C. Important Milestones in Product Development

The applicant submitted a PRE-IND _____ requesting comments regarding their plan to submit an IND followed by an NDA for the use of tinidazole for the single-dose treatment of trichomoniasis and giardiasis. The original pre-IND submission consisted of a briefing document that contained 200 references as well as copies of selected articles regarding the clinical use of tinidazole for trichomoniasis and giardiasis as well as the toxicology and pharmacokinetics of the compound. The sponsor requested FDA input on whether the published clinical studies identified as pivotal trials along with multiple supporting studies precluded the need for confirmatory US studies for both requested indications. Additionally, FDA concurrence was requested regarding the design of a PK/bioavailability trial. The applicant intended to submit a 505(b)(2) application and request orphan drug status.

The FDA responded with the following comments in a letter dated May 12, 2000:

- Tinidazole belongs to a class of compounds associated with mutagenic and carcinogenic potential and the sponsor will most likely need to conduct a battery of mutagenicity/carcinogenicity studies.
- In the absence of such studies the package insert would need to contain a boxed warning similar to that of the metronidazole label.
- The methodology for the selection of literature articles designated as pivotal trials needs to be provided in order to eliminate the possibility of selection bias.
- Additional safety information from post-marketing sources should be obtained.
- A biolink should be established between Fasigyn® (the tinidazole product utilized in the referenced clinical studies), and the sponsor's product.
- Protocols and formal study reports for the pivotal studies should be submitted.
- A dissolution method would be required for approval.
- A food effect study is required.
- Data on the metabolism of tinidazole and its potential inhibitory and/or induction effect on cytochrome P450 should be submitted.
- Plans for dosing smaller children who cannot swallow tablets should be submitted.
- Information on the consumption of alcohol while on tinidazole was requested.
- The activity of tinidazole versus the cyst stage of *Giardia lamblia* was requested.

- The activity of tinidazole should be compared to that of other FDA approved drugs such as metronidazole or furoxone.

- [redacted]

The sponsor responded in a letter dated 6/19/00 and stated that:

- Tinidazole like other compounds of its class has been shown to be mutagenic. The mechanism of this action is via the activation of the nitro group by bacterial nitroeductase in an anaerobic environment and would not be expected to occur in an aerobic environment such as that of mammalian cells. Thus, conducting additional tests would not add meaningful information to product labeling. A similar argument was made regarding the need for additional reproductive studies where the sponsor stated that given the studies published in the literature, no further information would be necessary.

- Medline and Embase were the primary search vehicles for clinical studies. 28 studies were found regarding the use of tinidazole in trichomoniasis as single dose treatment. 8 were blinded comparative studies. The selection of 4 studies as pivotal was made based on size (the largest number of patients). 11 studies were found using tinidazole as treatment for giardiasis. An attempt was made to select the highest quality studies.

- The sponsor requested clarification on the collection of postmarketing safety data.

- Original protocols and study reports could not be submitted.

- The sponsor was willing to perform a bioequivalence study of their product versus the marketed Pfizer tinidazole product.

- No additional food effect studies were recommended given available information and a dissolution method would be developed,

- No drug metabolism studies were planned and it was expected that this section of labeling would be similar to that of metronidazole.

- The possibility of a pediatric formulation would be explored.

- The sponsor did not feel that there would be added value to conducting additional microbiology tests given the substantial body of literature that already exists.

A meeting between the sponsor and the agency took place on 9/11/00. The agency continued to request additional postmarketing safety data and specified the UK and Australia as likely sources. Additionally it was clarified that the agency wanted a fasting crossover study comparing the sponsor's and the marketed tinidazole products. The agency also requested that crushed tablets be analyzed in adults to determine acceptability in children.

There was disagreement regarding the following:

- The need for mouse micronucleus testing that as per the sponsor would not contribute meaningful information.

- The need for additional reproductive toxicity studies because the submitted studies were old and not performed under GLP conditions.

- The need for carcinogenicity studies given that the sponsor was amenable to using metronidazole carcinogenicity labeling in their label as well as the minimal risks associated with the proposed single dose regimen.

[redacted]

On 3/14/2001 the agency sent a FAX response to the sponsor stating the following:

- The potential need for additional carcinogenicity and mutagenicity studies will be dependent on a critical evaluation of the literature articles submitted to an original IND.

- Regarding the need for additional repeat dose toxicity studies, the sponsor has submitted data on the use of tinidazole in rates. However published data submitted on the use of this compound in dogs and monkeys contain only brief statements on results. The right of reference to the unpublished data should be obtained.

- Reviewable articles regarding reproductive toxicology studies in rats and mice were provided and results from a rabbit study were cited. The rabbit study needs to be submitted and a segment II study in pregnant rabbits may still be need.

- Given the short duration of the proposed treatment of trichomoniasis and giardiasis, the need for carcinogenicity studies is unlikely.

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 use of tinidazole in the treatment of 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. This determination was based on the overall similarity of the results of multiple worldwide trials as opposed to an independent review of the data. Additionally, the known toxicity profile of metronidazole, the sponsor's acceptance of BLACK BOX WARNINGS and other PRECAUTIONS from the metronidazole label into the tinidazole label and the submission of ADRs from the UK and Australia, bolstered the adequacy of the applicant's proposed NDA submission. The applicant did not submit adequate efficacy or safety data to support anything beyond the requested single dose regimen

A conference call was held between the Pharmacology toxicology reviewers and the applicant on August 6, 2001 where it was agreed that no new genotoxicity or carcinogenicity studies were needed but that a reproductive toxicity study and a repeat dose non-rodent toxicity study were necessary. The former would need to be submitted prior to an NDA submission but the latter could be part of a Phase IV commitment. Final comments regarding the protocols of these studies were faxed to the applicant on 6/12/2002. Chemistry and manufacturing issues were also discussed independently on August 30, 2001.

In discussions regarding the BA/BE protocol on March 12, 2002, it was suggested that the applicant include at least 24 subjects in their study and that ETOH usage should be restricted for at least 72 hours post dosing. The sponsor ultimately assessed 18 subjects in this study.

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 and the maximum approved total duration of treatment is 7 days.

E. Important Issues with Pharmacologically Related Agents

Tinidazole is a nitroimidazole, closely related to metronidazole. It is the applicant's position that given the extensive worldwide use of tinidazole for the requested indications, the repetition of preclinical and clinical trials in the US would be of no added value. Proposed product labeling includes all potential safety and adverse event information included in the current 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 process produces short-lived metabolites that damage bacterial DNA and leads to cell death that occurs regardless of the growth phase of the organism indicating activity against non-dividing organisms. This process requires a low oxidation-reduction potential and explains why metronidazole is more 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 adverse events 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 *Clostridium difficile* colitis as well as with pancreatitis. More common GI adverse events include nausea, diarrhea, a metallic taste, stomatitis, and a dry mouth. Reversible neutropenia, dark urine, burning of the vagina or the urethra and *Candida 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 studied 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.

Dose reduction is not necessary in patients with renal disease and normal hepatic function although if the GFR is less than 10 mL/min a 50% reduction is recommended. Metronidazole is removed by hemo- but not by peritoneal dialysis. Finally, doses should be reduced by at least 50% in subjects with liver disease.

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 unspecified liver alterations.

