The effect of tinidazole (single 2 gm dose) treatment on vaginal flora in 134 trichomoniasis patients was investigated in one study[101]. The vaginal secretions from the patients were collected before treatment, at 7 to 10 days and 4 to 6 weeks post-treatment, and examined for the presence of *Lactobacillus* microscopically. The details of the microscopic method used to determine presence of *Lactobacillus* were not included. Also, it is unclear if the bacteria were quantitated. At 4 to 6 weeks post-therapy (i.e. 2nd follow-up), an increase in *Lactobacillus* was observed in 69.9% patient, flora remained unchanged in 17.7% patients, and decreased in 0.9% patients treated with tinidazole (Table 71). No comparator was used in this study. Based on this result, the sponsor has concluded that tinidazole does not inhibit most isolates of vaginal lactobacilli.

Table 71: Examination of vaginal secretion; before and after a single dose of tinidazole (2000mg). Döderlein's bacillus = *Lactobacillus*

Examination		First follow-up (134 patients)		Second follow-up (113 patients)	
Before	After	No.	%	No.	%
Döderlein's bacillus					
Negative	Positive	54	40.3	61	54 0
Positive	Increased	8	6.0	18	15 9
Positive	Unchanged	25	18.7	11	9 7
Negative	Unchanged	31	23 1	9	8 0
Positive	Negative			1	0 9
Not known		16	11.9	13	11 5

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3.2. Giardiasis:

The sponsor has included 23 publications to support the efficacy of tinidazole in the treatment of giardiasis. Of the 23 published studies, 18 studies evaluated the efficacy of a single 2 gm dose of tinidazole in adults and the comparable 50 mg/kg dose in children (sponsor's proposed dose). The remaining 5 studies used the following doses: 150 mg BID x 7 days, 0.5 to 1 gm single dose, 1.5 gm single dose and 1-1.5 gm x 3 days. For the purpose of this review, only 17 studies using the proposed single dose of 2 gm tinidazole in adults and 50 mg/kg in children or identified as pivotal studies (3 studies conducted in adults and 1 in children-shown as bold in Table 74) by the sponsor were analyzed for efficacy. One study provided only the cure rates without details of the study in an abstract and was excluded from analysis. These studies were conducted in India, Thailand, Iran, Finland, Egypt, France and Bangladesh. None of these studies were double blinded (see Table 74). Five studies were open label. Metronidazole, ornidazole, albendezole or placebo, were used as the comparator in the remaining 12 studies.

Unconcentrated and/or concentrated stool samples were used for the detection of the *G. lamblia* cysts in 13 of the 17 studies. Two or more stool samples were examined in 10 of the 13 studies. The details of the method used for evaluation of parasitological outcome were not specified for 4 of the 17 studies. The raw data on the parasite counts using unconcentrated versus concentrated stools were not provided in these studies. Based on the limited information, no conclusions can be drawn on the sensitivities of the 2 methods i.e., examination of unconcentrated versus concentrated stool sample.

A successful parasitological outcome was observed in 710/773 (92%) patients treated with the proposed single 2 gm dose of tinidazole at 2 to 8 weeks post therapy (15 studies, reference# 112, 126-135, and 137-140 in Table 74). In one study (Jokipii, 1982)[127] that used a single 1.5 gm dose of tinidazole, parasitological success was observed in 45/50 (90%) patients. Therapeutic cure rates (combined clinical and parasitological outcomes) were provided for 370 of the 773 patients, suggesting a correlation between clinical and parasitological outcomes (8 studies, reference# 112, 126-129, 131, and 135 in Table 74). The clinical outcomes were not provided for the remaining patients. Also, no information was available on the occurrence of relapse in the patients. Overall, the efficacy of tinidazole (92%) was better than metronidazole (52%) or albendazole (50%) but comparable to ornidazole (90-95%). The susceptibility of isolates from these patients to tinidazole was not measured *in vitro*.

Table 74: Summary of all clinical studies using single dose tinidazole (1.5 to 2 gm or 50 mg/kg) for the treatment of giardiasis.

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical and Parasitological Outcome	
							Tinidazole (%)	Comparator (%)
Bakshi, 1978 (India)[128]	SB, R, MC	186 children	50 mg/kg	MTZ (50 mg/kg)	Unconcentrated and concentrated stool samples	Clinical and parasitological cure at 16 days post-therapy	83/94 (88%)	MTZ: 43/92 (47%)
Jokipii, 1982 (Finland)[127]	SB, R, C	100 adults	1.5 gm	OR (1.5 gm)	Unconcentrated and concentrated stool samples; cysts quantified; duodenal aspirate tested	Absence of cysts in 3 fecal samples at 1, 2, 4, 8 weeks	45/50 (90%)*	OR: 45/50 (90%)*
Jokipii, 1979 (Finland)[129]	SB, R, C	85 adults	2 gm	MTZ(2.4gm x 1 or 2 days)	Unconcentrated and concentrated stool samples; cysts quantified;	Clinical cure and absence of cysts in 3 fecal samples at 1, 2, 4, 8 weeks	26/28 (93%)	MTZ: 13/26 (50%)-2.4 gm MTZ: 24/31 (77%)-2.4 gm x 2 days
Kyronseppa, 1981 (Finland)[130]	R, C	50 adults	2 gm	MTZ (2 gm x 2 days)	Concentrated stool samples	Clinical cure and absence of cysts in 2 stool samples at 2 and 4 weeks post-therapy	22/25 (88%)	MTZ: 19/25 (76%)
Gazder, 1977 (India)[131]	R, C	100 children	50 mg/kg	MTZ (50 mg/kg)	Unconcentrated and concentrated stool samples;	Clinical cure and absence of cysts in stool sample 16 days post-therapy	40/50 (80%)	MTZ: 18/50 (36%)
Nigam, 1991 (India)[132]	R, C	75 adults + children (10-16 years)	50 mg/kg	MTZ (50 mg/kg)	Concentrated stool samples	absence of cysts in stool sample 12 days post-therapy	39/40 (97%)*	MTZ: 19/35 (54%)*
Krishnamurthy, 1978 (India)[133]	OL, R, C	60 children	50 mg/kg	MTZ (50 mg/kg)	Examination of stool sample (no details given)	Clinical cure and absence of cysts in stool sample 12 days post-therapy	29/30 (97%)	MTZ: 15/30 (50%)

