occurred 10 days later and was again treated with a 10 day course of tinidazole and symptoms disappeared, and no adverse effects were reported."

MO Comment: Although the severe neurologic events are of concern, they are related to metronidazole. A similar concern may be present with tinidazole use due to the similarity of the compounds but a conclusive relationship is not possible.

7.2.10 Post-marketing Experience

Data from the UK and Australia's post-marketing surveillance was submitted by the sponsor as of August, 2000. Adverse events are listed in Table 7.25 along with the proportion of all events ascribed to the specific line item. Allergic events were noted to be more frequent that present in the submitted data. Gastrointestinal and neurological events were also evidently present in higher proportion that other events. As with all spontaneous reporting systems, denominator data is lacking and adequate utilization data was not submitted. The reason that allergic-type reactions such as urticaria, facial edema and rash were more prominent than in the submitted literature may be related to reporting bias but the specific reasons for this variation cannot be ascertained.

Table 7.30: Adverse Events from Australia and UK Spontaneous Post Marketing Reporting Systems

Adverse Event	% All Adverse Events	Adverse Event	% All Adverse Events
Urticaria	7.3	Hypotonia	0.3
Pruritus	5 8	Paranoia	0 3
Nausea	4.8	Depression NOS	0 3
Taste Altered	4.5	Anxiety	0.3
Fatigue/malaise	4.5	Euphoria	0.3
Diarrhea NOS	3 5	Constipation	0 3
Vomiting	3.5	Dysphagia	0.3
Headache NOS	3.3	Steatorrhoea	0.3
Rash NOS	3.0	Rectal Hemorrhage	0.3
Face oedema	2.5	Gingivitis	0.3
Dizziness	2.3	Dental disorder NOS	0.3
Paraesthesia	2 3	Dry mouth	0.3
Dizziness	2.3	Salivary gland enlargement	0 3
Abdominal pain	2 3	Stomatis	0.3
Rash erythematous	2 0	Weight increase	0 3
Rash maculo-papular	1 8	Hepatamegaly	0.3
Flushing	1 5	Jaundice cholestatic	0 3
Anorexia	1.3	Glossitis	0 3
Dyspnoea	1 3	Tongue discoloration	0 3
Hepatic function abnormal NOS	1.0	Anaphylactoid reaction	0 3
Taste Loss	1 0	Rash Morbilliform	0 3
Hypotension	1 0	Fixed eruption	0 3
Fever	1 0	Larynx oedema	0 3
Athralgia	1 0	Alopecia	0 3
Bronchospasm	1 0	Skin exfoliation	0 3
Oedema	1 0	Pulmonary embolism	0 3
Confusion	0 8	Atrial fibrillation	0 3
Hepatitis	0 8	Cerebrovascular accident	0 3
Tongue oedema	0 8	Chest Pain	0 3
Oedma periorbital	0 8	Hypercapnia	0 3
Oedma peripheral	0.8	Hypoxia	0 3
Rigors	0 8	Cyanosis	0 3
Sweating Increased	0 8	Aponea	0 3
Abnormal urine	0.8	Involuntary respiratory noises	0.3
Syncope	0.5	Stridor	0.3
Vertigo	0 5	Thrombocytopenia	0 3
Tremor	0 5	Hypokalemia	0 3
Neuropathy	0 5	Epistaxis	0.3
Neuritis	0.5	Congenital abnormality NOS	0 3
Hemiparesis	0.5	Anencephalic foetus	0.3
Vision abnormal	0 5	Heart malformation	0 3
Dystonia	0.5	Death - fetal	0.3
Ataxia	0.5	Hypothyroidism	0.3
Psychosis	0 5	Rectal Hemorrhage	0 3
Hallucination	0 5	Dental disorder NOS	0 3
Photosensitivity reaction	0 5	Pallor	0 3
Weight decrease	0.5	Pain	0 3
Palpitation	0 5	Unexpected therapeutic effect	0 3
Tachycardia	0 5	Prothrombin activity increased	0.3
Neutropenia	0 5	Rhabdomyolysis	0.3
Alcohol Interaction	0.5	Arthritis	0 3
Myalgia	0 5	Euphoria/giddiness	0.3
Somnolence	0 3	Frequent erection	0 3
Convulsions - Gran Mal	0.3	Lactation puerperal decreased	0.3
Coma	0 3	Abortion	0.3
Insomnia	0 3	Renal Pain	0 3
Cranial nerve lesion	0 3	Albuminuria	0 3
Paralysis	0 3	Anuria	0 3
Diplopia	0 3	Hematuria	0 3
Sensory disturbance	0.3	Urinary Retention	0 3
Hypoaesthesia	0.3	Lymphadenopathy	0 3
Extrapyrmadial disorder	0.3	Purpura	0 3
Hypertonia	0.3	Death - fetal	0.3

Adequacy of Patient Exposure and Safety Assessments

7.2.11 Extent and Adequacy of Overall Clinical Experience

NDA 21-618 has been submitted under Section 505(b)(2) of the US Food, Drug & Cosmetic Act which permits approval on the basis of data presented the scientific literature. This submission is specifically classified as a *literature-based* 505(b)(2) since the application for approval relies on studies that "*were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted*" (21 CFR 314.54). Other sources of data included in this review are foreign labeling and sponsor submitted evaluation which will also be included in this review. The sponsor has submitted a total of 360 references of which 93 were submitted for safety evaluation. Of the 93 submitted literature citations 17 were excluded as noted in Table 1.

Table 7.31: Submitted Literature

Indications	# Studies Submitted	# Studies Excluded	Study Number (s)	Reason for Exclusion	# Studies Included for Evaluation	# Subjects Included in Evaluation
Trichomoniasis	34	4	94, 184, 277,278	Patient population and doses combined, no safety data provided	30	1874
Giardiasis	24[1]	4	187, 186, 189, 272	No safety data provided and data discrepancies in the article	20	697
Intestinal amebiasis	20[2]	4	287, 288, 289, 291	No safety data provided, unspecified dose, or no linkage of dose to AE	16	685
Amebic Liver Abscess	15[3]	5	294, 295, 298, 301, 302	No safety data provided or only an abstract provided	10	213
TOTAL					**76**	**3,515**

[1] *Salih et. al considered two studies given trial design*
[2] *Welch et. al. mixed population of amebiasis and giardiasis with no safety data or methods*
[3] *Mather et. al. considered two studies given trial design*

When studied populations or doses were combined the ability to provide drug effect attribution is not possible. Similarly, should efficacy data be reported but no data presented on safety, no conclusion can be drawn regarding adverse events in the patients that received tinidazole. In published literature that either (1) does not explicitly state the questions or organ systems that were evaluated or (2) peripherally mentions that there were no adverse events, a significant amount of uncertainty arises regarding the study quality and reporting bias of the investigators. For these reasons (as shown in Table 7.31) the studies denoted above were excluded from the review.

Trichomoniasis

34 studies were submitted for the indication of trichomoniasis. 4 studies were considered inadequate for review. Reference #92 (Apte) had combined drug schedules, patient populations and doses such that safety data could not be adequately interpreted. Reference #184 (Aimakhu) incorporated no safety data in the publication. Reference # 277 (Berec) incorporated no safety data in the publication. Reference #278 (Akinla) also provided no safety data. Overall, 30 studies were considered evaluable (*Table 7.32*) for safety and included 1,874 patients, of which 1,600 were available for follow-up in the cited references. When more than one dose or duration was used in the same reference, they were considered separate studies for the purposes of review.