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 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 [redacted] 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. Briefly, tinidazole appears to be more cidal than metronidazole with lower MIC and MLC values versus a number of pathogens including *Trichomonas vaginalis, Giardia duodenalis, Giardia lamblia* and others. Activity has also been demonstrated versus Gram (-) anaerobes and Gram (+) anaerobes. The mechanism of action is via formation of a metabolic product in which the nitro group is reduced. This redox potential can be attained only under anaerobic conditions.

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 such subjects 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

Trichomoniasis:

The applicant identified 34 publications where a 1 or 2 gram single dose of tinidazole was used to treat trichomoniasis. Nine of the studies were blinded, comparative studies using the single 2 gram dose. Five of these trials were identified by the applicant as pivotal studies in an arbitrary fashion but primarily based on patient numbers. All were considered randomized, controlled trials of the 2 gm single dose of tinidazole by their respective authors. Five hundred eighty-six females and 201 males were enrolled in these 9 trials. The sponsor also identified as supportive studies an additional 4 small double-blind comparative trials that enrolled 77, 50, 29, and 31 patients respectively.

B. Tables Listing the Clinical Trials

Single Dose Tinidazole Use in Trichomoniasis							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Roseman (28), 1973	S. Africa	2g tinidazole	open-label (wt mt. Dx)	31 F	1 and 4 wks	1 wk: 28/31 (90.3%) 4 wk: 24/24 (100%)	1/31 (3%)
Milek (2), 1974	Switzerland	1.5g tinidazole (n=98) 1.6g tinidazole (n=75) 1.8g tinidazole (n=79) 2g tinidazole (n=134)	open-label, dose range, multi-center (wt mt. Dx)	386 F	7-10 days 4-6 wks	1.5g: 84.5% 1.6g: 88% 1.8g: 92.4% 2g: 94%	2g dose: 10/134 (7.5%) 3/123 partners (2.4%)
Swarz (6), 1974	Europe	2g tinidazole	open-label, multi-center (wt mt. Dx)	251 F	1-2 wks 4-6 wks	245/251 (97.6%) 1 wk 216/221 (95.3%) 4 wks	46/299 (15.3%) includes 48 partners
Weidenbach (22), 1974	Germany	2g tinidazole (n=43) 2g metronidazole (n=21)	open-label, randomized, comparative (wt mt. and culture Dx)	64 F	1 and 6 wks	tin: 40/43 (93%) mtz: 20/21 (95%)	tin: 8/43 (18%) mtz: 12/21 (57%)
Dellenbach (12), 1974	France	2g tinidazole	open-label (wt mt. Dx)	32 F	1 and 6 wks	1 wk: 31/32 (97%) 6 wks: 29/32 (90.6%)	none reported by pts or partners
Schmor (8), 1974	Austria	2g tinidazole	open-label (wt mt. Dx)	50 F	6-10 days 4-6 wks	49/50 (98%) at both visits	18/50 (36%)
Schellen (15), 1974	Netherlands	2g tinidazole	open-label (wt mt. Dx)	53 F	10th day next cycle 2 months	46/49 (94%)	7/49 (14%) 3/38 males (7.8%)
Bedoya (16), 1974	Spain	2g tinidazole	open-label	15 F	4 days	14/15 (93%)	2/15 (13%) bitter taste

Single Dose Tinidazole Use in Trichomoniasis							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
			(wt mt. Dx)				0/12 partners (0%)
Wallin (5), 1974	Sweden	1.6g tinidazole (n=68 pts) 2g tinidazole (n=58 pts)	open-label, randomized (culture Dx)	115 F 11 M	1 and 4 wks	52/56 (93%) on 1.6g 45/47 (96%) on 2g 10/10 males (100%)	11% of all pts
Rees (31), 1974	Kenya	2g tinidazole (n=15) placebo (n=14)	double blind, placebo controlled, prison population wt. mt. Dx	29 F	4, 5, 7 days	8/10=80% tin 0/10=0% placebo	Headache more prevalent than placebo 5/15 vs. 1/14
Mati (32), 1974	Kenya	2g tinidazole (n=16) placebo (yeast tablets) (n=15) partners also treated	double blind, placebo controlled wt. mt. Dx	31 F	7 days	16/16 - 100% tin 4/15 - 26.7% placebo	4/16 tin pts reported minor side effects, vs. none in placebo group
Fantini (35), 1974	N/A	2g tinidazole open label	open label	25 M	N/A	22/25 (88%)	N/A
Ali (29), 1975	Bangladesh	2g tinidazole	open-label (wt mt. Dx)	39 F	7, 14, 30 days	29/36 (80%)	9/36 (22%)
Aimakhu (33), 1975	Nigeria	2g tinidazole (n=25) 200 mg metronidazole tid x 7d (n-25) partners also treated	double blind, randomized wt. mt. and culture Dx	50 F	3, 5, 15 days	96% - tin 100% - mtz	4 pregnant patients treated w/tin. All babies normal. No side effects volunteered.
Akinla (36), 1975	Africa	2g tinidazole (n = 24)	open-label	24 F	7 days	23/24 (94%)	Bitter taste, nausea, dizziness

Single Dose Tinidazole Use in Trichomoniasis							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
Massa (37), 1976	Chile	2g tinidazole	open-label	30 M	7 - 14 days	25/30 (83.3%)	N/A
Ward (10), 1976	Australia	2g tinidazole	open-label (wt mt. Dx, culture-cure)	25 F	1 wk	25/25 (100%)	3/25 (12%)
Pavlovic (38), 1976	Croatia	2g tinidazole	open-label	35 F 30 M	8 days	F 32/35 (91.4%) M 28/30 (93%)	none
Hillstrom (9), 1977	Sweden	2g tinidazole (n=45) 1.5g ornidazole (n=45)	double-blind, randomized (culture Dx)	90 F	1 wk, 1 month	41/43 tin (95%) 45/45 ornid (100%)	9/43 - tin (21%) 6/45 - ornid (13%)
Jones (30), 1977	Australia	2g tinidazole	open-label (wt mt. Dx, culture-cure)	50 F	1 wk	39/41 (95%)	19/41 (46%)
Psaroudakis (13), 1977	Greece	2g tinidazole (2nd dose to failures at 1st follow up)	open-label (Pap smear & culture Dx)	66 F	3-5 days	43/58 (74%) 48/49 (98%) 2nd follow up	10/58 (17%)
Anjaneyulu (19), 1977	India	2g tinidazole (n=50) 2g metronidazole (n=50)	randomized, comparative	100 F	4, 8, 12 days	47/50 tin (94%) 32/50 mtz (64%)	tin - 52% mtz - 82%
Kawamura (18), 1978	Japan	1g tinidazole (n=39) 1g metronidazole (n=34)	open-label	73 M	7-14 days	100% - tin 100% - mtz	6/39 - tin (15%) 4/34 - mtz (12%)
Apte and Packard (17), 1978	Asia	2g tinidazole	open-label, multi-center (wt mt. Dx)	859 F	8-21 days	818/859 (95.2%)	82/859 (9.5%)
Beric (39), 1978	Germany	2g tinidazole	open-label	200 F	8 days	99.5% tinidazole	Tin: 2 pts. (1%)