* parasitological outcome alone; N = number of patients; Studies in bold represent studies identified as pivotal by sponsor
R = randomized; SB = single blind, OL = open label; C = comparative, MC = multicenter;
TZ = tinidazole; MTZ = metronidazole, OR = ornidazole; ALB = albendezole; P = placebo;

Table 74: Continued

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical and Parasitological Outcome	
							Tinidazole (%)	Comparator (%)
Farahmandian, 1978 (Iran)[134]	OL	175 adults + children + 35 controls	50 mg/kg, 2 gm max	-	Examination of stool by merthiolate-iodine formaldehyde concentration	absence of cysts in 3 consecutive stool samples 4 days post-therapy	156/165 (95%)*	Untreated Control: 10/30 (30%)*
Jokipii, 1978 (Finland)[135]	OL	26 adults	2 gm	-	Unconcentrated and concentrated stool samples	absence of cysts in 3 consecutive stool samples 5 week post-therapy	24/26 (92%)*	-
El Masry, 1978 (Egypt)[136]	C	75 adults and children	2 gm	Placebo	Examination of 3 stool samples by merthiolate-iodine formaldehyde concentration	absence of cysts in 10 consecutive stool samples 3-5 week post-therapy	53/55 (96%)*	Placebo: 2/20 (10%)*
Apte, 1978 (8 countries-Asia)[114]	OL, MC	74 children	50 mg/kg	-	Examination of stool sample (no details given)	Clinical cure and absence of cysts in stool sample at 15 to 90 days post-therapy	65/74 (88%)	-
Sabchareon, 1980 (Thailand)[137]	OL, C	84 hospitalized children	2 gm	MTZ (2 gm) OR (2gm) Placebo	Unconcentrated stool samples daily	Clinical cure and absence of cysts in 3 stool samples at 30 days post-therapy	18/21 (86%)	MTZ: 11/21 (52%) OR: 21/22 (95%) Placebo: 0/20 (0%)
Bouree (1982) (France)[138]	OL	310 adults and 90 children	2gm -adults 50-70 mg/kg children	-	Unconcentrated and concentrated samples	NS	97.4%-adults[#] 88.8% -children[#]	-

*parasitological outcome alone; [#] endpoint for outcome measurement not specified

N = number of patients; R = randomized, SB = single blind; OL = open label; C = comparative;
MC = multicenter, TZ = tinidazole; MTZ = metronidazole; OR = ornidazole; P = placebo; ALB = albendazole

Table 74: Continued

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical and Parasitological Outcome	
							Tinidazole (%)	Comparator (%)
Speelman, 1985 (Bangladesh)[139]	SB, R, C	63 adults and children	50 mg/kg, max 2 gm	MTZ (60 mg/kg)	Unconcentrated and concentrated samples	absence of cysts in 3 stool samples at 1 to 4 weeks post-therapy	16/17(4%)*	MTZ: 9/16 (56%)*
Petterson, 1975 (Finland)[140]	OL	53 adults, 9 children	2 gm-adults	-	Concentrated stool samples	absence of cysts in 2 stool samples at 4 to 6 weeks post-therapy	45/49 (92%)*	-
Pengsaa, 1999 (Thailand)[141]	R, C	113 children	50 mg/kg	ALB (400 mg x 3 days)	Examination of stool sample (no details given)	absence of cysts in 2 stool samples at 1 to 2 weeks post-therapy	49/51 (96%)*	ALB: 31/62 (50%)*
Suntornpoch, 1981 (Thailand)[142]	OL, C	121 children	50 mg/kg	MTZ (20 mg/kg x 5 days) OR (50 mg/kg)	Examination of stool sample (no details given)	Clinical cure and absence of cysts in stool sample at 3 weeks post-therapy	45/48 (94%)	MTZ: 32/33 (97%) OR: 38/40 (95%)

*parasitological outcome alone; N = number of patients, R = randomized; SB = single blind; OL = open label; C = comparative;
MC = multicenter, TZ = tinidazole, MTZ = metronidazole, OR = ornidazole; P = placebo; ALB = albendazole

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3.3. Amoebiasis:
The efficacy of tinidazole was evaluated for the treatment of intestinal and hepatic amoebiasis.

3.3.1. Intestinal amoebiasis:
The sponsor has included 26 publications to support the efficacy of tinidazole in the treatment of intestinal amoebiasis. Of the 26 studies, 12 evaluated the efficacy of the proposed dose (2 gm or 50 mg/kg for 3 days) of tinidazole for treatment of intestinal ameobiasis. The remaining 14 studies used the following doses: 600 mg BID x 5 days, 2 gm QD x 2 days, 2 gm single dose, 1-1.5 gm single dose or QD x 3 days, 1.5 gm QD x 10 days, 150-300 mg TID x 5 days and 0.5 ml oral suspension for 2 days. For the purpose of this review, only 12 studies that used the proposed dose of tinidazole for the treatment of amoebiasis were analyzed. Of the 12 studies, the sponsor was unable to obtain the publication for one study and provided only cure rates. This study was excluded due to insufficient information for review. The remaining 11 studies conducted in India, Bangaldesh, South Africa, and Phillipines are summarized in Table 76. Of these 11 studies, the sponsor identified 4 non-blinded, randomized, comparative studies, as pivotal studies (shown as bold in Table 76). All were conducted in India and used metronidazole (2 gm x 3 days) as the comparator. Additionally, metronidazole was the comparator in 1 supportive double-blinded study. The remaining 6 studies were open label. In 9 of the 11 studies, stool samples were examined by unconcentrated and/or concentrated methods for detection of parasites at baseline and at different time points post-treatment. However, data on the number of cysts/trophozoites at the different time points were not provided using the two methods and the amount of stool examined was not specified. Details of the parasitological evaluation methods for the remaining 2 studies were not provided. The endpoint in these studies was clinical cure and absence of cysts and trophozoites in stool samples at 28-30 days post-therapy. One study (Chunge, 1989)[144], measured the clinical and parasitological outcome on day 6 post-therapy.