Table 7.32: Evaluable Studies for Safety (Trichomoniasis)

	Reference #	Author		Reference #	Author
1.	26	Milek	16.	92	Schellen
2.	27	Gabriel	17.	93	Bedoya
3.	28	Oprassersawat	18.	95	Kawamura
4.	81	Wallin	19.	96	Anjaneyulu
5.	81	Wallin	20.	97	Rao
6.	82	Swarz	21.	98	Bloch
7.	83	Jones	22.	99	Weidenbach
8.	84	Thavabalan	23.	104	Chaisilwattna
9.	85	Schmor	24.	180	Rosemann
10.	86	Hillstrom	25.	181	Rees
11.	87	Ward	26.	182	Mati
12.	88	Quartararo	27.	183	Ali
13.	89	Dellenbach	28.	185	Chaudhuri
14.	90	Psaroudakis	29.	276	Sucharit
15.	91	Lyng	30.	279	Patil

For the studies submitted in support of trichomoniasis, all studies used a one time oral treatment ranging from 1.6g to 2.0g in adults. 27 of the 30 studies included provided a one time 2.0g dose of tinidazole. 3 of the studies used alternate doses. Specifically, reference #81 (Wallin) used a dose of 1.6g, reference # 276 (Sucharit) used a dose of 1.8g and reference #95 (Kawamura) used a dose of 1g (table 7.33). 162 patients received doses less than the 2.0g dose for which the sponsor is seeking the indication of trichomoniasis

Table 7.33: Dose Distribution in Trichomoniasis Trials

Reference	Dose	# Studies	# Subjects
95 (Kawamura)	1.0 g	1	39
81 (Wallin)	1.6 g	1	68
276 (Sucharit)	1.8 g	1	55
All Others	2.0 g	27	1712
Total		**30**	**1874**

Giardiasis

24 studies were submitted for the indications of giardiasis. 4 studies were considered inadequate for review. Reference # 186 (Sterner) lacked relevant safety data. Reference #187(El Masry) lacked relevant safety data. Reference #189 (Farahmandian) lacked relevant safety data and reference #272 (Pengsaa) reported disparate data such that 11 patients were unaccounted when comparing data tables. Overall, 18 citations were considered evaluable (*Table 7.34*) for safety and included 697 patients, 614 of which were available for follow-up in the cited references. When more than one dose or duration was used in the same reference, they were considered separate studies for the purposes of review.

Table 7.34: Evaluable Studies for Safety (Giardiasis)

	Reference #	Study
1	114	Bassily
2	118	Bakshi
3	120	Danzig
4	121	Jokipii
5	122	Pettersson
6	123	Salih
7	125	Levi
8	126	Jokipii
9	127	Speelman
10	128	Gadzer
11	129	Gadzer
12	130	Sabchareon
13	131	Kryonseppa
14	188	Jokipii
15	190	Krishnamurthy
16	191	Nigam
17	214	Pettersson
18	264	Suntornpoch

For the studies submitted in support of the giardiasis indication doses ranging from 50 mg/kg to 2.0 g were used for both pediatric and adult populations (*Table 7.35*).

Table 7.35: Dose Distribution in Giardiasis Trials

Population	Dose	Duration (Days)	# Studies	# Subjects
Adult	150 mg bid	7	1	19
	150 mg/kg bid	7	2	66
	1.0 g	1	1	37
	1.5 g	1	1	50
	2.0 g	7 (1 study) 1 (3 studies)	4	108
SUBTOTAL			**9**	**280**
Pediatric	50 mg/kg	1	4	222
	1.0-1.5 g	1	1	38
	2.0 g	1	1	21
SUBTOTAL			**6**	**281**
Both	50 mg/kg	1	2	76
	2.0 g	1	1	30
SUBTOTAL			**3**	**106**
Not Provided	150 mg/kg bid		1	30
Total			**20**	**697**

A total of 4 studies that included 108 patients received tinidazole at the 2.0g dose for which the sponsor is seeking the indication for giardiasis in adults, 1 of which had a duration of therapy of 7 days (references 126). The other 3 studies each had a one time dose duration (references 122, 131, and 188).

The sponsor also seeks a pediatric giardiasis indication at a single dose of 50 mg/kg (up to 2g). Of the submitted literature, 4 studies utilized a one time 50mg/kg dose (references 118, 128, 190, and 264) and 1 study utilized a 2g dose (reference # 130).

Amebiasis

Intestinal Amebiasis

Since the sponsor is seeking an indication for both intestinal amebiasis as well as amebic liver abscess at different durations they will be reviewed separately. 19 studies were submitted for the indication of intestinal amebiasis of which 4 were not considered evaluable (references 287,288,289 and 291). Reference #287 (Prakash) provides no safety data. Reference #288 describes dosage as volume/kg body weight such that an actual dose is not provided. Reference #289 (Scragg) provides no specific safety data. Reference #291 (Zuberi) is not interpretable since multiple doses were used without linkage to the adverse events described. Overall, 16 studies (14 references) were considered evaluable (Table *7.36*) for safety and included 685 patients, of which 613 were available for follow-up in the cited references. When more than one dose or

duration was used in the same reference, they were considered separate studies for the purposes of review.

Table 7.36: Evaluable Studies for Safety (Intestinal Amebiasis)

	Reference #	Author
1	112	Joshi
2	113	Prakash
3	114	Bassily
4	116	Garcia
5	117	Misra
6	118	Bakshi
7	193	Misra
8	194	Misra
9	195	Mabadaje
10	196	Singh
11	197	Swami
12	284	Ahmed
13	285	Islam
14	290	Scragg

For the indication of intestinal amebiasis, doses ranges from 50mg/kg to 2g with durations ranging from 1-10 days of therapy (*Table7.37*).

Table 7.37: Dose Distribution in Intestinal Amebiasis Trials

Population	Dose	Duration (Days)	# Studies	# Subjects
Adult	600 mg	5	2	143
	2.0 g	3	5	260
Subtotal			**7**	**403**
Pediatric	50 mg/kg	3	2	65
	60 mg/kg	1	1	25
Subtotal			**3**	**90**
Both	600 mg bid	5	2	60
	1.5 g	10	1	18
	2.0g	1 (1 study), 2 (1 study), 3 (1 study)	3	114
Subtotal			**6**	**192**
Total			**16**	**685**

A total of 5 studies which included 206 patients received tinidazole at the 2.0g dose for which the sponsor is seeking the indication for intestinal amebiasis in adults, all

of whom received therapy for 3 days and of which 249 patients were available for follow-up in the citations (references 117, 118, 194, 196, and 197). A total of 2 studies that included 65 patients received tinidazole at the 50 mg/kg dose for which the sponsor is seeking the indication of intestinal amebiasis in pediatric patients, all of whom received the drug for 3 days (references 284 and 290). An alternate dose of 60 mg/kg x 3 days was utilized in another group of pediatric patients (25 patients, reference 290).

Amebic Liver Abscess

15 studies were submitted for the indication of amebic liver abscess, of which 5 were considered inadequate for evaluation (references 294, 295, 298, 301 and 302). References 294 (Esesarte), 295 (Hatchuel), 298 (Lassere), 301 (Scragg), and 302 (Simjee) provided no specific safety data. Overall 10 studies (9 references) were considered evaluable for safety and included 213 patients (*Table 7.38*). When more than one dose or duration was used in the same reference, they were considered separate studies for the purposes of review.