Single Dose Tinidazole Use in Trichomoniasis							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
		(n=100 F, 84 M) 5g metronidazole (PO and IVG) over 10 days n = 100 F and 5 g over 10 days to 91 M		175 M		97.4% metronidazole	nausea MTZ: 13% of pts. Nausea, gastric upset
Rao (20), 1978	India	2g tinidazole (n=30) 2g metronidazole (n=30)	open-label, randomized, comparative (wt mt. Dx)	60 F	4, 8, 12 days	100% in both groups	10/29 - tin (34.5%) 24/30 - mtz (80%)
Sucharit (40), 1979	Thailand	1.8 g tinidazole	open-label	55 F	7 days	100%	none
Chaisilwattana (43) 1980	Thailand	2 g tinidazole (n = 52) 1.5 g ornidazole (n = 55)	Double-blind comparative	107 F	4, 7, 14 days	98% tin 98% orn	13.5% tin 31% ornid
Chaudhuri (34), 1980	Netherlands	2g tinidazole (n=38F) 2g carnidazole (n=39F) partners treated	double blind, randomized (wt. mt.)	77 F + partners	1, 2 wk	94.7% tin 100% carnid	tin - 12/76 pts 15.8% carnid - 25/78 pts 32.1% tin carnid nausea 3 pts 17 pts vomiting 0 pts 6 pts
Lyng (14), 1981	Denmark	2g tinidazole (female pts) 2g tinidazole or placebo (partners)	partner tx: double-blind, randomized	137 F 68 M (tin) 69 M (placebo)	1-2 wks 1 month	132/137 (96.4%)	5/137 F (3.7%) 5/68 M (7.4%) 5/69 M placebo (7.3%)
Gabriel (3), 1982	United Kingdom	2g tinidazole (n=49) 2g metronidazole (n=46)	single blind, randomized (wt mt. and	95 F	14 days	40/42 - tin (95.3%) 39/40 - mtz (97.5%)	none in either group

Single Dose Tinidazole Use in Trichomoniasis							
Study Author/Yr.	Country	Treatment	Study Design	# Patients	Follow Up	Cure Rates	S/E's
			culture Dx)				
Patil (42), 1983	India	2g tinidazole (n=45 F, 45 M)	open-label,	45 F 45 M	5 - 10 days	93% F 100% M	none
Bloch (21), 1985	S. Africa	2g tinidazole (n=58) 2g metronidazole (n=59) 2g benzoyl mtz (n=44)	open-label, comparative	161 F	7, 14 days	100% - mtz 100% - benzoyl mtz 95% - tin	22% - mtz 7.5% - benzoyl mtz 13% - tin
O'Prasertsawat (4), 1992	Thailand	2g tinidazole (n=65) 1.6g mtz (split dose) (n=67)	double blind, randomized	132 F	6-16 days	100% - tin 98.5% - mtz	tin - 55 events mtz - 53 events
Otturi (43), 1973	Argentina	Tinidazole 150 mg bid x 7 days (n = 50) Tinidazole 2 g single dose (n = 60)	comparative	110	N/A	7 d 78% (39/50) 5 d 76% (46/60)	Single dose better tolerated than 7 day

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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. The maximum approved total dose is 12 grams in liver abscess and the maximum approved total duration of treatment is 7 days.

D. Literature Review

- **The Medical Letter, April 2002; Drugs for Parasitic Infections**: Trichomonas: drugs of choice include metronidazole 2 grams once or 500 mg BID for 7 days or tinidazole: 2 grams once or 500 mg BID (pediatric dosages 15 mg/kg/day orally in 3 doses for 7 days or 50 mg/kg once per drug respectively).

- **CDC Recommendations for the treatment of trichomoniasis 2002**: Metronidazole 2 grams once or 500 mg BID for 7 days

V. Clinical Review Methods

A. How the Review was Conducted

All publications submitted in support of the NDA were independently reviewed and summarized by the MO. Only efficacy was assessed in this review.

The 5 studies identified as pivotal by the applicant as well as 4 additional studies considered supportive were entered into an EXCEL database. The quality of the studies was assessed according to the JAHAD scoring system (Assessing the quality of reports of randomized clinical trials: Is blinding necessary?, Jahad AR et al, Controlled Clinical Trials 17:1-12 (1996).

B. Overview of Materials Consulted in Review

Thirteen volumes were submitted in support of the trichomoniasis indications.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

It was not possible to independently determine if the publications that were submitted in support of this submission adhered to accepted ethical standards. 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

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

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

All publications submitted in support of the NDA were independently reviewed and summarized by the MO. Only efficacy was assessed in this review.

The 5 studies identified by the applicant as pivotal as well as the additional 4 studies considered supportive were entered into an EXCEL database. The quality of the studies was assessed according to the JAHAD scoring system (Assessing the quality of reports of randomized clinical trials: Is blinding necessary?, Jahad AR et al, Controlled Clinical Trials 17:1-12 (1996).

C. Detailed Review of Trials by Indication

Trichomoniasis:

Summaries of the 5 pivotal studies follow:

- **Gabriel, 1992, UK (3)**: Comparative, single-blind, randomized trial of tinidazole 2 gm single dose versus 2 gm single dose of metronidazole in 95 female subjects. Entry criteria specified a positive wet mount and culture. Clinical and microbiologic follow-up was performed at 14 days post treatment. 49 subjects received tinidazole and 46 metronidazole with cure rates of 40/42 (95.3%) and 39/40 (97.5%) per arm respectively. No adverse events were reported.

***Medical Officer's Comment**: Information on dropouts was not provided.*

- **O'Prasertsawat, 1993, Thailand (4)**: Comparative double-blind, randomized trial of tinidazole 2 gm single dose versus 1.6 gm dose of metronidazole (split dose) in 132 female subjects. Entry criteria specified a positive wet mount and culture. Follow-up was performed at 6 - 18 days post treatment (mean 8.6). 65 subjects received tinidazole and 67 metronidazole with clinical and microbiologic cure rates of 65/65 (100%) and 66/67 (98.5%) per arm respectively. Adverse events included 55 reports from 65 subjects including bitterness (37%), anorexia (17%), nausea (20%), vomiting (3%) on the tinidazole arm as compared to 24%, 19%, 18%, and 6% per AE respectively on the metronidazole arm. All Adverse events were mild and did not require treatment.

***Medical Officer's Comment**: 13 metronidazole and 15 tinidazole patients were listed as withdrawals, however no explanation was provided and no information regarding how these subjects were handled in the analyses was provided.*

- **Hillstrom, 1977, Sweden (9)**: Comparative double blind, randomized trial of tinidazole 2 gm single dose versus 1.5 gm single dose of ornidazole in 90 female subjects and 52 male partners. Entry criteria specified a positive wet mount and culture. Follow-up was performed at 1 week and 1 month post treatment. 45 subjects received tinidazole and 45 ornidazole with cure rates of 43/45 (95%) and 45/45 (100%) per arm respectively at 1 week and 37/40 (92.5%) versus 41/42 (97.6%) at 1 month. Adverse events were reported from 9/43 (21%) of female tinidazole recipients as compared to 6/45 (13%) of ornidazole recipients and included taste changes, loose stools, and insomnia. None of the adverse events required treatment and all were mild.