A successful clinical and parasitological outcome was observed in 341/369 (92%) intestinal amoebiasis patients treated with tinidazole (from 9 studies, see reference#126, 143-150 in Table 76) compared to 114/209 (55%) treated with 2 gm metronidazole for 3 days (see reference# 126, and 143-145 in Table 76), at 28 to 30 days post-therapy. The parasitological and clinical outcomes were provided separately for 90 of the 369 patients (2 studies, reference#146 and 150 in Table 76). The parasitological outcome (98-100%) correlated with clinical outcome (88-98%) on day 30 after initiation of therapy. However, the correlation of parasitological outcome (51%) with clinical outcome (100%) was poor in another study (Chunge, 1989)[144], when measured at 6 days post-therapy. The occurrence of relapse was not measured in these studies. Also, the *in vitro* susceptibility of isolates from these patients to tinidazole or metronidazole was not measured.

One study (Bakshi et al, 1978)[128], evaluated the parasitological outcome in the patients passing trophozoites versus those passing cysts (Table 76). Patients treated with tinidazole showed similar parasitological outcome in trophozoite passers (88%) versus cyst passers (93%). However, patients treated with metronidazole showed a lower parasitological outcome (47%) in cyst passers compared to trophozoite passers (73%). Overall, the efficacy of tinidazole was better than metronidazole for the treatment of amoebiasis.

Table 76: Summary of all clinical studies using tinidazole (2 gm or 50 mg/kg for 3 days) for the treatment of intestinal amoebiasis.

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical and Parasitological outcome	
							Tinidazole (%)	Comparator (%)
isra, 1977 ndia)[145]	R, C	60	2 gm QD x 3 days	MTZ (2 gm QD for 3 days)	Unconcentrated and concentrated stool samples	Clinical cure and absence of cysts and trophozoites in stool sample at 30 days after initiation of therapy	27/30 (90%)	MTZ: 16/30 (53%)
ngh, 1977 ndia)[146]	R, C	60	2 gm QD x 3 days	MTZ (2 gm QD for 3 days)	Unconcentrated and concentrated stool samples	Clinical cure and absence of cysts and trophozoites in stool sample at 30 days after initiation of therapy	25/27 (93%)	MTZ: 17/29 (59%)
vami, 1977 ndia)[147]	R, C	60	2 gm QD x 3 days	MTZ (2 gm QD for 3 days)	Microscopic examination of stool (details not given)	Clinical cure and absence of cysts and trophozoites in stool sample at 30 days after initiation of therapy	28/29(97%)	MTZ: 15/27 (56%)
akshi, 1978 ndia)[128]	SB, R, C	257	2 gm QD x 3 days	MTZ (2 gm QD for 3 days)	Unconcentrated and concentrated stool samples	Clinical cure and absence of cysts and trophozoites in stool sample at 30 days after initiation of therapy	38/43 (88%) – trophozoite passers; 85/91 (93%)-cyst passers	MTZ: 22/30 (73%) – trophozoite passers; 44/93 (47%)-cyst passers
lam, 1975 angladesh)[148]	OL	49	2 gm QD x 3 days	-	Clinical, parasitological and sigmoidoscopic examination (no details given)	Cure on day 30 after initiation of therapy	48/49 (98%) - parasitological cures; 44/50 (88%) - clinical cure; Both 43/50 (86%)	-
ragg, 1977 outh Africa)[149]	OL	25 children	60 mg/kg x 3 days	-	Unconcentrated smear and zinc-sulfate flotation	Clinical cure and absence of cysts and trophozoites in stool sample at 28 days after initiation of therapy	24/25 (96%)	-

= number of patients, R = randomized; SB = single blind; OL = open label; C = comparative; MC = multicenter;
= tinidazole; MTZ = metronidazole; Studies identified by the sponsor as pivotal are shown in bold.

Table 76: Continued.

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical and Parasitological outcome	
							Tinidazole (%)	Comparator (%)
arcia, 1978 hillipines)[150]	OL	4	50 mg/kg QD x 3 days	-	Unconcentrated stool samples daily	Clinical cure and absence of cysts in 3 stool samples at 30 days post-therapy	4/4 (100%)	-
pte and Packard, 978 (Asia)[114]	OL, MC	443 adults and 44 children	2 gm QD x 3 days	-	Unconcentrated and concentrated samples	Not specified	95%*	-
cragg, 1976 South Africa)[151]	OL	30 children	60 mg/kg QD x 3 days	-	Unconcentrated smear and zinc-sulfate flotation	Clinical cure and absence of cysts and trophozoites in stool sample at 28 days after initiation of therapy	28/30(93%)	-
hmed, 1976 Bangladesh)[152]	OL	40 children	50 mg/kg QD x 3 days	-	Unconcentrated stool sample	absence of cysts and trophozoites in stool sample at 30 days after initiation of therapy	40/40 (100%)-parasitological cure 39/40 (98%)-clinical cure	-
hunge, 1989 Kenya)[144]	DB, R, C	225	2 gm QD x 3 days (Fasigyn and generic TZ)	MTZ: 400 mg TID x 5 days (Flagyl and generic MTZ)	Unconcentrated and concentrated samples	absence of cysts and trophozoites in stool sample at 6 days post-therapy.	parasitological cures: 30/59 (51%)-Fasigyn 15/64 (23%- generic TZ; 100% - clinical cure all groups	parasitological cures: 24/49 (49%)-Flagyl 18/53 (34%)-generic MTZ; 100% - clinical cure all groups

ndpoint for efficacy measurement not specified
= number of patients; R = randomized; SB = single blind; OL = open label, C = comparative; MC = multicenter;
Z = tinidazole, MTZ = metronidazole,

