98.1% TNZ 98% ORN	wt. mt.	14 d
Gabriel , 1982	42	SB, R, C	metronidazole	95.2% TNZ 97.5% MTZ	Culture	14 d
Hillstrom , 1977	40	DB, R, C	ornidazole	92.5% TNZ 100% ORN	Culture	1 mo
Chaudhuri, 1980	38	DB, R, C	carnidazole	94.7% TNZ 100% CARN	wt. mt.	2 wk
Aimakhu , 1975	25	DB, R, C	metronidazole	96% TNZ 100% MTZ	Culture	15 d
Mati, 1974	16	DB, R, C	placebo	100% TNZ 26.7% PLAC	wt. mt.	7 d
Rees, 1974	10	DB, R, C	placebo	80% TNZ 0 PLAC	wt. mt.	7 d

D B = Dou

ble blinded, R = Randomized, C = Comparative
TNZ = tinidazole, MTZ = metronidazole, ORN = ornidazole, PLAC = placebo, CARN = carnidazole

Thirteen of the publications submitted in support of the single dose treatment of trichomoniasis indication reported on retreatment of tinidazole failures with a second dose of tinidazole. These trials were methologically disparate and the nature of the reports was often only a mention of retreatment. Forty-two patients who failed an initial course of treatment with a 2g single dose of tinidazole treatment for trichomoniasis were retreated with a second single 2 g dose of tinidazole and 71.4% (30/42) of these patients were successfully cured. In many cases it was unclear if the patient had a relapse or was reinfected. The MO determined that a second 2 gm dose of tinidazole appeared to be effective in the treatment of relapses but could not make labeling recommendations based on the poor quality of the information provided.

Eleven publications were submitted in support of the efficacy of tinidazole in males. Only 7 of these trials utilized a single 2g dose of tinidazole and were considered pertinent to the requested indication. One hundred forty-two male subjects with trichomoniasis received a single 2 gm dose and 134 were considered cured (94.3%). It was concluded that a single 2 gram dose of tinidazole appeared efficacious in the treatment of trichomoniasis in male subjects and can be recommended for use. Comparative

statements regarding the superior efficacy of tinidazole versus metronidazole in male subjects cannot be made based on the data submitted for review.

Data supporting the 2 gram single oral dosing regimen of tinidazole in men from the 4 trials (one comparative and 3 open label) can be seen in the following table:

Tinidazole Treatment of Trichomoniasis in Males
Published Studies with Male Efficacy Data

Study, year	# TNZ pts.	Treatment	Study Design	Follow Up	Cure Rates
Beric, 1978 [39]	80 M	TNZ 2g (n=80) MTZ 5g over 10 days(n=91)	Open-label, comparative	8 days	TNZ: 100% MTZ: 98%
Massa, 1976 [37]	30 M	TNZ 2g	Open- label	7-14 days	83% (25/30)
Wallin, 1974 [5]	7 M	TNZ 1.6g (n=4) TNZ 2g (n=7)	Open-label, dose ranging	1 week, 1 month	100% (10/10)
Fantini, 1974 [35]	25 M	TNZ 2g	Open- label	Not stated	88% (22/25)

NOTE: All subjects had pre and post-treatment parasitological assessments of urine.

[redacted]

B. Safety: See safety review

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 17, 2003
Date Review Completed: April 14, 2004

Generic Name: Tinidazole

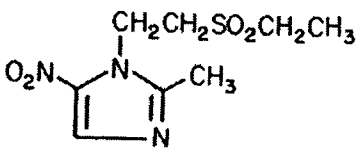
Laboratory code: CP 12,574

Proposed Trade Name: Tindamax™

Proprietary Name: Fasigyn® (Pfizer, UK)

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

B. Proposed Indications and Dosages:

1. Trichomoniasis: 2 gram single dose PO
2. [redacted]

Applicant's proposed labeling:

INDICATIONS and USAGE:

[redacted]

The organism should be identified by appropriate diagnostic measures. Culture is significantly more sensitive than wet mount for detecting *T. vaginalis*. Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, partners of infected patients should be treated simultaneously in order to prevent reinfection.

DOSAGE AND ADMINISTRATION

Trichomoniasis: In both females and males: a single 2g dose to be taken with food. Since trichomoniasis is a sexually transmitted disease, sexual partners should be treated with the same dose and at the same time. [redacted]

CLINICAL STUDIES

Trichomoniasis
Tinidazole (2g single dose) use in trichomoniasis has been well documented in over 34 published reports involving over 2,800 patients treated with tinidazole. In nine published blinded, comparative studies of the 2g tinidazole dose a combined efficacy rate of 96.2% of 425 patients was achieved. The majority of these studies also included treatment of the male partner.

Efficacy of Tinidazole (2g single dose) for Trichomoniasis

	% Cured (cures/total)
Summary of 9 blinded, comparative studies	96.2% (409/425)

[redacted]

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

Tinidazole is a metronidazole-like compound with activity against protozoa and anaerobic bacteria. The applicant is seeking to market this product in the US for the single dose 2 gm treatment of trichomoniasis and giardiasis in adults and as a 50 mg/kg single dose in children. This compound has been studied outside the US and is listed in a variety of references including "The Medical Letter", as the drug of choice for these indications despite limited US availability. At present in the US it can only be obtained through mail order compounding pharmacies.

Tinidazole was originally developed by Pfizer and since the 1970's has been marketed under the trade name of Fasigyn® throughout most of the world excluding the US. For reasons that have not been clarified Pfizer did not develop the product further in the US.

Oral tinidazole is completely absorbed, its elimination half-life is 12 –14 hours or twice that of metronidazole. Published reports have shown that tinidazole at equivalent dosing to metronidazole has similar efficacy (90 – 100%), and that MLC levels are lower than those of metronidazole.

As per the applicant, there is extensive information available relative to the safety of this compound with over [redacted] 2 gram prescriptions issued for the proposed indications worldwide in 1996 and 1997. The adverse reactions associated with tinidazole are similar to those of metronidazole and are primarily from the GI tract including nausea, vomiting, diarrhea, abdominal pain, anorexia, and metallic taste. Serious but rare adverse events include peripheral neuropathy and convulsions.

The nitroimidazoles comprise the only class of drugs useful for the oral or parenteral therapy of trichomoniasis. Of these, only metronidazole is readily available in the United States and approved by the FDA for the treatment of trichomoniasis. In randomized clinical trials, the recommended metronidazole regimens have resulted in cure rates ranging between 90% - 95%.

2002 CDC Recommendations for Vaginal Trichomoniasis:

Metronidazole 2 g orally in a single dose or 500 mg BID for 7 days.

"Certain strains of *T. vaginalis* can have diminished susceptibility to metronidazole. Infections caused by most of these organisms respond to higher doses of metronidazole. If treatment failure occurs with either regimen, the patient should be re-treated with metronidazole 500 mg twice a day for 7 days. If treatment failure occurs again, the patient should be treated with a single, 2-g dose of metronidazole once a day for 3-5 days.

Patients with laboratory-documented infection who do not respond to the 3-5 day treatment regimen and who have not been reinfected should be managed in consultation with a specialist; evaluation of such cases should ideally include determination of the susceptibility of *T. vaginalis* tat present, the CDC is recommending metronidazole 3 grams PO daily as well as 1.5 grams intravaginally daily for 14 days."