Table 7.38: Dose Distribution in Intestinal Amebiasis Trials

	Reference #	Author
1	118	Bakshi
2	119	Khokhani
3	198	Mathur
4	292	Abiose
5	293	Cervantes
6	296	Islam
7	297	Kundu
8	299	Mendis
9	300	Quaderi

For the indication of amebic liver abscess all studies (*Table 7.39*) used a dose of 2g but the duration of therapy varied from 2-3 days. There was no study that evaluated only pediatric patient but reference 296 (Islam) included both adult and pediatric patients, albeit in small numbers (N=16). Although excluded from the pooled evaluation, reference 301 (Scragg) evaluated 25 pediatric patients and is discussed below.

Table 39: Dose Distribution in Amebic Liver Abscess Trials*

Population	Dose	# Studies	# Subjects
Adult	2.0 g	9	197
Adult and Pediatric	2.0 g	1	16
Total		**10**	**213**

**Note: reference 301 (Scragg) utilized two doses and two duration regimens – 10 children received a dose of 57 mg/kg for 5 days. Due to observed efficacy the authors lowered the dose to 50 mg/kg and truncated the duration to 3 days.*

Description of Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Primary Source Data

As stated above, the primary source of data submitted were literature publications regarding the safety and efficacy of tinidazole for the indications of trichomoniasis, giardiasis, intestinal amebiasis and amebic liver abscess. In attempting to determine the adverse event profile from the submitted literature those studies that employed blinding and randomization in their study design were considered to harbor the most tenable drug-related events compared with uncontrolled studies. The type of reporting was also evaluated such that those studies that queried subjects regarding specific signs or symptoms are considered to be more representative of a drug-related event than in those studies where the reporting was spontaneous or not specified. Of the 77 studies evaluated only 5 were randomized and double-blinded. Of these 5 studies only two employed a specific patient query with categorization outlined in Table 7.40.

Overall, 39% of the studies used some form of randomization, 39% were either active or placebo controlled and 7% were double blinded. As denoted above, however, only 5 studies (references 28, 86, 182, 185, and 299) were randomized and blinded, with only 2 of these studies describing a specific patient query used to evaluate drug safety (reference 28 and 185).

Table 7.40: Submitted Data Quality

	# Studies	% Studies	# Subjects	% Subjects
Randomization				
Yes	30	39	1238	35
No	37	48	1891	54
Not Provided	10	13	386	11
Total	**77**		**3515**	
Type of Control				
None	35	45	1649	47
Active	38	79	1609	46
Placebo	4	5	257	7
Total	**77**		**3515**	
Blinding				
Not Provided	27	35	1046	30
Open Label	41	53	1885	54
Single Blind	2	3	79	2
Double Blind	7	9	505	14
Total	**77**		**3515**	
Reporting				
Not Provided	39	51	1477	42
Spontaneous	16	21	837	24
Non Specific Query	8	10	247	7
Specific Query	14	18	954	27
Total	**77**		**3515**	

MO Comment: As detailed above, 65% of studies were either not randomized or the type of randomization was not provided, 53% of the studies were not controlled or the type of control was not provided and 86% were not double blinded. Furthermore, the type of safety reporting was highly inconsistent between studies.

The goal of comparing randomized, blinded studies to all studies was to provide a means of evaluating the verisimilitude of the larger dataset given a small one with more controlled data. Therefore, the initial set of studies evaluated were the 5 randomized, blinded studies with particular focus on the 2 trials that utilized a specific query of the studies patients (*Table7.41*).

Table 7.41: Submitted Randomized, Blinded Trials

Indication	Reference #	Author	Duration (Days)	Population	Control	Reporting
Trichomoniasis	28	Oprassersawat	1	Adult	Active	Specific Query
Trichomoniasis	86	Hillstrom	1	Adult	Active	Spontaneous
Trichomoniasis	182	Mati	1	Adult	Placebo	Nonspecific Query
Trichomoniasis	185	Chaudhuri	1	Adult	Active	Specific Query
Amebic Liver Abscess	299	Mendis	3	Adult	Active	Not Provided

1 study that was blinded and randomized provided tinidazole for a 3 day course (reference 299) for the treatment of amebic liver abscess but the type of reporting utilized was not described. The other 4 references included patients for the indication of trichomoniasis at a one time dose of 2.0g.

Secondary Source Data

Secondary source data included (1) foreign labels (12 labels submitted), (2) spontaneous adverse event reporting from Australia and the United Kingdom, and (3) safety data from the sponsor's BA/BE study. The labels from the following countries were submitted: Australia, Belgium, France, Germany, India, Japan, Netherlands, South Africa, Spain, Sweden, Switzerland, and the UK. These labels include data regarding recommended usage, adverse events, interactions, precautions as well as contraindications.

The spontaneous reporting data submitted from Australia and the UK includes events captured from market introduction (1975 and 1982 for Australia and the UK, respectively) through August, 2000. 48 adverse events were reported in the UK during that period and 350 events were reported in Australia during that period.

The sponsor conducted a BA/BE study in 18 healthy volunteers that received 2g of tinidazole three times with a one week washout between dosing. Two of these dosing regimens used the sponsor's tinidazole and one dose used Pfizer's tinidazole (Fasigyn). Subjects were queried at each blood draw about possible adverse events.

Adequacy of Overall Clinical Experience

78 studies were considered adequate for review and included 3,515 tinidazole exposures. There were 3,085 patients available for follow up with 282 documented adverse events noted. There were 11 dedicated pediatric studies that included 417 tinidazole patients with 24 documented adverse events. There were 10 other studies that included both adult and pediatric tinidazole exposures. Of these studies there were 248 patients available for follow up of which there were 21 documented adverse events. There were 5 studies that included 200 men with tinidazole exposure of which 15 experienced an adverse event.

Doses ranges from 50 mg/kg to 2g with the duration of exposure ranging from 1-7 days. The data regarding safety of the 2g dose extended to 3 days with reasonable data. Once study that captured efficacy data of tinidazole at the longer exposure of 7 days (2g dose) did not capture safety data.

Study designs varied widely. Most of the trials were open label (41) with only seven described as double blinded. 30 studies were considered randomized, 5 of which were also double blinded. Only 2 of these trials had a specific query established for

safety evaluation, neither of which were placebo controlled. The majority of studies were either active controlled (38) with only 4 placebo controlled.

MO Comment: Given the breadth of the primary source data that includes adult, pediatric, and male patients as well as the dose and duration requested for approval adequate information is available for ascertainment of drug safety. Contextual evidence is furthermore provided by secondary sources (spontaneous reporting, foreign labels and BA/BE study).