3.3.2. Hepatic amoebiasis (amoebic liver abscess):

The efficacy of tinidazole for the treatment of amoebic liver abscess was described in 18 publications. Of these 18 studies, 14 studies evaluated the efficacy of the proposed dose of tinidazole (2 gm or 50 mg/kg for 3 to 5 days). Of these 14 studies, the sponsor was unable to obtain the publications for 2 studies and provided only cure rates. For the purpose of this review, these 2 studies and 4 other studies that used dosage regimens (800 mg TID for 5 days, 1 gm BID x 1 day, 1.2-1.5 gm single or divided doses, 2 gm x 2 days) other than the proposed dose were excluded from analysis. The sponsor identified 7 studies as pivotal studies for evaluating the efficacy of tinidazole for the treatment of amoebic liver abscess (shown as bold in Table 77). All these 7 studies were randomized and used metronidazole (2 gm x 3 days or 400 mg TID for 5 days) as the comparator. The remaining 5 studies were open label. The diagnosis of amoebic liver abscess in all the studies was based on clinical and radiological findings and/or presence of trophozoites in liver aspirates. Besides presence of trophozoites in liver aspirate, presence of amoebic antibodies by CIE or positive results using the amoebic gel diffusion assay at baseline were used to aid diagnosis in 2 studies (Simjee, 1985 and Scragg, 1977)[153,154]. However, the details of the methods were not provided.

The endpoint for efficacy evaluation in 10 of the 12 studies was cure by clinical and radiological criteria at 20-30 days post-therapy while in the remaining 2 studies, the clinical and radiological assessments were made at 5-10 days after initiation of therapy. No parasitological evaluations were performed in these studies. A successful clinical outcome was observed with tinidazole treatment in 91% (310/339) patients with amoebic liver abscess (all studies, Table 77) compared to 74% (89/120) patients treated with metronidazole (2 gm x 2-5 days, see references 126, 151, 153-156 in Table 77). The efficacy of tinidazole was comparable to a 2 gm x 5 days metronidazole regimen but better than the 400 mg TID x 5 days metronidazole regimen. No information was available on relapse in these patients. Overall, tinidazole was effective in the treatment of amoebic liver abscess.

Table 77: Summary of all clinical studies using tinidazole (2 gm or 50 mg/kg for 3-5 days) for the treatment of amoebic liver abscess.

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical outcome	
							Tinidazole (%)	Comparator (%)
Kundu, 1977 (India)[155]	R, C	18	2 gm QD x 3 days	MTZ (2 gm QD for 3 days)	Liver aspiration examined for trophozoites; radiological scan	Clinical cure on day 30 post-treatment	8/9 (89%)	MTZ: 3/9 (33%)
Islam, 1978 (Bangladesh)[156]	R, C	31	2 gm QD x 3 days	MTZ (2 gm QD for 3 days)	Clinical and radiological findings, liver aspirate when necessary	Cure by clinical criteria on day 20 after initiation of therapy	15/16 (94%)	MTZ: 12/15 (80%)
Khokhani, 1977 (India)[157]	R, C	19	2 gm QD x 2 days	MTZ (2 gm QD for 2 days)	Liver aspiration examined for trophozoites; radiological scan	Cure by clinical and radiological criteria on day 30 post-treatment	10/10 (100%)	MTZ: 5/9 (56%)
Mathur, 1977 (India)[158]	SB, R, C	36	2 gm QD x 2-3 days	MTZ (2 gm QD for 2 days)	Liver aspiration examined for trophozoites; radiological scan	Cure by clinical criteria on day 30 post-treatment	14/14 (100%)-3 days 11/11 (100%)-2 days	MTZ: 10/11 (91%)
Bakshi, 1975 (Bangladesh)[128]	R, C	99	2 gm QD x 2 days	MTZ (2 gm QD for 2 days)	Liver aspiration examined for trophozoites; radiological scan	Cure by clinical criteria on day 30 post-treatment	48/50 (96%)	MTZ: 37/49 (76%)
Simjee, 1985 (S. Africa)[153]	SB, R, C	48	2 gm QD x 5 days	MTZ (2 gm QD for 5 days)	Liver aspiration examined for trophozoites; amoebic gel diffusion	Cure by clinical and radiological criteria on day 5 post-treatment	17/21 (80%)	MTZ: 22/27 (81%)
Mendis, 1984 (Sri Lanka)[159]	R, DB, C	34	2 gm QD x 3 days	MTZ: 400 mg TID x 5 days	Clinical and radiological findings	Clinical cure at end of treatment (day 5)	13/16 (81%)	MTZ: 6/18 (33%)

N = number of patients; R = randomized, SB = single blind, OL = open label; C = comparative;
TZ = tinidazole; MTZ = metronidazole; Studies shown in bold were identified as pivotal by the sponsor.

Table 77:Continued

Study (country)	Design	N	Tinidazole dose	Comparator (dose)	Diagnosis	Endpoint	Clinical outcome	
							Tinidazole (%)	Comparator (%)
Apte and Packard, 1978 (Asia)[114]	OL	82	2 gm QD x 3 days	-	Liver aspiration examined for trophozoites; radiological scan	Cure by clinical and radiological criteria on day 30 post-treatment	77/82 (94%)	-
Cervantes, 1975 (Mexico)[160]	OL	30	2 gm QD x 3 days	-	Clinical and radiological findings; amoebic antibodies by CIE	Cure by clinical and radiological criteria 10 and 20 days	28/30 (93%)	-
Scragg, 1977 (S. Africa)[154]	OL	25	50 mg/kg x 3-5 days	-	Liver aspiration examined for trophozoites; amoebic gel diffusion in 23 patients	Clinical cure up to 6 months	23/25 (92%)	-
Abiose, 1976 (Nigeria)[161]	OL	20	2 gm QD x 3 days	-	Liver aspiration examined for trophozoites; radiological scan	Clinical cure up to 6 months	18/20 (90%)	-
Quaderi, 1978 (Bangladesh)[162]	OL	35	2 gm QD x 2-3 days	-	Liver aspiration examined for trophozoites when possible; radiological scan	Cure by clinical criteria on day 30 post-treatment	9/16 (56%)- 2 days; 19/19 (100%)- 3 days	-

N = number of patients, R = randomized, SB = single blind, OL = open label, C = comparative;
TZ = tinidazole; MTZ = metronidazole, DB = double-blind; CIE = counterimmunoelectrophoresis.