***Medical Officer's Comment**: As per the applicant, "regarding the male recipients, 25 received tinidazole and 27 ornidazole with symptomatic improvement in 2 – 3 days on both arms"; however, a review of the publication by the MO revealed that no efficacy was reported for the male partners. Additionally, no explanation for the late dropouts was provided.*

- **Lyng, 1981, Denmark (14)**: Double-blind, placebo-controlled trial of a 2 gm single dose of tinidazole in male partners in conjunction with open label treatment of female partners with a single 2 gm tinidazole dose. Entry criteria specified a positive culture. 149 females and 149 males were treated and follow-up occurred at 1 –2 weeks post treatment and at 1 month after resumption of intercourse. Efficacy in females was 66/68 (97%) at the first visit and 56/61 (91.8%) at the second with a relapse rate of 5.1%. In the placebo-treated males the rates were 66/69 (96%), 45/62 (72.6%) and the relapse rate was 23.7%. Of 5 initial failures after retreatment, 1 was lost to follow-up, 3 were cured, and 1 remained positive. An additional 7 patients were found to be positive after a second follow-up visit. In total 9 subjects were cured after retreatment. 3.7% of females versus 7.4% of tinidazole treated males and 7.3% of placebo treated males had unspecified adverse events.

***Medical Officer's Comment**: Information was not provided on withdrawals, method of diagnosis in male partners or how efficacy was assessed in these subjects. All females were treated in an*

open non-comparative fashion despite the applicant's contention that the study is DB, placebo controlled.

- **Chasilwattana, Thailand 1980 (43)**: Comparative double-blind, randomized trial of tinidazole 2 gm single dose versus 2 gm single dose of ornidazole in 120 female subjects and an unspecified number of male partners. Entry criteria specified a positive wet mount. 107 females that received TNZ were evaluable as were 55 that received ORN. Patients were assessed at 4, 7, and 14 days post-treatment. Cure rates were not provided. The author assessed symptom resolution. As per the applicant, Day 4 efficacy for TNZ was 100% and at day 14 it was 98.1%. For ORN the respective numbers were 98.1% at both assessments.

Medical Officer's Comment: *No method of randomization or an explanation of withdrawals was provided. Up to 15% of patients were concurrently treated for other vaginal infections. Efficacy assessments were done only by symptom assessment.*

The following are 4 supportive blinded and comparative studies:

- **Chaudhuri, 1980 (35):** Comparative double-blind, randomized trial of tinidazole 2 gm single dose versus 2 gm single dose of carnidazole in 77 couples (38 TNZ, 39 CNZ). Entry criteria specified a positive wet mount. Patients were assessed at 7 and 14 days post-treatment. 1 CNZ and 4 TNZ subjects were assessed only at the final visit. Efficacy was 100% for CNZ and 36/38 (94.7%) for TNZ. Safety was reported. 18 CNZ subjects complained of nausea as compared to 4 TNZ subjects.

Medical Officer's Comment: *Author mentions randomization but method was not provided. No efficacy was provided for males and one efficacy rate is reported for both visits.*

- **Aimaku, 1975 (34):** Comparative double-blind, randomized trial of tinidazole 2 gm single dose versus 2000 mgm of metronidazole TID x 7 days in 127 females and an unspecified number of male partners. (57 TNZ, 50 MNZ). Entry criteria specified a positive wet mount and culture. Patients were assessed at 3, 8, and 15 days post treatment. Efficacy was 100% for MNZ at the 8 and 15 day visits (25 of 29 subjects were evaluable) and was 24/25 (96%) for TNZ at both visits. There were no adverse events.

Medical Officer's Comment: *Withdrawals were accounted for. Method of randomization inappropriate (nurse picks sealed card from basket). Final assessment was made by wet mount.*

- **Mati, 1974 (32):** Randomized, double-blind, placebo-controlled trial of 2 gm single dose tinidazole in 31 women. Diagnosis and final assessment were made by wet mount. 16 women received tinidazole with 100% efficacy. Of the 15 placebo recipients, all diagnosed with yeast, 4 had resolution of symptoms. Patients were questioned regarding side effects. Four had events including 2 episodes of nausea, 2 of epigastric pain, and 1 headache.

Medical Officer's Comment: *Method of randomization was paired envelopes. No dropouts.*

- **Rees, 1974 (31):** Randomized, double-blind, placebo-controlled trial of 2 gm single dose

tinidazole in 29 women of whom 20 were considered evaluable. Assessments were performed at 4, 5, and 7 days post-treatment. 8/10 TNZ recipients and none of the placebo recipients were considered cured. Adverse events were reported, and were primarily GI in nature.

***Medical Officer's Comment**: Method of randomization not reported, no statistical analysis performed. No apparent blinding of physician,*

Synopses of the 25 other trials submitted by the applicant in support of the trichomoniasis indication can be found in Appendix A of this document. These studies were primarily open non-randomized trials of the 2 gm single dose regimen in women. Efficacy rates ranged from 80 – 100%.

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Table 3: Tinidazole 2g Single Dose for Trichomoniasis

Combined Efficacy Rate for 5 Pivotal and 4 Supporting Randomized, Blinded, Controlled Trials

Study	# TNZ pts evaluable	Partner Treatment	Design	Avg. Age	# Cured	% Cured	Method of Cure	Follow-up Period
Lyng (14) 1981*	137	68 yes 69 no	DB, R, C	34.9	132	96.4%	Culture	1 – 2 wk
O'Prasertsawat (4), 1992*	65	yes	DB, R, C	35.7	65	100%	Culture	6 – 16 d
Chaisilwattana (43), 1980	52	yes	DB, R, C	-----	51	98.1%	wt. mt.	14 d
Gabriel (3), 1982	42	no	SB, R, C	-----	40	95.2%	Culture	14 d
Hillstrom (9), 1977	40	yes	DB, R, C	33	37	92.5%	Culture	1 mo
Chaudhuri (34), 1980	38	yes	DB, R, C	-----	36	94.7%	wt. mt.	2 wk
Aimakhu (33), 1975	25	yes	DB, R, C	-----	24	96%	Culture	15 d
Mati (32), 1974	16	yes	DB, R, C	-----	16	100%	wt. mt.	7 d
Rees (31), 1974	10	N/A (prisoners)	DB, R, C	-----	8	80%	wt. mt.	7 d
TOTAL	**425**	----	----	----	**409**	**96.2%**	----	----

* Lyng: 50% of males not treated, also measured efficacy at approximately 60 days post therapy: 91.8% (males treated), 72.6% (males not treated)

MO Discussion and Conclusions regarding efficacy of the 2 gm single dose regimen of tinidazole for the treatment of trichomoniasis in women:

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

Efficacy of the 2 g single tinidazole dose was assessed at various timepoints post-treatment (one week to one month) and ranged between 92% and 100%. In two trials [Gabriel (3), O'Prasertsawat (4)] where single dose tinidazole was compared to single dose metronidazole, comparable efficacy was shown between treatment arms [tinidazole 40/42 (95.2%), metronidazole 39/40 (97.5%) and tinidazole 65/65 (100%), metronidazole 66/67 (98.5%) in each trial respectively]. Similar efficacy was shown when single dose tinidazole was compared to 1.5g single dose ornidazole, [Hillstrom (9): tinidazole 43/45 (95.6%), f/u: 37/40 (92.5%), ornidazole 45/45 (100%), f/u: 41/42 (97.6%) and Chaisilwattana (43): tinidazole day 4 52/52 (100%), day 14 98.1%, metronidazole Days 4 and 14 98.1%].

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

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

Four additional studies were considered supportive of the 2 gm single dose regimen in women by the applicant and were reviewed. Two were double-blind, placebo-controlled studies (Rees (32), 1974 and Mati (31), 1974) that enrolled 29 and 31 tinidazole patients respectively. Ten of twenty-nine and 16/31 tinidazole recipients were considered evaluable with efficacy of 80% vs. 0% placebo and 100% vs. 26.7% placebo when assessed by wet mount only at approximately 1 week post-treatment. The quality scores of these studies were 3 and 2 respectively.