General Methodology

To adequately characterize the 78 studies submitted, an Microsoft Excel database was compiled with all relevant variable for the safety evaluation. Variable used to evaluate the submitted studies included the following:

- Indication
- Reference number
- Author
- Dose
- Duration
- Number of patients in study
- Number of patients available at follow up
- Population studied
- Randomization
- Study design
- Control used
- Type of AE reporting
- Adverse Events:
  - Fever
  - Taste change
  - Dry mouth
  - Nausea
  - Vomiting
  - Abdominal pain
  - Anorexia
  - Headache
  - Weakness
  - Dizziness
  - Ataxia
  - Rash
  - Dysesthesia
  - Pruritis
  - Sweating
  - Dark uring
  - Laboratories
  - Other Adverse events

Once the primary data was collected from the submitted publications queries were conducted related to adverse events as impacted by dose, duration, study design, and other listed variables as denoted above and described in section 7.1. Figure 3 below provides examples of the pivot table used to evaluate the submitted data. An example is provided below. The studies that are related to adult evaluations (Figure 4a) are 55 in number and the subgroup of these studies that were randomized are 22 in number. The actual studies can then be localized and reviewed for validation.

Figure 4a: Excel Tinidazole Pivot Table – Studies of Adult Patients

Imidazole Naive	(All)
Popn (Age)	Adult
Schedule	(All)
Randomized	(All)
Control	(All)
Study Design	(All)
Reporting	(All)
Indication	(All)
Tinidazole Dose	(All)

Data	Total
Count of Study	55
Sum of Number of Patients (T)	2754
Sum of Patients Available for FU(T)	2390
Sum of (T)# Patients with Aes	237

Figure 4b: Excel Tinidazole Pivot Table – Adult Randomized Studies

Imidazole Naive	(All)
Popn (Age)	Adult
Schedule	(All)
Randomized	yes
Control	(All)
Study Design	(All)
Reporting	(All)
Indication	(All)
Tinidazole Dose	(All)

Data	Total
Count of Study	22
Sum of Number of Patients (T)	912
Sum of Patients Available for FU(T)	781

MO Comment: The cataloguing of submitted studies allowed for easy cross referencing of any specific adverse event across all evaluable studies. Drop down menus for each of the variable listed above (e.g., schedule, randomized, control, design, reporting, indication and dose) allow for the evaluation of the specific subgroup of interest, such as adult studies that were randomized.

7.2.12 Pooling Data Across Studies to Estimate and Compare Incidence

Pooled Data vs. Individual Study Data

As previously stated, attempting to establish a true adverse event incidence is exceedingly difficult given the heterogeneity of submitted data. Variations and study

design, types of adverse events reporting utilized as well as indication evaluated greatly impact the reported events. Data was therefore pooled and described respectively in section 7.1. Had individual trials been evaluated independently safety findings would have been inconclusive due to the size of the studies (most were small), safety endpoints used (most did not describe the safety methodology or relied on spontaneous reports), and marked variations in study quality based on randomization, type of control, and blinding. Pooling data allowed for a more robust evaluation of the submitted data from these disparate sources, providing increased confidence in estimated adverse event rates.

7.2.13 Explorations for Predictive Factors

Due to the aforementioned heterogeneity of study designs, follow up and populations evaluated, predictive factors for adverse events are not possible to evaluate due to a lack of data granularity.

Safety Conclusions

As stated in this review the ability to adequately ascribe safety concerns or the lack thereof are a reflection of a markedly heterogeneous dataset that was submitted from the published literature. Blinded studies with well described safety evaluations are lacking. Given the disparity in adverse event incidence between spontaneous reporting, specific queries and nonspecific queries there are intrinsic limitations in interpreting proposed adverse event incidences.

Nonetheless, metronidazole, a nitroimidazole that has been widely used in the US market has a very similar safety profile as that present in the evaluated dataset. Similar types of events are present in the Flagyl® label as are seen in the spontaneous reports from Australia and the UK. For the 2g multi-day dose, tinidazole has relatively fewer adverse events that metronidazole as compiled by the sponsor (Table 11.4.4.3, sponsor's ISS).

Table 7.42: Tinidazole vs. Metronidazole common adverse effects from directly comparative studies 2g and multi-day dose comparison

	Tinidazole	Metronidazole

GI Nausea	8.8%	26.5%
Vomiting	3.4%	8.9%
Dyspepsia / cramps / epigastric discomfort	1.9%	5.8%
Metallic/bitter taste	9.9%	9.8%
Anorexia	4.5%	16.1%
CNS Dizziness	0.6%	0.3%
Weakness/fatigue/malaise	0.5%	1.2%
Other Headache	0.9%	1.6%
Total % (N) of patients w/ adverse effects	18.5% (202/1089)	28.7% (282/981)

Since tinidazole has been used in similar clinical situations as metronidazole and does not appear to carry any added toxicity, it is unlikely that at the recommended dose and duration that the drug would carry undue risk to patients that meet indications for usage. The data provided in table 7.42 are however, only estimate. Due to the disparity in the pooled citations these values are considered unstable.

Based on the severe adverse events evident from spontaneous reporting in Australia and the UK as well at least one documented case of a potentially causal LFT abnormality, patients with neurologic or hepatic impairment may have an increased risk of an adverse event with tinidazole use. It is noted in the Flagyl® label that plasma clearance of metronidazole is decreased with decreased liver function.

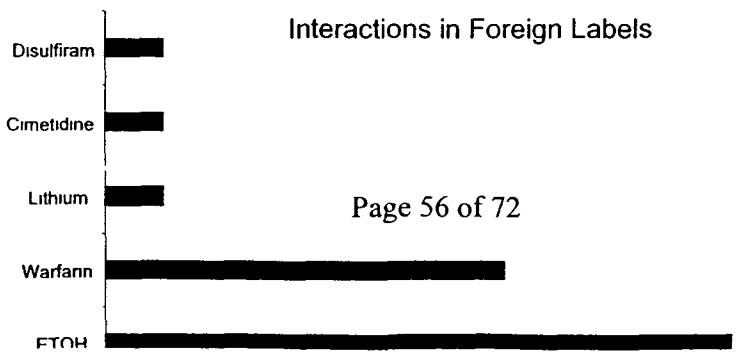
To better characterize longer durations of use in these patient populations further as well as in populations that have inherent decreased liver function (e.g., geriatric) . Further studies would need to be conducted in order to adequately ascribe any safety concerns for similar patients.

ADDITIONAL CLINICAL ISSUES

Drug-Drug Interactions

There are 5 interacting medications listed in foreign labels, the relative frequencies noted in figure 5. Medications of concern are disulfiram, cimetidine, lithium and warfarin. Similar to other imidazoles, alcohol ingestion can cause an antabuse (disulfuram-like) reaction and should commonly be avoided as noted in these labels.

Figure 5: Interactions in Foreign Labels



As denoted in the Flagyl® label, concerns regarding each of the drugs listed in Figure 5 are related to specific reported toxicities. Alcoholic patients that use metronidazole concurrent with alcohol have reported psychotic reactions. Cimetidine, a drug that decreases the microsomal liver enzyme activity, can prolong the half-life and decrease clearance of metronidazole. The converse has likewise been reported with hepatically metabolized drugs such as Lithium or Warfarin, whose half lives can be significantly elevated with short courses of metronidazole.

Not describe in foreign labels yet present in the Flagyl® label are potential interactions with inducers of microsomal enzymes such as Phenytoin or Phenobarbital. This can reduce the drug levels of metronidazole and impact efficacy. There have also been reported cases of impaired clearance of phenytoin with concomitant metronidazole administration.

Pediatrics

For children with giardiasis there were 6 studies that were described as solely including pediatric patients (reference 118 (Bakshi), 120 (Danzig), 128 (Gadzer), 130 (Sabchareon), 190 (Krishnamurthy) and 264 (Suntornpoch)). 3 separate doses of tinidazole were used in these trials, including 50 mg/kg (4 studies), 1-1.5g (1 study), and 2g (1 study) each for one time dosing.