3.4. *Helicobacter pylori* infection:

The activity of omeprazole (20 mg) and clarithromycin (250 mg) in combination with metronidazole (400 mg; OCM) or tinidazole (500 mg; OCT) against *Helicobacter pylori* infection was evaluated[163]. This is a single blinded study in which eighty five patients (>18 years of age), with documented duodenal ulcer (DU), who tested positive for serum *H. pylori* IgG antibodies by ELISA, and ^{14}C-breath test (UBT), were randomly assigned to receive either OCT or OCM twice a day for one week. Six to eight weeks following completion of treatment, patients were given a UBT to check for eradication of *H. pylori*. Eradication was confirmed by repeat UBT. Therefore, no endoscopies, histology and culture characterization were performed.

The results of the study show that *H. pylori* infection was eradicated in 36 out of 41 patients receiving OCM, this was confirmed by repeat UBT. Of the 5 patients that failed treatment, one had non-compliance issues due to vomiting. In the OCT treatment group, complete eradication was observed indicating 100% eradication rate (Table 78). Individuals receiving OCT reported fewer side effects than those on OCM. It appears that the success of OCT over OCM may be due to the administration of higher doses of tinidazole (500 mg) compared with metronidazole (400 mg).

Table 78: Table. Comparison of the two H. pylori eradication groups

	OCM	OCT	
Number of patients	41	44	
Males	31	39	
Females	10	5	p = 0.12
Mean age (SD)	57 (10.9)	61.7 (11.3)	p= 0.052
Successful eradication	36 (87.8%)	44 (100%)	p = 0.023
Patients reporting side effects	23 (52.2%)	17 (41.5%)	p=0.32
Details of side effects reported by the patients			
Diarrhoea	8	2	
Abdominal discomfort	7	3	
Bad taste	5	1	
Mouth ulcers	2	1	
Nausea	2	5	
Headaches	4	2	
Personality changes	1	5	

Other side-effects reported by 2 or less patients included tiredness, vomiting, sore throat, off-colour, constipation, urine odour, polyuria, cramps, vertigo, mouth ulcers, insomnia, dark tongue and hallucinations

In another study, the effect of tinidazole on *H. pylori* eradication was evaluated in 141 patients above the age of 18[164]. *H. pylori* infected patients attending an open access endoscopy clinic with dyspepsia were enrolled. Colonization was confirmed by histology (two antral and two corpus biopsies using Giemsa stain), rapid urea test (from one antral biopsy) and ^{13}C-urea breath-test. One antral biopsy was obtained and either stored at 4°C or incubated at 36°C under microaerophilic conditions on selective or non-selective Mueller-Hinton agar containing 5% horse blood for 72 hours. Antibiotic sensitivity was not determined by the agar dilution method but by the E-test and disc diffusion method. The disc diffusion technique used involves impregnating a disc with 5 µg metronidazole and placing it onto a lawn of evenly growing bacterial cells. There are no 5-nitroimidazole MIC interpretative standards established for *H.*

pylori. The authors considered isolates with inhibition zone diameters of <20 mm as resistant to 5-nitroimidazole.

Patients were administered omeprazole 20 mg QD (n = 23) or BID (n = 119), clarithromycin 250 mg BID, and tinidazole 500 mg, for 7 days. Eradication was determined by repeat ^{13}C-urea breath test 4 weeks following the completion of therapy. *H. pylori* was isolated and cultured from those individuals in whom therapy failed and from a proportion of those that had successful eradication. The overall eradication rate was 125/141, the eradication rate for OCT was 90% (62/69) for patients with isolates that were sensitive to 5-nitroimidazole. An eradication rate of 93% (42/45) was observed for isolates that were resistant to 5-nitroimidazoles (Table 79).

Table 79. Success of OCT in treating *H pylori* according to antibiotic resistance assessed by disc diffusion test (Mast diagnostics).

	Pattern of *Helicobacter pylori* antibiotic resistance			
	Fully sensitive	Metronidazole-resistant	Clarithromycin-resistant	Dual resistar
Treatment success (n = 106)	62	42	1	1
Treatment failure (n = 13)	7	3	0	3

OCT Omeprazole (20mg o d or b d) clarithromycin (250mg b d) and tinidazole (500mg b d) for 7 days

3.5. Bacterial Vaginosis:

There were 8 publications on clinical studies examining efficacy of tinidazole for the treatment of BV using the proposed dose (summarized in Table 80). Placebo or metronidazole was used as a comparator. Please note that the inclusion criteria and efficacy endpoints for the different studies varied. None of the studies used the gram stain nugent score (which is based on the morphotype score of the *Gardnerella/Bacteroides* species and curved gram-variable rods relative to that of the *Lactobacilli* species in the vaginal specimen) for evaluating efficacy. Of the 8 studies, 3 [Ekgren *et al.*, (1988)[165], San Sanz *et al.*, (1985)[166] and Mohanty *et al.*, (1987)[68]] used absence of *G. vaginalis* in vaginal specimens by culture as an efficacy endpoint. Columbia-nalidixic acid agar with 5% human blood and the Wilkins Chalgren agar with 10% horse blood were used for culture of *G. vaginalis* under anaerobic conditions in the studies by San Sanz *et al.*, (1985)[166] and Mohanty *et al.*, (1987)[68], respectively. However, the media used for culture of *G. vaginalis* in the study by Ekgren *et al.*, (1988)[165] was not specified. The results in Table 80 show that tinidazole was as effective as metronidazole in improving symptoms of BV. Overall, 50-65% patients treated with tinidazole showed absence of *G. vaginalis* by culture at ≥ 2 weeks after initiation of therapy. Efficacy against pathogens other than *G. vaginalis* associated with BV was not measured.