Finally, the applicant provided 2 publications of open comparative trials of the 2 gm single dose regimen in women. In one [Chandhuri (35)], the 2 gram single dose of tinidazole was compared to carnidazole. Seventy-seven subjects were enrolled of whom 38 tinidazole recipients were

included in the efficacy analysis. 94.7% as documented by wet mount at 2 weeks were considered cured. The quality score of this study was 3. In a similar study by Aimaku (34), the comparator utilized was metronidazole. Fifty-seven subjects were enrolled of whom 27 tinidazole recipients were considered evaluable. 96% as determined by culture results at 15 days were considered cured. The quality score of this study was 2.

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

Medical Officer's Comments regarding the claims of efficacy in the re-treatment of tinidazole failures:

Thirteen of the publications submitted in support of the single dose treatment of trichomoniasis indication reported on retreatment of tinidazole failures with a second dose of tinidazole. Forty-two patients who failed an initial course of treatment with a 2g single dose of tinidazole treatment for trichomoniasis were retreated with a second single 2 g dose of tinidazole and 71.4% (30/42) of these patients were successfully cured.

Table 4
Published Literature Reports of 2g Tinidazole Re-treatment of Tinidazole Failures in Trichomoniasis

Study, Year	# of Patients Treated	TNZ Dose	Cure/Outcome	Prior TNZ Dose
Swarz, 1974 [6]	1	2 g	1/1 (100%)	2 g
Akinla, 1975 [36]	1	2 g	1/1 (100%)	2 g
Beric, 1978 [39]	1	2 g	0/1 (0%)	2 g
Wallin, 1974 [5]	2 2	1.6 g 2 g	1/2 (50%) 1/2 (50%)	1.6 g 2.0 g
Schmor, 1974 [8]	1	2 g	1/1 (100%)	2 g
Dellenbach, 1974 [12]	3	2 g	3/3 (100%)	2 g
Psaroudakis, 1977 [13]	6	2 g	5/6 (83%)	2 g
Lyng, 1981 [14]	12	2 g	9/12 (75%)	2 g
Massa, 1976 [37]	5	2 g	3/5 (60%)	2 g
Bedoya, 1974 [16]	1	2 g	0/1 (0%)	2 g
Bloch, 1985 [21]	3	2 g	2/3 (67%)	2 g
Weidenbach, 1974 [22]	3	2 g	2/3 (67%)	2 g
Roseman, 1973 [28]	1	2 g	1/1 (100%)	2 g
TOTAL	**42 pts. (40)**	—	**30/42 (71%)**	—

Comments: A review of the selected articles revealed that although retreatment was reportedly effective in 30 of the 42 cases no general conclusions could be drawn as the trials were methologically disparate and the nature of the reports was often only a mention of retreatment. In many cases it was unclear if the patient had a relapse or was reinfected. To conclude, the MO could not make labeling recommendations based on the information provided for the effectiveness of tinidazole in the treatment of relapses. For synopses of the trials please see Appendix A.

[redacted]

Medical Officer's Comments regarding trichomoniasis symptom relief with a single 2 gram tinidazole dose:

As per the applicant, trichomoniasis symptom relief is usually seen within 2 – 4 days after a single 2g dose of tinidazole. In support of this statement, the applicant referred to six trials [Chaisilwattna (43), Milek (2), Jones (30), Schmor (8), Dellenbach (12), and Psaroudakis (13)] that provided some data regarding time to relief of symptoms following a single 2 g dose of tinidazole (see Table 5). The MO determined that the quality of the cited trials including the methods of data collection were inadequate in order to allow for labeling claims. For example, in the Milek study, of 134 women who received the 2 gm tinidazole dose only 78 were questioned regarding the timing of symptom resolution. Of these, 78 only 44 patients responded to the question of when they felt subjective improvement.

In general, it would be expected that subjects would experience symptomatic improvement with a 2 – 4 day period post-treatment.

Study, Year	n	Female Symptom relief post 2g single dose therapy
Chaisilwattna, 1978 [43]	52 pts.	• 94% (49/52) symptom free on day 3
Milek, 1974 [2]	61 pts.	• 74% (45/61) discharge stopped on day 3 • 70% (31/44) marked subjective improvement of all symptoms on day 3
Jones, 1977 [30]	26 pts.	• 83% (21/26) symptom free on day 3
Schmor, 1974 [6]	49 pts.	• 100% (49/49) symptom free (no malodorous discharge, burning or dysuria) at 2 - 4 days
Dellenbach, 1974 [12]	32 pts.	• 100% of patients symptom free at 3 – 4 days
Psaroudakis, 1977 [13]	54 pts.	At 3 – 5 days: • 90% (49/54) pts reported disappearance of dyspareunia • 81% (26/32) reported disappearance of generalized pelvic pain • 100% (26/26) reported disappearance of dysuria

Medical Officer's Comments regarding the claims of efficacy in the treatment of males:

The applicant claims that 11 of the submitted studies show that tinidazole has consistent efficacy in males (83% - 100%). Similar efficacy was not shown with single dose metronidazole therapy in males in 4 studies where tinidazole and metronidazole efficacy in males was compared.

Comment: The applicant submitted 11 studies reporting treatment outcomes in 435 male patients with trichomoniasis following tinidazole therapy. Only 7 of these trials utilized a single 2 g dose of tinidazole (Wallin 1974 [5], Beric 1978 [39], Pavlovic 1976 [38], Fantini 1974 [35], Chune-Kamrai [?], Massa 1976 [37], Patil 1983 [42]); One trial used a single 1g dose (Kawamura 1978 [18]) and 3 trials used a regimen of 150 mg BID for 7 days (Bandtlow 1972 [15], Lahon 1972 [227], Theerman 1973 [?]).
Note: (?) denotes reference not submitted.

The MO reviewed only the 2 gm single dose trials as this is the dose requested by the applicant.

Comment: Two of the studies cited by the applicant, Fantini (35) and Chune-Kamrai were not provided for review and thus were not accepted for use in determining the efficacy of a single 2 gm tinidazole dose in male subjects. Full descriptions of the 5 trials reviewed by the MO that utilized a single 2 gm dose can be found in APPENDIX A of this review. Specific to the issue of the efficacy in male subjects, the MO found that of

the 5 trials reviewed, one by Pavlovic (38) was completely lacking in detail and thus could not be utilized (abstract only). Another by Beric (39) did not specify how many male subjects were treated although the author cited 100% efficacy. From the remaining three trials, it appeared as if 117 male subjects in total received a single 2 gram dose of tinidazole [Wallin (7), Beric (80), and Massa (30)]. In all 3 trials a parasitological evaluation of the urine was performed both at enrollment and at follow-up. One hundred twelve of 117 subjects (95.7%) were considered cured.

Addendum: Subsequent to the review of this section, the applicant submitted the Fantini (35) publication translated from Spanish. In that publication, tinidazole was studied in 25 male subjects with urethritis that appeared to be caused by *Trichomonas vaginalis*. Diagnosis was made by examination of the urinary sediment and all subjects received a single 2 gm dose of tinidazole. Disappearance of the trichomonas was observed in 22 of 25 subjects (88%); it was unclear at what timepoint this assessment was made.

Based on the above, the number of male subjects with trichomoniasis that received a single 2 gm dose increased to 142 of whom 134 were considered cured (94.3%).