There was insufficient data from children with amebic liver abscess but one author did remark on the safety outcome of these children at the recommended dose. Reference 301 (Scragg), in which 25 children with amebic liver abscess (ages 3 months to 6 years) were treated with a 5 day course of tinidazole, stated that *"tolerance was excellent with no toxic effects shown by the blood counts, liver function tests, blood ureas, and urines."*

Similarly, children with intestinal amebiasis were evaluated with no significant adverse event reports. A total of 2 studies that included 65 patients received tinidazole at the 50 mg/kg dose for which the sponsor is seeking the indication of intestinal amebiasis in pediatric patients. All received the drug for 3 days (references 284 and 290). A group of pediatric patients received a dose of 60 mg/kg for 3 days (25 patients, reference 290). There were no adverse events reported in the cited pediatric studies.

OVERALL ASSESSMENT

Conclusions on Available Data

Although not all studies provided safety information, most patients were available for evaluation with 14.6% unavailable in the submitted trichomoniasis studies, 12% of patients were unavailable in the giardiasis studies, 10.5% of patients were unavailable in the intestinal amebiasis studies and .5% were unavailable in the hepatic liver abscess studies. No drug attributed deaths were present in the submission. Similarly, no serious adverse events were evident from the presented data and no clinically significant abnormal laboratory values were found.

Common adverse events were similar in the submitted literature for trichomoniasis, giardiasis and amebiasis (including amebic liver abscess). The most common events were evident in the gastrointestinal and neurological category with taste change, nausea, weakness and dizziness being the most common. When compared with metronidazole there were similar events reported with a similar frequency. In comparing event rates between the sponsor's evaluation and the FDA evaluation rates were similar for trichomoniasis with 8.6% patients experiencing an adverse event (FDA review) compared with 10.9% patients experiencing an adverse event (Sponsor review). The difference in rates is attributable to variations in study inclusion and evaluation based on study quality/safety reporting.

Similar events related to gastrointestinal and neurological events were noted in the giardiasis trials. Taste change, nausea, vomiting, headache and dizziness being some of the most common. In comparing event rates between the sponsor's evaluation and the FDA evaluation rates were similar for giardiasis with 11.6 % patients experiencing an adverse event (FDA review) compared with 11.1 % patients experiencing an adverse event (Sponsor review). Specific differences were an increase in adverse events related to abdominal pain, anorexia, vomiting, nausea and taste change in the FDA review. The differences in rates are attributable to variations in study inclusion and evaluation based on study quality/safety reporting given the exclusion of 318 patients from the FDA review.

Similar events related to gastrointestinal and neurological events were noted in the amebiasis trials. Taste change, nausea, vomiting and weakness being some of the most common. In comparing event rates between the sponsor's evaluation and the FDA evaluation rates were similar for amebiasis with 10.9 % patients experiencing an adverse event (FDA review) compared with 15.5 % patients experiencing an adverse event (Sponsor review). The differences in rates are attributable to variations in study inclusion and evaluation based on study quality/safety reporting given the exclusion of 318 patients from the FDA review.

There were no significant differences in adverse events reported based on gender or age group. In looking at comparative trials of tinidazole with metronidazole similar types of events were described with a trend toward fewer events with tinidazole. Enhanced safety is however difficult to attribute given the variations in safety reporting. There were significant variations in study design, types of reporting (spontaneous or specific query) as well as unaccounted patients at study completion. Specifically, in

focusing on trichomoniasis trials, tinidazole has a higher (not lower) incidence of weakness (.8% vs. 0). In focusing on intestinal amebiasis trials, tinidazole has a higher incidence of metallic taste than metronidazole (13.1% vs. 7.3%). In focusing on giardiasis trials tinidazole has a higher incidence of vomiting/anorexia (6.0% vs. 3.1%). In focusing on amebic liver abscess tinidazole has a higher incidence of dizziness than metronidazole (2.7% vs. 1.4%). Attempting to confidently ascribe comparative safety is therefore difficult.

Recommendation on Regulatory Action

Tinidazole has been widely used for more than two decades in non-US markets. In addition to the current literature submission, the sponsor has submitted tinidazole labels from 12 foreign regulatory agencies outlining the recommended use and specific safety concerns related to tinidazole. Of importance to note in these foreign labels is the potential relative benefit in tinidazole use given its once daily dosing compared with the twice or thrice daily dosing required with metronidazole. Data submitted to the FDA regarding the safety of tinidazole for the treatment of trichomoniasis, giardiasis, and amebiasis are generated from literature publications from different decades that employed different trial designs, different types of safety reporting as well as use of different dosages and schedules of tinidazole. A separate analysis was conducted to insure that the FDA's evaluation was consistent with the sponsor's evaluation regarding the safety of tinidazole.

Overall safety evaluation was conducted based on the sought indications, trichomoniasis, giardiasis, intestinal amebiasis and hepatic liver abscess. There are no deaths or serious adverse events considered related to tinidazole use. Similarly, adverse events considered related to tinidazole use for the specific indications sought were of similar quality and frequency between the sponsor's and FDA's evaluation. The majority of events described in the submitted publications were categorized as either gastrointestinal or neurological. The most frequent gastrointestinal events reported were nausea, taste change, anorexia, and vomiting for all indications evaluated. The most frequent neurological events reported were weakness, dizziness, and headache for all indications evaluated. Other events reported were pruritis, rash, and darkened urine.

Use of tinidazole in children for the four indications sought was likewise not found to harbor risks greater than those reported in the adult populations. Tinidazole use during pregnancy after the first trimester was submitted in the form of 3 literature reports that likewise do not indicate an elevated risk albeit significant narrative data was insufficient to make specific conclusions.

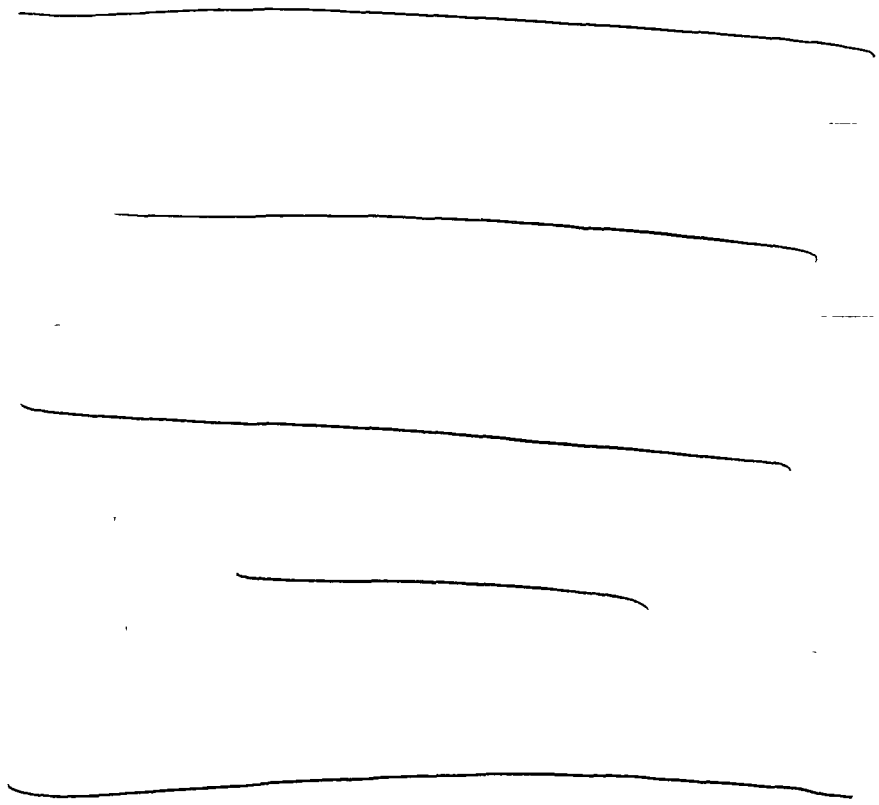
Overall the literature submitted to the FDA regarding the safety of tinidazole for the treatment of trichomoniasis, giardiasis, intestinal amebiasis and hepatic liver abscess are sufficient. Although quantitative comparison is not possible to validate in the submitted literature, there is an obvious trend to fewer adverse events reported for tinidazole when compared with metronidazole which is a clear benefit as well as the obvious shorter duration of therapy. Furthermore, the following key issues support the safety of tinidazole use for the proposed indications:

5. A minimal spectrum of risk based on the adverse event evaluation conducted
6. Congruency of adverse event evaluation between the sponsor and FDA
7. Lack of events with significant severity, frequency or unexpected character
8. Utilization history in non-US markets for more than two decades without significant adverse event reporting

Tinidazole is therefore considered safe for the proposed dosages and durations sought for the treatment of trichomoniasis, giardiasis, intestinal amebiasis and hepatic liver abscess, respectively.

Labeling Review

Draft Labeling For Tinidazole Tablets



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

(b4)

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

/s/

Carl Kraus
5/17/04 12:43:00 PM
MEDICAL OFFICER

Leonard Sacks
5/17/04 02:25:22 PM
MEDICAL OFFICER

Steven Gitterman
5/18/04 04:30:46 PM
MEDICAL OFFICER

Renata Albrecht
5/18/04 05:10:25 PM
MEDICAL OFFICER

Edward Cox
5/18/04 06:25:50 PM
MEDICAL OFFICER

Medical Officer's Review
of
NDA 21, 681
Tinidazole

Giardiasis

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Tinidazole should be approved for the treatment of Giardiasis in adults and children.

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

There are no specific Phase 4 studies recommended at this time. Further experience in the pediatric population especially for those under 3 years of age may be pursued as required by other regulations.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

There was no active clinical research program. The data for the support of this NDA came from the experience in the medical literature. Twenty-three trials encompassing 2300 patients, 1600 of whom received tinidazole, were submitted by the Applicant and reviewed.

B. Efficacy

Twenty-three papers were provided as supportive of this indication. Nineteen reports utilized a single dose of tinidazole. Fifteen of these publications presented sixteen comparative clinical trials using a single dose of tinidazole. There was one

blinded study (Bakshi) which was performed in children where the investigators who reviewed the stools were blinded to therapy but it is not stated if the patients were blinded and two single blind studies in adults. All three of these blinded trials were selected as pivotal. Five additional pivotal reports presented six randomized open label comparative trials. Seven of the remaining trials were comparative but not randomized. Four of these seven trials were presented as supportive because of their large enrollment of mostly pediatric patients. The remaining 3 trials were single agent studies.

Eight reports (nine trials) of those submitted were considered pivotal by the FDA for this application. Eight utilized a single dose of 2.0 g or 50 mg/kg/day of tinidazole and eight of these trials were comparative to metronidazole. One compared single dose tinidazole 1.5 g to single dose ornidazole 1.5 g. The subjects in these trials were almost all under 40 and approximately half were children. About 60%of enrollees were male and 40% were female. The results of these trials are presented in the table below.

TABLE 1. Single Dose Tinidazole for Giardiasis

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

- *Comparator was Ornidazole; Adapted from data from NDA's 21,681*

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

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

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

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

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

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

C. **Safety:**

Please see the safety review by Dr. Carl Kraus

D. **Dosing**

Adults 2g po in a single dose
Children 50mg/kg in a single dose

E. **Special Populations**

Giardiasis is primarily a disease of those under 40 and is more common in children than adults. Three-hundred eighty-four of the 719 subjects in the eight studies presented above were under 18 with an average age of approximately 6 in the pediatric studies. In the other studies ages ranged from 10 to 61 but with less than 5% over 40. Mean age was often in the low to mid 30s. Of the 733 enrollees of the eight considered studies 425 were male and 308 were female. No racial or ethnic background was provided on the subjects but some inferences can be made by the country where the studies were performed. Four were performed in India, 3 in Finland, and one studied expatriates living in Bangladesh. No further information of the country of origin of the expatriates is provided.

Clinical Review

I. Introduction and Background

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

a. Identifying Information:

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

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

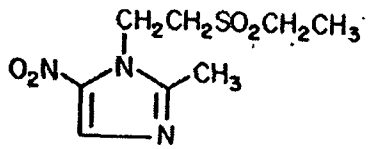
Generic Name: Tinidazole

Laboratory code: CP 12,574

Proposed Trade Name: Tindamax™

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

Chemical structure:



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

Pharmacologic Category: 2-methyl-5-nitroimidazole

Dosage Form: 250 and 500 mg Tablets

Route of Administration: Oral

Related Drugs: Metronidazole

B. Proposed Indications and Dosages:

1. Giardiasis 2 gram single dose PO for adults

50 mg/kg(max 2g) as a single dose PO for children

APPEARS THIS WAY
ON ORIGINAL

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

In April 2003 the USFDA approved Alinia (nitazoxanide) Oral Suspension to treat diarrhea caused by cryptosporidia and Giardia in children aged 1 to 11. positive patients has not yet been assessed. Furazolidone is considered a second line agent with cure rates of 70-80% in the treatment of giardiasis and is approved in the US. Hemolytic anemia can occur in G6PD patients. It was until recently the only anti-Giardia drug available in liquid form. Metronidazole is approved in US for the treatment of amebiasis

Other agents not approved in the US but used elsewhere include quinacrine, paromomycin (sometimes used in pregnant patients) and other nitromidazoles such as ornidazole.

C. Important Milestones in Product Development

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

The applicant initially submitted a PRE-IND requesting comments regarding their plan to submit an IND followed by an NDA for the use of tinidazole for the treatment of trichomoniasis and giardiasis.

IND 62,292 was submitted on April 4, 2001 (CDER stamp date April 6, 2001). The submission consisted of an outline for a bioequivalence study as well as literature based summaries of clinical trials used for trichomoniasis and giardiasis. After review of the submission, the applicant was informed that that the published trials submitted by the sponsor for the 2 gm single dose of tinidazole for the treatment of vaginal trichomoniasis would be adequate to support an NDA.