Table 80: Clinical studies using tinidazole 2 g single dose for one or two days for treatment of bacterial vaginosis.

Study	Design	N	Comparator (dose)	Endpoint	TZ Dose	Success rate for TZ	Success rate for comparator
Ekgren (1988)[165]	R, DB	247	placebo	-ve clue cells; -ve *G. vaginalis* (2 weeks after initiation of therapy)	2g X1 d 2g X 2d	50% (42/82) 73% (61/84)	4% (3/81)
Vutyavanich (1993)[167] *	R, DB	243	placebo	≤ 2 symptoms (4 weeks after initiation of therapy)	2g	72% (83/116)	63% (74/117)
Paavonen (1984)[168]	R, DB	33	placebo	Symptom cure (2 weeks after initiation of therapy)	2g	71% (12/17)	38% (6/16)
Van Der Meijden (1983)[169]	R, DB	26	placebo	≤ 1 symptoms (4 weeks after initiation of therapy)	2g	46% (6/13)	7% (1/13)
Mohanty (1987)[68]	Pros, OL	180**	MTZ (2 g for 1 day)	-ve *G vaginalis* ≤ 1 symtpoms (1 weeks after initiation of therapy)	2g	92% (72/78)^ 95% (19/20)#	79% (50/63)^ 89% (17/19)#
Buranawarodomkul (1990)[170]	R, OL	100	MTZ (500 mg b.i.d for 7 days)	≤ 3 symtpoms (1-2 weeks after initiation of therapy)	2g	86% (43/50)	92% (46/50)
San Sanz (1985)[166]	OL	80	MTZ (500 mg b.i.d for 7 days)	Symptom cure -ve *G. vaginalis* (4 weeks after initiation of therapy)	2g	65% (26/40)	74% (29/39)
Schindler (1991)[171]	R, OL	75	MTZ (400 mg vaginal tablet for 5 days)	≤ 2 symptoms (2 weeks after initiation of therapy)	2g	97% (36/37)	84% (32/38)

*In this study, 64% of patients treated with tinidazole were stated to have heavy growth of *G. vaginalis* at 4 weeks after initiation of therapy.
^ relapse of *G. vaginalis* was 14% in the tinidazole arm and 21% in the metronidazole arm at >2 weeks after discontinuation of therapy.
**39 had concurrent trichomoniasis
#patients with *G vaginalis* and *T. vaginalis*.
N = number of subjects; R = randomized; DB = double-blind; OL = open label;
Pros = prospective; TZ = tinidazole; MTZ = metronidazole.

4. CONCLUSIONS:

The sponsor is seeking approval of tinidazole for the treatment of trichomoniasis giardiasis and amoebiasis (intestinal and hepatic).

Mechanism of action:
Chemically, tinidazole is a 5-nitroimidazole. Tinidazole is reduced by cell extracts of *Trichomonas*. The reduction of the nitro group of tinidazole results in generation of free radical anion, which may be responsible for the anti-protozoal activity of the drug.

Chemically reduced drug was shown to cause damage to purified *E. coli* DNA *in vitro*. Additionally, the drug caused DNA base changes and DNA strand breakage in bacterial or mammalian cells.

The mechanism by which tinidazole exhibits activity against *G. lamblia* and *E. histolytica* is not known.

Activity *in vitro*:

T. vaginalis:
The *in vitro* activity of tinidazole against the trophozoite stage of 15 *T. vaginalis* strains and 233 clinical isolates was examined in 14 different laboratories using 3 different medium (Table 20). The incubation period in these studies varied between 24 and 72 hours. The doubling time of *T. vaginalis* is 6 hours in Diamond's medium and drug effect would be observed between 24 to 72 hours in this media. However, such information is lacking for other growth media. Because of lack of standardized *in vitro* susceptibility testing procedures, it is difficult to interpret and compare the data published by various investigators. The tinidazole MICs (defined as concentration at which no motility is observed) against the different strains ranged from 0.4 to 150 µg/ml under aerobic conditions, and from 0.4 to 25.0 µg/ml under anaerobic conditions. The tinidazole MICs against the clinical isolates varied from 0.05 to 12.5 µg/ml. Whether testing was done under aerobic or anaerobic conditions was not specified. the tinidazole MICs varied from 12.5 to > 400 µg/ml under aerobic conditions and 0.3 – 25 µg/ml under anaerobic conditions. Please note that there are no interpretive criteria for susceptibility of *T. vaginalis* to metronidazole. One study[172] showed that metronidazole MICs of ≥400 and >12.5 µg/ml, under aerobic and anerobic conditions, respectively, may correlate with clinical resistance (treatment failure with 2 courses of 2 gm metronidazole). However, the number of isolates tested was small and the susceptibility patterns of isolates from patients treated with different approved dosage regimens for metronidazole were not examined. The activity of tinidazole was comparable to metronidazole against a majority of the strains and clinical isolates.

***G. lamblia*:**
The activity of tinidazole was measured against the trophozoite stage of 22 strains and 59 isolates of *G. lamblia* using different media, incubation periods (2 hours to 7 days), inoculum sizes and methods in 9 laboratories (Table 32). Irrespective of the assay conditions, the tinidazole MIC values (defined as the concentration of the drug required to alter morphology, viability, adherence or motility) against the trophozoite stage of *G. lamblia* strains ranged from 0.32 - 1.0 µg/ml. The tinidazole IC_{50} values against the strains ranged from 0.03 to 0.29 µg/ml. Against the clinical isolates, the tinidazole MIC values (0.1 to 6.2 µg/ml) and IC_{50} values (0.09 – 25.0 µg/ml) were variable. The doubling time for the trophozoite stage of *G. lamblia* varies from 12 to 44

hours. Hence, it is unclear if measurement of drug activity at 2 hours would provide useful information. The different assays gave comparable activity when tested against the same strain. A 3 - 4 fold variation was observed in the activity of tinidazole measured on different days against the same strain. Overall, the activity of tinidazole was similar to metronidazole and furazolidone. Tinidazole in combination with doxycycline, mefloquine or furazolidine does not appear to be antagonistic against the P1 and BRIS/82/HEP/41 strains of *G. lamblia* by the growth inhibition and adherence assays.