In conclusion, a single 2 gram dose of tinidazole appeared efficacious in the treatment of trichomoniasis in male subjects and can be recommended for use. Comparative statements regarding the superior efficacy of tinidazole versus metronidazole in male subjects cannot be made based on the data submitted for review.

Table 6
Tinidazole Treatment of Trichomoniasis in Males
List of Published Studies with Male Efficacy Data considered Reviewable by the MO

Study, year	Country	Treatment	Study Design	Patients receiving 2 gm tinidazole N = 117	Follow Up	Cure Rates
Beric, 1978 [39]	Germany	TNZ 2g (n=80) MTZ 5g over 10 days(n=91)	Open-label, comparative	80 M	8 days	TNZ: 100% MTZ: 98%
Massa, 1976 [37]	Chile	TNZ 2g	Open- label	30 M	7-14 days	83% (25/30)
Wallin, 1974 [5]	Sweden	TNZ 1.6g (n=4) TNZ 2g (n=7)	Open-label, dose ranging	7 M	1 week, 1 month	100% (10/10)
Fantini, 1974 [35]	Argentina	TNZ 2g	Open- label	25 M	Not stated	88% (22/25)

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

(b4)

D. Efficacy Conclusions

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

Efficacy of the 2 g single tinidazole dose was assessed at various timepoints post-treatment (one week to one month) and ranged between 92% and 100%. In two trials, [Gabriel (3), O'Prasertsawat (4)] where single dose tinidazole was compared to single dose metronidazole, comparable efficacy was shown between treatment arms [tinidazole 40/42 (95.2%), metronidazole 39/40 (97.5%) and tinidazole 65/65 (100%), metronidazole 66/67 (98.5%) in each trial respectively]. Similar efficacy was shown when single dose tinidazole was compared to 1.5 g single dose ornidazole, [Hillstrom (9): tinidazole 43/45 (95.6%), f/u: 37/40 (92.5%), ornidazole 45/45 (100%), f/u: 41/42 (97.6%) and Chaisilwattana (43): tinidazole day 4: 52/52 (100%), day 14: 98.1%, metronidazole Days 4 and 14: 98.1%].

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

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

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

Finally, the applicant provided 2 publications of open comparative trials of the 2 gm single dose regimen in women. In one [Chandhuri (35)], the 2 gram single dose of tinidazole was compared to carnidazole. Seventy-seven subjects were enrolled of whom 38 tinidazole recipients were included in the efficacy analysis. 94.7% as documented by wet mount at 2 weeks were

considered cured. The quality score of this study was 3. In a similar study by Aimaku (34), the comparator utilized was metronidazole. Fifty-seven subjects were enrolled of whom 27 tinidazole recipients were considered evaluable. 96% as determined by culture results at 15 days were considered cured. The quality score of this study was 2.

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

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

Eleven publications were submitted in support of the efficacy of tinidazole in males. Only 7 of these trials utilized a single 2g dose of tinidazole and were considered pertinent. One hundred forty-two male subjects with trichomoniasis received a single 2 gm dose and 134 were considered cured (94.3%). It was concluded that a single 2 gram dose of tinidazole appeared efficacious in the treatment of trichomoniasis in male subjects and can be recommended for use. Comparative statements regarding the superior efficacy of tinidazole versus metronidazole in male subjects cannot be made based on the data submitted for review.

[redacted]

VII. Integrated Review of Safety

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

VIII. Conclusions and Recommendations

A. Conclusions

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

- The MO could not make labeling recommendations based on the information provided for the effectiveness of tinidazole in the treatment of relapses.

- A single 2 gram dose of tinidazole appeared efficacious in the treatment of trichomoniasis in male subjects and can be recommended for use. Comparative statements regarding the superior efficacy of tinidazole versus metronidazole in male subjects cannot be made based on the data submitted for review.

- [redacted]

B. Labeling Recommendations

The applicant's proposed labeling should be revised as follows:

INDICATIONS and USAGE:

Trichomoniasis: Tindamax™ oral tablets are indicated for the treatment of trichomoniasis caused by [redacted] *T. vaginalis* in both female and male patients. The organism should be identified by appropriate diagnostic [redacted] Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, partners of infected patients should be treated simultaneously in order to prevent reinfection.

DOSAGE AND ADMINISTRATION

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

CLINICAL STUDIES

Trichomoniasis

Tinidazole (2g single oral dose) use in trichomoniasis has been ~~well~~ documented in [redacted] 34 published reports from the world literature involving over 2,800 patients treated with tinidazole.[21,43] In [redacted] four published blinded, randomized, comparative studies of the 2g tinidazole single oral dose where efficacy was assessed at time points post-treatment ranging from one week to one month [redacted] reported cure rates ranged from 92% to 100% (n= total subjects). In four published blinded, randomized, comparative studies where efficacy was assessed by wet mount, reported cure rates ranged from 80% to 100% (n=116 total subjects) [redacted]

[redacted] Parasitological evaluation of the urine was performed both pre and post-treatment and reported cure rates ranged from 83% to 100%.

[redacted]

IX. Appendix A:

- **Roseman, 1973[28]**

In this open-label trial, conducted in South Africa, 31 female patients with trichomoniasis were treated with a single 2g dose of tinidazole. Where possible, the partners were also treated. Diagnosis of trichomoniasis was based on symptoms and the presence of trichomonads in a wet mount preparation of the vaginal discharge. Follow-up examinations were scheduled at one and four weeks post-therapy. Thirty-one patients returned for follow-up at one week and 28/31 were considered cured at this visit (90.3% cure rate). Of the 3 failures one was retreated and cured. At the four week follow-up, 24 patients returned and all were considered cured. Symptom relief was rapid, generally occurring within three days of therapy. Only one patient complained of side effects, which was a metallic taste following therapy.

- **Milek, 1974[2]**

In this open-label, dose-ranging trial, 386 females with trichomoniasis were treated with one of four different tinidazole regimens: 1.5g in 98 patients, 1.6g in 75 patients, 1.8g in 79 patients, and 2g in 134 patients. All treatments were given as a single dose and the study was conducted by eight gynecologists in Switzerland. Diagnosis and outcome assessment was based on wet mount examination of vaginal discharge observing for the presence of trichomonads. Follow-up visits were scheduled for 7-10 days and 4-6 weeks post-treatment. Response rates at the first follow-up visit were as follows: 84.5% (82/98) in the group treated with 1.5g, 88% (66/75) in the group treated with 1.6g, 92.4% (73/79) in the group treated with 1.8g, and 94% (126/134) in the group treated with 2g of tinidazole. Results at the 4-6 week visit were similar, with efficacy rates ranging from 83.7% (with the 1.5g dose) to a high of 93.5% with the 2g dose of tinidazole. In the group treated with the 2g dose, side effects were reported by 10/134 patients for a rate of 7.5%. The partners of 123 of these women were also treated concurrently, and among these men there were only three cases of side effects (2.4% incidence). The authors concluded that a 2g dose of tinidazole produces an effective cure for trichomoniasis with few side effects and is a suitable treatment for the partner.