The applicant requested orphan-drug designation on January 31, 2002, for tinidazole in the treatment of giardiasis submitted pursuant to

Section 526 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bb). On May 29, 2002, the applicant was informed that this designation was possible only for the giardiasis

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

D. Other Relevant Information

Tinidazole is approved for use in the UK, Australia, Austria, Belgium, Costa Rica, El Salvador, Finland, France, Germany, Guatemala, Honduras, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, South Africa, Spain, Sweden, and Switzerland. In the UK it is approved for the following indications: urogenital trichomoniasis; giardiasis; intestinal amoebiasis; amoebic liver abscess; non-specific vaginitis; prevention of postoperative infections; treatment of anaerobic infections; acute ulcerative gingivitis; and for the eradication of *Helicobacter pylori* associated duodenal ulcers. The maximum approved total dose is 12 grams in liver abscess or intraabdominal infection and the maximum approved total duration of treatment is 6 days. The dosage regimen that is approved in most countries for giardiasis is a single oral dose of 2 grams for adults and 50-60mg/kg for children.

E. Important Issues with Pharmacologically Related Agents

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

Review of Metronidazole: Mayo Clin Proc, August 1999, Vol 74; page 82: Metronidazole is a synthetic drug that enters cells by passive diffusion and is activated by a reductive process. This produces short-lived metabolites that damage bacterial DNA and lead to cell death. This occurs regardless of the growth phase of the organism and thus there is activity against non-dividing organisms. This process requires a low oxidation-reduction potential and explains why metronidazole is active against anaerobes and less against aerobes. Oral absorption is almost 100% and is not affected by food whereas vaginal absorption is very poor. The drug is metabolized by the liver into several compounds and ultimately metronidazole and it metabolites are excreted primarily in the urine. In general it is well tolerated. The most serious AEs involve the CNS although they are rare unless large doses are used or treatment is prolonged. Metronidazole can cause seizures, encephalopathy, cerebellar dysfunction and peripheral neuropathy. The latter is usually reversible after discontinuation of treatment although resolution

may require a prolonged period. The other CNS effects usually resolve with treatment discontinuation.

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

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

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

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

The pharmacokinetics of tinidazole in patients with severe renal impairment (CrCL < 22 mL/min) are not significantly different from the pharmacokinetics seen in healthy subjects. Therefore, no dose adjustments are necessary in patients with severe renal impairment. However during hemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from approximately 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. Thus, if tinidazole is administered on a day when dialysis is performed, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the hemodialysis. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis (CAPD) has not been investigated.

There is no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies. In the absence of data on tinidazole, usually recommended doses should be administered cautiously in such patients receiving tinidazole.

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

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

Single-dose toxicity studies:

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

Repeat-dose toxicity studies:

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

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

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

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

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

Genetic Toxicology:

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

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

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

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

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

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

Special Toxicity Studies:

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

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

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

Microbiology:

The MO defers to the microbiology reviewer.

The Applicant presented data from several published studies which compared the in vitro efficacy of tinidazole and metronidazole for *Giardia lamblia.* The results of most studies showed the MCI's for tinidazole were equal to or lower than those for metronidazole for this parasite. The results from studies with more than 1 isolate are summarized in the table below. These MICs for *Giardia* are not standardized.

Please see below.

Study	# Isolates	Tinidazole MIC (ug/ml)	Metronidazole MIC (ug/ml)	Relative Potency TNZ vs MTZ
Jokipii (32)	N/A	0.2-12.5	1.6-50	4-8
McIntyre (199)	13	0.7	0.99	1.4
Gordts (274)	25	0.1-<0.5	0.1-<1.0	1-2
Gordts (304)	9	<0.5	<0.5-1	1-2
Ponce-Macotela (275)	4	1-4	---	---
Smith (220)	18	0.74(ID50,um)	1.19(ID50,um)	2.5

Adapted from Table presented on p.10-14 of NDA

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics and Pharmacodynamics

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

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

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

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

IV. Description of Clinical Data and Sources

A. Overall Data

Giardiasis:

Twenty-three papers were provided as supportive of this indication. Nineteen reports utilized a single dose of tinidazole. Fifteen of these publications presented sixteen comparative clinical trials using a single dose of tinidazole. There was one blinded study (Bakshi) which was performed in children where the investigators who reviewed the stools were blinded to therapy but it is not stated if the patients were blinded and two single blind studies in adults. All three of these blinded trials were selected as pivotal. Five additional pivotal reports presented six randomized open label comparative trials. Seven of the remaining trials were comparative but not randomized. Four of these seven trials were presented as supportive because of their large enrollment of mostly pediatric patients. The remaining 3 trials were single agent studies.

C. **Postmarketing Experience**

Tinidazole is approved for use in the UK, Australia, Austria, Belgium, Costa Rica, El Salvador, Finland, France, Germany, Guatemala, Honduras, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, South Africa, Spain, Sweden, and Switzerland. In the UK it is approved for the following indications: urogenital trichomoniasis; giardiasis; intestinal amoebiasis; amoebic liver abscess; non-specific vaginitis; prevention of postoperative infections; treatment of anaerobic infections; acute ulcerative gingivitis; and for the eradication of *Helicobacter pylori* associated duodenal ulcers. It is approved in most countries as a single dose of 2 grams or a pediatric dose of 50mg/kg as a single dose for the treatment of giardiasis. The maximum approved total dose is 12 grams.

D. **Literature Review**

- **The Medical Letter, April 2002; Drugs for Parasitic Infections**:
- Giardiasis : drugs of choice include metronidazole 250 mg TID for 5 days
- Giardiasis : alternatives include quinacrine 100 mg po TID x 5 days , tinidazole 2 grams once, furazolidone 100 mg po qid for 7 to 10 days and paromomycin 25-35mg/kg/d in 3 doses for 7 days. Pediatric Dosing is available for all of the above.

This NDA is a review of all the published clinical trials of the use of tinidazole in the treatment of Giardiasis.

V. Clinical Review Methods

A. How the Review was Conducted

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

Only efficacy was assessed in the review.

B. Overview of Materials Consulted in Review

Seventeen volumes were submitted in support of the giardiasis indications.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

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

E. Evaluation of Financial Disclosure

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

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

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

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

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

4.There are insufficient data to determine if there is any difference in relapse rate between tinidazole and metronidazole.

5.

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

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

C. **Detailed Review of Trials by Indication**

Giardiasis:

Twenty-three papers were provided as supportive of this indication. Nineteen reports utilized a single dose of tinidazole. Fifteen of these publications presented sixteen comparative clinical trials using a single dose of tinidazole. There was one blinded study (Bakshi) which was performed in children where the investigators who reviewed the stools were blinded to therapy but it is not stated if the patients were blinded and two single blind studies in adults. All three of these blinded trials were selected as pivotal. Five additional pivotal reports presented six randomized open label comparative trials. Seven of the remaining trials were comparative but not randomized. Four of these seven trials were presented as supportive because of their large enrollment of mostly pediatric patients. The remaining 3 trials were single agent studies.

Type of Study (Single Dose of 1.5 g or greater or pediatric equivalent)	**Number of Studies**	**Number Using Parasitologic cure**
Double Blind Randomized Controlled	1	1
Single Blind Randomized Controlled	2	2
Open Label Randomized Controlled	6	6
Open Label Comparative or Placebo Controlled (no description of randomization)	7	7
Open Label single agent	3	3

Pivotal Studies

- **Jokipii, 1979, Finland,(126)**: Comparative single blind, randomized trial of tinidazole 2 gm single dose versus 2.4 gm of metronidazole either once or once daily for 2 days. There were 85 adult patients enrolled, 37 men and 48 women. No age ranges were given. All had recently acquired symptomatic, parasitologically confirmed giardiasis; however no listing of symptoms was provided. Patients were followed up at 1, 2, 4,and 8 weeks. There was no mention of how many stool samples were reviewed at entry or at each followup. Failure was not clearly defined but appeared to be parasitological failure. Parasitologic clearance for 8 weeks was achieved in 93% of patients receiving tinidazole, 50% of those who received a single dose of metronidazole patients and 77% of those who received 2 doses of metronidazole. Symptom and parasitological concordance was close to identical. There were 2 tinidazole patients with persistent flatulence but negative stools; 2 single dose metronidazole patients with persistent flatulence, and abdominal discomfort but negative stools; and 3 patients with 2 days of metronidazole who also had abdominal symptoms with negative stools. These patients are probable failures according to WHO criteria. Drug absorption and PK data were obtained. The t1/2 of tinidazole was 13 hours and that of metronidazole was 9.5 hours. No correlation was made between serum levels and success or failure.