The activity of tinidazole against the cyst stage of *G. lamblia* was not measured *in vitro*.

E. histolytica:
The *in vitro* activity of tinidazole against the trophozoite stage of *E. histolytica* strains was examined in 3 different laboratories using liver marmite serum or Locke's medium. The MIC defined as concentration of the drug required to completely inhibit growth at 24 or 48 hours was measured. The doubling time for the trophozoite stage of *E. histolytica* is about 8 hours. Hence, drug effect would be observed at 24 to 48 hours of incubation. The activity of tinidazole against the 14 clinical isolates (MIC range = 0.3 to 2.5 μg/ml) of *E. histolytica* was similar to that observed against the 36 laboratory strains (MIC range = 0.063 to 1.25 μg/ml). The activity of tinidazole against the strains and clinical isolates was comparable to metronidazole.

The activity of tinidazole against the cyst stage of *E. histolytica* was not measured *in vitro*.

Bacteria associated with bacterial vaginosis:
The sponsor has included studies conducted in 11 different laboratories to support the *in vitro* activity of tinidazole against various anaerobic bacteria associated with bacterial vaginosis. The testing methods used in these studies varied. Only one of the studies used the NCCLS method for susceptibility testing of anaerobes. However, the *in vitro* activity of tinidazole against various isolates of *G. vaginalis* (n = 812), *Bacteroides* species (n = 9), *Mobiluncus* species (n = 22), *Pervotella* species (n = 218) and *Porphyromonas* species (n = 43) was similar to metronidazole under the conditions tested. The tinidazole MIC_{90} values against *G. vaginalis* isolates tested in 7 laboratories varied between 1.6 and >256 μg/ml. The tinidazole MBCs against the *G. vaginalis* isolates were 2 to 4 fold higher than the MICs. Testing in 5 laboratories showed the tinidazole MIC_{90s} against *Bacteroides* sp. to range from 0.12 to 128 μg/ml. The tinidazole MBCs against the *Bacteroides* sp. were 2 to 8 fold higher than the MICs. The tinidazole MICs against *Mobiluncus* sp. and *Pervotella* sp. tested in one laboratory ranged from 0.5 to 256 μg/ml. For *Fusobacterium* sp., *Peptostreptococci* sp., and *Porhyromonas* sp., the results of susceptibility testing showed that the tinidazole MIC values were ≤ 2 μg/ml against all 3 bacterial species. The tinidazole MIC_{90} against the *Lactobacillus* species were >32-fold higher than against the anaerobic bacteria associated with bacterial vaginosis other than *G. vaginalis*.

C. difficile:
Tinidazole was more active against some 5-nitroimidazole resistant strains and metronidazole was more active against 5-nitroimidazole sensitive strains of *C. difficile* in one study. However, the criteria used to characterize the strains as resistant or sensitive were not described. Another comparative study shows tinidazole to be less active than metronidazole against *Clostridium* sp. The NCCLS criteria were not used to determine the susceptibility of these organisms.

***H. pylori*:**
The activity of tinidazole and metronidazole appear to be similar against *H. pylori*. In one study, the NCCLS guideline for anaerobic organisms was used to characterize the susceptibility of 53 clinical isolates of *H. pylori* to 5-nitroimidazole. Anaerobic pre-incubation significantly decreased the tinidazole and metronidazole MIC values against *H. pylori*. In another study, tinidazole was 2-fold more active than metronidazole against 18 clinical isolates of *H. pylori*. In one drug combination study, the combination of clarithromycin and tinidazole appear to be slightly more effective than the combination of clarithromycin and metronidazole.

Activity *in vivo*:

***T. vaginalis*:**
In mice infected intravaginally with trophozoite form of *T. vaginalis* mixed with *C. albicans*, a 1.41 mg/kg dose of oral tinidazole was required for 50% reduction in trophozoite count. A higher tinidazole dose (7.5 mg/kg) was required to have a similar effect in mice infected by the intraperitoneal route. In these 2 mouse models, a 1.4 to 2.6 fold higher dose of metronidazole compared to tinidazole was required for treatment.

The suppression of infection in 95% of mice infected intraperitoneally with the *T. vaginalis* TR strain required a dose of 8.8 mg/kg tinidazole. A 3 fold higher dose of tinidazole was required for suppression of infection in mice infected subcutaneously with the same strain. A 5 to 6 fold higher dose was required for suppression of infection in mice infected subcutaneously with the *T. vaginalis* [redacted] strain compared to the TR strain.

The tinidazole ED_{50} values against *T. foetus* in the intraperitoneal mouse model ranged between 10 and 26 mg/kg. The tinidazole ED_{50} values using the intraperitoneal mouse model were 2 to 3.5 fold lower than the ED_{50} values in the subcutaneous mouse model.

***G. lamblia*:**
In suckling mice infected intragastrically with trophozoite forms of *G. lamblia*, tinidazole was more active than metronidazole in reducing trophozoite counts in intestinal tissue, at 2 days post-treatment.

***E. histolytica*:**
In rats infected intracecally with the trophozoite stage of *E. histolytica*, tinidazole ($\geq$ 50 mg/kg) was effective in decreasing the severity of infection (based on reduction in trophozoites and improvement in the pathology of the intestinal tissue), at 24 hours post-treatment.

In hamsters, tinidazole (100 mg/kg) was effective in preventing development of amoebic liver abscess in hamsters. Parasite burden in the tissue was not measured.

Drug resistance:
The development of resistance to tinidazole by *T. vaginalis*, *G. lamblia*, and *E. histolytica* has not been examined *in vitro* or *in vivo*.

Cross-resistance:
In vitro, an increase in tinidazole MIC correlated with increases in metronidazole MIC against *T. vaginalis* strains and isolates from patients who failed metronidazole therapy, suggesting cross-resistance between the two drugs.

The cross-resistance between tinidazole and metronidazole was not examined against *E. histolytica* and *G. lamblia in vitro* or *in vivo*.