- **Swarz, 1974[6]**

In a trial of 251 women with trichomoniasis carried out at 10 European centers under a uniform protocol, treatment with 2g of tinidazole was evaluated. Diagnosis was based on a positive vaginal swab. All patients were followed up at 1-2 weeks and 4-6 weeks post-treatment. At the first follow-up visit, 245/251 women (97.6%) were cured of their infection. From the 245 cured patients, 221 were re-examined at the 4-6 week visit with 216/221 still free of trichomonas vaginalis. This represents a relapse rate of 2.26% and an overall cure rate of 95.3%. 48 male partners were also treated although a method of diagnosis was not provided. 5 subjects were retreated and 3 were cured although the article did not specify the time of reevaluation. Side effects were solicited from all female patients and 48 male partners who were treated. A total of 46 side effects were reported for an overall incidence of 15.3%. Of these side effects, 25 (8.3%) were gastrointestinal, but they were of a mild degree and were not considered to be an objection to the use of the drug. The authors concluded that the 2g tinidazole single dose regimen could be considered as an established method of therapy for trichomoniasis.

- **Weidenbach, 1974[22]**

An open-label study, conducted in Germany, examined the treatment of 64 patients with trichomoniasis randomized to either a single 2g dose of tinidazole (n=43) or a single 2g dose of metronidazole (n=21). Diagnosis was made by both wet mount and culture for trichomonads,

and was repeated at 7 days and 6 weeks after treatment. Women were hospitalized for one week to observe side effects. At one week following therapy 40/43 (93%) women on tinidazole and 20/21 (95%) women on metronidazole were considered cured. 3 of the initial failures were retreated and 2 were cured and were reassessed at 1 and 6 weeks post-treatment with evidence of parasitological eradication. One subject remained a failure and no further details were provided. Eleven side effects were reported by 8/43 (18%) patients on tinidazole and 18 side effects were reported by 12/21 (57%) patients on metronidazole. The authors concluded that a single 2g dose of either tinidazole of metronidazole are equally effective for treating trichomoniasis, but the incidence and severity of side effects are lower in tinidazole treated patients.

- **Dellenbach, 1974[12]**

A French study of 32 women with trichomoniasis diagnosed by symptoms and wet mount examination of vaginal secretions were treated with a single 2g dose of tinidazole. The partners of 29 patients were also treated with the same regimen. Follow-up visits were at one and six weeks post-treatment. At the one week visit, 31/32 patients were cured (97%), with 29/32 remaining cured at six weeks. 3 patients were retreated and all were cured.
Patients and the treated partners were questioned about side effects, none being reported.

- **Schmor, 1974[6]**

Fifty Austrian women with trichomoniasis diagnosed by wet smear of vaginal discharge and symptoms were treated with a 2g single dose of tinidazole. Sexual partners were also advised to get treatment. Following treatment (6-10 days later), 49/50 (98%) were free of infection and remained so at 4-6 weeks post-therapy. Symptoms generally disappeared within 2-4 days after therapy. One subject was retreated and appeared to be cured after this course. At a later follow-up visit, one subject was found to be positive for trichomonads although it was not clear if it was the same subject. Side effects were volunteered in two women, and in 18 upon direct questioning. These were described as insignificant and not really disturbing.

- **Schellen, 1974[15]**

A study of 53 women with a diagnosis of trichomoniasis, based on symptoms and examination of cresyl blue colored preparation of vaginal secretions, were treated with a 2g single dose of tinidazole (in the Netherlands). The sexual partners of 38/53 women were also treated with the same regimen. Follow-up examinations were conducted on the 10th day of the next menstrual cycle and in many cases two months afterwards. Of the 49 women returning for follow-up, 46 were cured (94%). Side effects were reported in 7 females (14%) and 3 males (7.8%) – all were mild.

- **Thavabalan, 1974[7]**

In the United Kingdom, 43 women with trichomoniasis diagnosed by findings on a wet smear of vaginal secretions and symptoms, were treated with a single 2g dose of tinidazole. Patients were re-examined at 1, 3-4 and 6-8 weeks following therapy. Of the 32 women with follow-up data, 30 (94%) were cured. No patients experienced any G.I. disturbances.

- **Quartararo, 1974[11]**

22 Italian women with trichomoniasis diagnosed by presence of trichomonads in wet smear and Pap smears were given a single 2g dose of tinidazole. At one and six weeks post-treatment,

21/22 (95%) of patients were considered cured. No side effects were reported by any of the patients.

- **Bedoya, 1974[16]**

15 Spanish women with trichomoniasis diagnosed by wet smear identification of trichomonads were treated with a single 2g dose of tinidazole. The sexual partners of 12 of the women were also treated. The fourth day following therapy, 14/15 (93%) of patients were cured. One subject was retreated with an unspecified dosage of tinidazole and again failed treatment. This subject had also failed multiple course of metronidazole treatment.
Side effects were reported by two patients (bitter taste) and none of the males.

- **Wallin, 1974[5]**

126 female Swedish patients with trichomoniasis diagnosed by culture were randomized to treatment with either a single 1.6g dose of tinidazole (68 patients) or a 2g dose (58 patients). Return visits were scheduled for one and four weeks post-therapy. Forty percent of the partners were also treated with 150 mg of tinidazole, BID for seven days. Of the 103 women returning for a follow-up visit, 93% were cured in the group receiving 1.6g (52/56) and 96% (45/47) receiving 2g of tinidazole were cured. 11 men were diagnosed by urethral scraping or culture (numbers not specified). Of these, 7 received the 2 gm dose; the remaining 4 received 1.6 gm. In addition to these 11 40% of sexual partners of the 58 women that received tinidazole were treated with 150 mm BID of tinidazole for 7 days. 10 men were evaluated for efficacy and all were cured. The dose of the subjects lost to follow-up was not specified. 2 patients were retreated with a second 2 gm dose of tinidazole as were 2 patients with a 1.6 gm dose of tinidazole. One patient in each group failed treatment. Side effects were reported by 11% of the patients treated.

- **Ali, 1975[29]**

An open-label study of 39 women with trichomoniasis diagnosed by wet mount identification of trichomonads was carried out in Bangladesh. Patients were treated with a single 2g dose of tinidazole and follow-up examinations scheduled for 7, 14 and 30 days post-therapy. At the 7 day follow-up, 29/36 (80%) patients were considered parasitological cures. One additional patient experienced symptom relief. Mild side effects (nausea, headache and dry mouth) were noted in 9 patients (22%).

- **Ward, 1976[10]**

An open-label trial of 25 Australian women with a wet mount diagnosis of trichomoniasis studied the effect of a 2g single dose of tinidazole seven days following treatment. Based on culture results at follow-up, all 25 women were considered cured. Only three patients (12%) complained of mild side effects.

- **Jones, 1977[30]**

An open-label study of 50 Australian women with trichomoniasis diagnosed by wet mount identification of trichomonads was carried out. Patients were treated with a single 2g dose of tinidazole. Patients were re-examined at one week by both wet mount and culture. Of 41 patients returning for follow-up, 39 (95%) were cured. Side effects, mild in nature, were reported by 19 patients.

- **Psaroudakis, 1977**[13]

An open-label study of 66 Greek women with trichomoniasis diagnosed by Pap smear and culture was performed. Patients and their partners were treated with a single 2g dose of tinidazole and asked to return for follow-up 3-5 days following therapy. Of the 58 patients returning, 43 (74%) were culture negative for trichomonads. Fifteen subjects who failed treatment were given a second 2g dose of tinidazole. At the second follow-up, 48/49 patients returning (98%) were culture negative and of the 15 retreated patients, only 6 returned and 5 of these subjects were cured. Side effects were mild and occurred in only 10 patients.