  No serious side effects were observed. The most frequent complaints were metallic or bitter taste, nausea, fatigue. There were a few reports of vomiting, headache, weakness or dizziness. Twenty four of twenty six single dose metronidazole patients reported side effects while in the tinidazole group 21 of 28 had similar complaints.

Medical Officer's Comment:. *The length of followup of 8 weeks is the strongest aspect of this study. In the single dose metronidazole group 4 of the 13 relapses occurred at 4 to 8 weeks. In the other 2 arms a number of relapses occurred at 2-4 weeks (7 in the 2 day metronidazole group and 2 in the tinidazole group.) Since giardia is not ususally acquired in Finland it is easy to determine relapse in comparison to other study sites where it may be difficult to differentiate relapse from reinfection. Since most of these infections were acquired abroad the time of acquisition could usually be determined. Randomization was as follows: administraion of single doses of tinidazole or metronidazole to alternate subjects until after 23 patients; then every other patient was given metronidazole 2.4g qd x 2d while the other half of the patients were alternated between single dose tinidazole or single dose metronidazole. It is not discussed as to why the addition of the metronidazole 2 day dosing was introduced in the middle of accrual. The assumption the MO makes is that it may have already been apparent single dose metronidazole was performing inferiorly The authors state that since such assignment was not completely random they compared the groups for duration of infestation, duration of symptoms, and semiquantitative assessment of cysts in the stool and found the groups similar in these characteristics at enrollment.*

In the discussion the authors report on six patients (not stating which of the treatments they received) who continued to report symptoms for several months with multiple attempts to identify Giardia in their stools being unsuccessful. Eventually the symptoms spontaneously resolved. The authors discussed the likelihood that this represented post giardiasis syndrome. They estimate this occurs in about 10% of those with giardiasis.

Jokipii, 1982, Finland (121): Comparative single blind, randomized trial of single dose tinidazole 1.5 gm versus single dose 1.5 gm of ornidazole in 100 adult subjects, 50 of who were female and 50 male. The mean age was 25. The enrollees were mostly university students who sought medical attention for gastrointestinal complaints and found to have *Giardia lamblia* cysts and/or trophozoites in the stool. Entry criteria specified symptoms (abdominal discomfort, nausea, fatigue, listlessness, diarrhea and flatulence) and a positive stool parastitologic examination after direct smear and/or formalin ether concentration of 3 stools obtained on 3 consecutive days. Followup was at 1, 2 ,4, and 8 weeks. Three stool samples were requested at each followup. Of the 100 evaluable patients 45 of 50 subjects who received tinidazole and 45 of 50 patients who received ornidazole had negative stools at 8 weeks. The parasitologic cure rate was 90% in each arm. Five ornidazole patients and 3 tinidazole patients redeveloped symptoms after 2 weeks but no Giardia was detected in the stools. These are considered probable failures by WHO criteria.

Drug levels were measured to determine if time to absorption would produce any effect on the degree of response. No effect was seen. This was performed to answer the question whether a prolonged time in the lumen would have any effect on efficacy.

Adverse events were common and mild and occurred about equally in both groups except there was more dizziness in ornidazole subjects (35 versus 10) and more bitter taste in tinidazole subjects. (17 versus 3)

***Medical Officer's Comment**: Results reported as parastiological success or failure. The patients who redeveloped symptoms did so after 2-4 weeks and are considered failures by WHO criteria. The rates reported to be consistent with the other studies presented were parasitologic success rates. However, if one included the probable failures the more realistic overall cure rate is 42/50 or 84% for tinidazole and 40/50 or 80% for ornidazole. These are also more representative of actual cure rates because of the longer followup period in this study which is more likely to capture relapse than in studes of shorter duration of followup.*

- **Kryonseppa, 1981, Finland (131)**: Open label, randomized trial comparing a single dose of tinidazole 2.0 grams to metronidazole 2.0 grams each day for 2 days. There were 29 men and 21 women enrolled with a mean age of 34-35. Entry criteria included parasitologic evaluation by formalin ether method of 2

consecutive daily stools. Followup was performed at 2 and 4 weeks and 2 stool specimens were examined at each time point. No mention was made of whether symptoms persisted or were eliminated by treatment. At 4 weeks followup 22/25 who received tinidazole and 19 of 25 who received metronidazole were free of Giardia in their stools.

Mild side effects were reported by 4 of 25 subjects who took tinidazole such as nausea, fatigue, and drowsiness. One patient on tindazole had prolonged nausea (3 weeks.) Seven of 25 patients who took metronidazole complained of gastrointestinal side effects-5 were mild but two subjects had severe nausea.

Medical Officer's Comment: *The lack of blinding, the failure to describe the randomization method, and the absence of information about the resolution of clinical symptoms are deficiencies in this study design. However, the results are based on a relatively hard endpoint (however there is some subjectivity in the detection of parasites in stool samples) and the high success rate of parasitologic clearance of the stools makes the results of this study worth noting.*

- **Bakshi, 1978 India (118)** Double blind, randomized multi-centered (3) trial of children with symptomatic giardiasis comparing a single dose of 50mg/kg of tinidazole versus a single dose of 50mg/kg of metronidazole. Actual mean doses were 61.8/kg for tinidazole versus 56.0mg/kg for metronidazole. Entry criteria were gastrointestinal symptoms consistent with Giardiasis and cysts or trophozoites in the stool. In the tinidazole group cysts were seen in the stool of 69 patients and trophozoites were seen in the stool of 31 patients. In the metronidazole groups cysts were seen in the stools of 72 patients and trophozoites were seen in the stools of 28 patients. It was not mentioned how many stool samples were examined at entry or at the 16 day followup examination. The mean ages were 5.8 years for the tinidazole group and 5.7 years for the metronidazole group. There were 200 children screened (125 males and 75 females) and 186 were enrolled: 94 received tinidazole and 92 received metronidazole. Success was defined as clearance of symptoms and parasites in stool at 16 days. Only 2 clinical failures without parasitologic failure were seen and they were both in the metronidazole group. Clinical Success rates were 88.3% for tinidazole versus 43% for metronidazole. Parasitologic success rates were 88.3% and 46.7% respectively.

  Mild gastrointestinal side effects were seen in 8.8% of tinidazole subjects and 2.2% of subjects on metronidazole.

Medical Officer's Comment: *Since no long term followup after 16 days was performed early relapses would not have been detected. The actual mean doses of drug show a 5.8mg/kg higher mean dose of tinidazole in comparison to metronidazole which may have conferred an advantage to the tinidazole group. The study was described as a single blind study by the Applicant but it is stated in*