Clinical Microbiology:
There are no standardized methods for measuring *in vitro* susceptibility of drugs against *T. vaginalis*, *G. lamblia*, and *E. histolytica*. Additionally, a correlation between *in vitro* activity and clinical outcome in patients with infections due to these pathogens has not been established.

In patients with **vaginitis due to *T. vaginalis***, a successful parasitological outcome was observed in 2131/2271 (95%) patients (29 studies) treated with tinidazole using the wet mount or culture method. Information on symptom resolution or relief was available for 357 of the 2271 patients. A correlation was observed between clinical and parasitological outcome in these 357 patients. A relapse rate of 5% was observed when both female patients and their male partners were treated with tinidazole, at 1 month post therapy. Tinidazole was as effective as metronidazole and other experimental drugs such as ornidazole and carnidazole.

In patients with **urethritis due to *T. vaginalis***, absence of trichomonads by wet mount or culture of urine sediments or urethral scrapings was observed in 96% (240/250) men treated with 2 gm tinidazole dose. Information on resolution of symptoms was available for 105 of the 250 patients. The parasitological outcome correlated with clinical outcome in these 105 patients. The relapse rates were not measured in male patients with urethritis. The efficacy of tinidazole was similar to metronidazole in patients with urethritis.

Overall, the efficacy of tinidazole in 565 male and female patients with trichomoniasis using the culture method varied from 74 - 100% compared to 80 - 100% in 1963 patients evaluated by the wet mount method. A direct comparison between wet mount and culture methods was made in 1 study (Psaroudakis *et al.*, 1977)[89]. The study showed that 40% of patients with a negative wet mount were positive by culture, suggesting that the culture method is more sensitive than wet mount. The greater sensitivity of culture using Diamond's medium or In Pouch test compared to wet mount has also been described in the literature[1,2].

In one clinical study, an increase in *Lactobacillus* was observed in 69.9% patients at 4 to 6 weeks post-therapy with a single 2 gm dose of tinidazole. The *Lactobacillus* flora remained unchanged in 17.7% patients and decreased in 0.9% patients treated with tinidazole (Table 71). Based on this, the sponsor has concluded that tinidazole does not inhibit most isolates of vaginal lactobacilli.

In patients (adults and children) with **giardiasis**, the parasitological outcome after treatment with tinidazole was measured using unconcentrated and concentrated stool samples in 13 studies. Two or more stool samples were examined in 10 of the 13 studies. Absence of cysts was observed in 710/773 (92%) adults and children with giardiasis at 2 - 8 weeks post-therapy. The clinical and parasitological outcome data were not provided separately but as combined therapeutic cure rates in 8 studies. In these studies, a correlation between clinical and parasitological outcomes was observed. No information was available on the occurrence of relapse in these patients. The efficacy of tinidazole was better than metronidazole or albendazole but comparable to ornidazole in these studies.

In patients (adults and children) with **intestinal amoebiasis**, the parasitological outcome after treatment with tinidazole was measured using unconcentrated and concentrated stool samples in 9 studies. A successful clinical and parasitological outcome was observed in 341/369 (92%) intestinal amoebiasis patients treated with tinidazole compared to 114/209 (55%) treated with 2 gm metronidazole for 3 days at 28 to 30 days post-therapy. The parasitological outcome correlated with clinical outcome when measured on day 30 after initiation of therapy. However, the correlation of parasitological outcome (51%) with clinical outcome (100%) was poor when measured at 6 days after discontinuation of therapy. The occurrence of relapse was not measured in these studies. Tinidazole showed similar parasitological outcome in trophozoite passers and cysts passers. The parasitological outcome in trophozoite passers treated with metronidazole (73%) was comparable to tinidazole (88%). However, the parasitological outcome in cyst passers treated with metronidazole (47%) was lower than tinidazole (93%).

In patients with **hepatic amoebiasis**, a successful clinical outcome was observed with tinidazole treatment in 91% (310/339) patients with amoebic liver abscess compared to 74% (89/120) patients treated with metronidazole (2 gm x 2-5 days). The parasitological outcome was not measured in these studies. The efficacy of tinidazole was comparable to a 2 gm x 5 days

metronidazole regimen but better than the 400 mg TID x 5 days metronidazole regimen. No information was available on relapse in these patients.

Overall, tinidazole was effective in the treatment of trichomoniasis, giardiasis, intestinal and hepatic amoebiasis.

Tinidazole alone was not effective in the treatment of *H. pylori* infection. However, a combination of tinidazole with omeprazole and clarithromycin was more effective than a combination of metronidazole, omeprazole and clarithromycin. However, this effect can be explained by the higher tinidazole concentration used in the study. Eradication was confirmed only by UBT and not endoscopies, histology and culture characterization. Therefore, it is difficult to make an accurate microbiologic assessment of this study.

All the published clinical studies examining the efficacy of tinidazole for the treatment of bacterial vaginosis varied with respect to inclusion criteria and efficacy endpoint. Only 3 studies used the microbiological endpoint of absence of *G. vaginalis* for efficacy evaluation. The absence of *G. vaginalis* was observed in 50-65% of the patients treated with tinidazole after 2 - 4 weeks of discontinuation of therapy. The efficacy of tinidazole in patients with bacterial vaginosis associated with organisms other than *G. vaginalis* was not measured.

5. LABEL:

5.1. Sponsor's proposed label:

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

[redacted]

6. RECOMMENDATIONS:

The NDA submissions are approvable with respect to Microbiology pending an accepted version of the label for the treatment of trichomoniasis, giardiasis and amoebiasis.

[redacted]

Kalavati Suvarna
Microbiologist, HFD-590

Avery Goodwin
Microbiologist, HFD-590

CONCURRENCES:

HFD-590/Deputy Dir. _____Signature _____Date
HFD-590/Micro TL _____Signature _____Date
CC:
HFD-590/Original IND
HFD-590/Division File
HFD-590/MO
HFD-590/Pharm
HFD-590/Chem
HFD-590/Review Micro
HFD-590/CSO/ChiC

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