- **Anjaneyulu, 1977**[19]

A randomized, comparative trial was carried out in 100 Indian women with trichomoniasis diagnosed by wet mount, with 50 women in each of two groups treated with a 2g single dose of tinidazole or metronidazole. Partner treatment occurred in 87.5% of cases. Parasitological cure was achieved in 94% of tinidazole treated patients as compared to 64% of those treated with metronidazole ($p<0.01$). The clinical response was 96% and 72% for tinidazole and metronidazole, respectively. Side effects were reported by 52% of tinidazole treated patients versus 82% of those treated with metronidazole ($p<0.01$). Of the side effects reported, tinidazole treated patients experienced milder and a fewer number of side effects than metronidazole treated patients. In a subgroup of women, 13/14 patients who had previously failed the standard 7-day course of metronidazole were cured after receiving 2g of tinidazole. The authors suggested that tinidazole can be effective in cases of trichomoniasis which do not respond to metronidazole.

- **Kawamura, 1978**[18]

In a study of 73 Japanese males infected with trichomoniasis (found in urine culture), 39 men were treated with a 1g dose of tinidazole and 34 were treated with 1g of metronidazole in a non-blinded, non-randomized fashion. Patients were re-examined 7-14 days post-treatment. All patients in both treatment groups were considered cured and side effects were infrequent and similar in both groups (6/39 tinidazole versus 4/34 metronidazole).

- **Apte and Packard, 1978**[17]

An open-label, multicenter trial in 8 (Asian) countries using a uniform protocol was carried out in 859 women with trichomoniasis diagnosed by wet mount identification of trichomonads in vaginal discharge, as well as signs and symptoms of the disease. Follow-up examinations were scheduled for 8-21 days post-therapy. Treatment consisted of a single 2g dose of tinidazole. Where possible, consorts were treated, but the number of partners receiving treatment was not reported. The overall cure rate was 95.2% (818/859 patients). Side effects were reported by 82 of the 859 patients (9.5%), consisting primarily of nausea, abdominal pain and vomiting.

- **Rao, 1978**[20]

Sixty Indian women diagnosed with trichomoniasis by wet mount examination were randomized to receive either a single 2g dose of tinidazole (n=30) or metronidazole (n=30). Consorts were treated where possible (number not reported). Follow-up visits were scheduled 4, 8 and 12 days post-therapy. A total of 59 patients returned for follow-up, with parasitological cure achieved in all patients in both groups. Complete relief of symptoms was obtained in 62% and 13% of

patients on tinidazole and metronidazole, respectively ($p<0.01$). Side effects were reported by 10 patients receiving tinidazole (34.5%) and by 24 patients (80%) receiving metronidazole ($p<0.01$). The number and intensity of the side effects was greater among the metronidazole treated patients as compared to the tinidazole treated patients.

- **Bloch, 1985**[21]

A randomized, prospective, open-label study of 161 South African women diagnosed with trichomoniasis based on wet mount examination were treated with one of the following regimens: 2g single dose of metronidazole (n=58), 2g single dose of tinidazole (n=59), or a 2g benzoyl metronidazole suspension (n=44). Patients were given drug for partner treatment, with a compliance rate of approximately 80% in all three groups. Follow-up visits were scheduled for 7 and 14 days post-therapy. Cure rates at day 14 were 100% for both metronidazole regimens and 95% for the tinidazole treated group. Of the 5 initial failures on tinidazole, 3 were retreated with resultant eradication of the parasite. One patient again relapsed and was retreated with metronidazole with an ultimate cure at 14 days. Side effects were reported by 22.4%, 7.5% and 13.3% of patients receiving metronidazole, benzoyl metronidazole suspension, and tinidazole, respectively.

- **Gulmezoglu, 1998**[23]

A systematic review comparing the effectiveness of various treatments for trichomoniasis in women was conducted by searching Medline from 1966-1996, Embase from 1986 to 1996, Science Citation Index from 1990 to 1996; reference list of existing reviews; through the manufacturers of metronidazole and tinidazole in the UK; the Cochrane Controlled Trials Register until October 1997, and informal discovery. Only randomized or quasi-randomized trials in nonpregnant women comparing different treatment strategies were included. A total of 45 of 124 identified studies were included in the review. Most trials were comparisons of different drugs or doses (31/45) and most trials meeting inclusion criteria were small (less than 100 patients in each comparison arm). Metronidazole was compared to tinidazole in 7 studies, 6/7 comparing short regimens of each drug. There were no parasitological failures in two of the trials; meta-analysis results indicated that a higher treatment failure rate (RR:3.13), higher clinical failure rate (RR:3.73), and higher side effect rate (RR:1.76) was seen with metronidazole. Six trials compared tinidazole to ornidazole, with no statistical differences in parasitological and clinical cure, although the ornidazole group had a higher incidence of side effects, which was most marked with fatigue (RR:0.18).

- **Massa, 1976 (37):** 30 males were treated with a 2 gm single dose of tinidazole. Diagnosis was based on the isolation of trichomonas in the urine. Initial eradication was obtained in 25 (83.3%) and after retreatment with a second dose in an additional 3 subjects. Note: No details given re follow-up.

- **Beric, 1978 (39):** 104 women and 80 partners received a single 2 gm dose concurrently with 100 women and 91 men who received metronidazole topical and PO. Diagnosis in men appears to have been made by microscopic examination of centrifuged urine. TOC was at 6 days post-treatment. 103 women of 104 (96%) were cured as were 80 men (method of assessment of cure in men not specified) One female was not cured after a

second dose. Similar results were obtained with metronidazole with 97 women and 89 men cured initially. After retreatment 1 woman and one man were still considered failures.

- **Akinla, 1975** (36): hospitalized subjects initially positive on culture and negative after 7 days, relapsed 34 days after treatment. Redoing again led to clearance at post-treatment day 7. No further follow-up was provided.

- **Patil:** 60 female subjects received tinidazole of whom 45 returned for follow-up. The publication does not state how many men were treated although examination of centrifuged urine was assessed at enrollment and follow-up. The authors state that there were no failures amongst the treated male subjects.

- **Pavlovic** 1976 (abstract): 35 women and 30 men were treated with an unspecified dose of tinidazole. 3 women and 2 men were found to be failures 8 days post-treatment. NOTE: Only the abstract was provided. No details of the trial including dose or method of diagnosis were provided.

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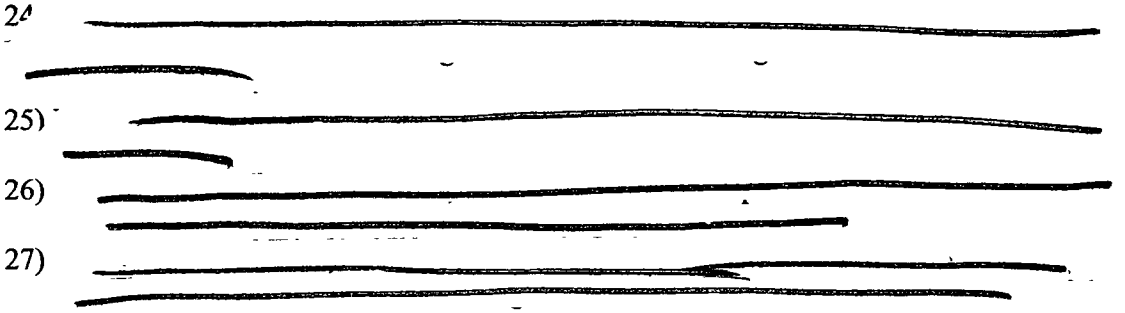

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