

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-618

21-681

21-682

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

FAX

Date 4/14/04

Pages including this cover page 4

To: Christina Chi, Ph.D.

FDA Div of Special Papers

301 227 2324

From: John Presutti

Presutti Laboratories
1607 N. Douglas Ave.
Arlington Heights, IL 60004
Phone: 847 359-7800
FAX: 847 359-7878
E-Mail presind@aol.com

Message:

H. Dr. Chi
Here is the form 3542a you
requested. We will formally submit it
when we do our next amendment.

John Presutti

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-618, 21-681, 21-682

NAME OF APPLICANT / NDA HOLDER
Presutti Laboratories

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
(proposed)

ACTIVE INGREDIENT(S) tinidazole	STRENGTH(S) 500 mg 250 mg
------------------------------------	---------------------------------

DOSAGE FORM
tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
--------------------------------	-------------------------	------------------------------

d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

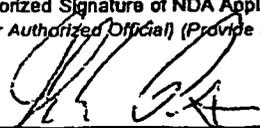
Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)



Date Signed

4/16/07

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Presutti Laboratories, John E. Presutti, President

Address

1607 N. Douglas Ave

City/State

Arlington Heights, IL

ZIP Code

60004

Telephone Number

(847) 359-7800

FAX Number (if available)

(847) 359-7878

E-Mail Address (if available)

presind@aol.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY FOR NDAs # 21-618, 21-681 & 21-682 Tindamax Tablets.

(note: NDA 21-618 was administratively split to NDAs 21-618, 21-681 & 21-682 during the review period).

Trade Name: **Tindamax™ tablets, 250 & 500 mg**

Generic Name: **Tinidazole**

Applicant Name: **Presutti Laboratories, Inc.**

HFD #: **590 (DSPIDP)**

Approval Date If Known: **May 17, 2004**

PART I : IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement? YES / x / NO / ___ /

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8.
505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / x, **clinical data from literature only** / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____ N/A _____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____ N/A _____

d) Did the applicant request exclusivity? YES / x / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **5 years New Chemical Entity exclusivity (because tinidazole is an NCE); 7 years orphan exclusivity for giardiasis and amebiasis (because both giardiasis and amebiasis received orphan designation).** ____

e) Has pediatric exclusivity been granted for this Active Moiety? YES / ___ / NO / x /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Request?

____ N/A _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade? YES / ___ / NO / x /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / x /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

NDA's 21-618, 21-681 & 21-682 Tindamax tablets: Exclusivity Checklist
7 of 8

Investigation #1 !
IND # ____ YES / __ / ! NO / __ / Explain: _____
!
!

Investigation #2 !
IND # ____ YES / __ / ! NO / __ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES / __ / Explain _____ ! NO / __ / Explain _____
!
!
_____ ! _____
!
_____ ! _____

Investigation #2 !
YES / __ / Explain _____ ! NO / __ / Explain _____
!
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / __ / NO / __ /

NDA 21-618, 21-681 & 21-682 Tindamax tablets: Exclusivity Checklist
8 of 8

If yes, explain: _____

Signature:

Date:

(Christina H. Chi, Ph.D.)

Title: Regulatory Project Manager

Signature of Office/Director:

Date:

(Mark J. Goldberger, M.D., M.P.H.)

Title: Office Director, ODE IV

Form OGD-011347 Revised 05/10/2004

cc:

Archival NDA

HFD-590/Division File

HFD-590/RPM/Christina Chi

HFD-610/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

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

/s/

Edward Cox
6/18/04 06:16:02 PM
for Mark J. Goldberger, MD, MPH

2. Claimed Exclusivity

Since tinidazole is a new chemical entity in the U.S., applicant is claiming 5 years of exclusivity under the provisions of 314.108 (b)(2).

In addition, applicant on April 18, 2002 was granted Orphan Drug Designation of tinidazole for the treatment of giardiasis.

The applicant has also recently filed for Orphan Drug Designation of tinidazole for the treatment of amebiasis.

5. DEBARMENT CERTIFICATION

Presutti Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 4, 2004

TO: NDA files of NDAs 21-618, 21-681 and 21-682 for Tindamax (tinidazole) Tablets 250 and 500 mg

THROUGH : Leonard Sacks, M.D.,
Team Leader, Division of Special Pathogen
and Immunologic Drug Products (DSPIDP), HFD-590

Renata Albrecht, M.D.
Director, Division of Special Pathogen
and Immunologic Drug Products (DSPIDP), HFD-590

Mark Avigan, M.D.
Acting Director, Division of Drug Risk Evaluation, HFD-430

FROM: Christina H. Chi, Ph.D., Regulatory Project Manager, DSPIDP

SUBJECT: **Preapproval Safety Conference for NDA 21,618, 21-681, and 21-682, Tindamax (tinidazole) tablets 250 and 500 mg.**

The Division of Special Pathogen and Immunologic Drug Products and the Division of Drug Risk Evaluation have concurred that a Pre-approval Safety Conference is not required for NDAs 21-618, 21-681 and 21-682 for Tindamax (tinidazole) Tablets for the following reasons:

- This drug product has been approved and marketed as a prescription drug in Australia, Asia, and many European countries for more than 20 years without significant adverse event reporting
- Minimal spectrum of risk based on the adverse event evaluation conducted
- Congruency of adverse event evaluation between the applicant and FDA
- Lack of events with significant severity or frequency or unexpected character

Therefore, while tinidazole is officially designated as a New Molecular Entity, it is believed that it will not have the potential for new toxicities if used according to the FDA approved labeling.

FAX

Date 5/17/04

Pages including this cover page _____

To: Christine Chi, PhD

fax 301-827-2321

From: John Presutti

Presutti Laboratories
1607 N. Douglas Ave.
Arlington Heights, IL 60004
Phone: 847 359-7800
FAX: 847 359-7878
E-Mail presind@aol.com

Message:

H. Dr. Chi,
Following is a letter re-affirming our
intentio. to conduct a phase 10 day for study.
John Presutti

Presutti

Presutti Laboratories, Inc.
1607 N. Douglas Avenue
Arlington Heights, IL 60004

Tel: 847-359-7800
Fax: 847-359-7878
presind@aol.com

May 17, 2004

Renata Albrecht, MD
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation
Food and Drug Administration
9201 Corporate Blvd. HFD 590
Rockville, MD 20850

Re: NDAs 21-618, 21-681, 21-682 (tinidazole)

Dear Dr Albrecht,

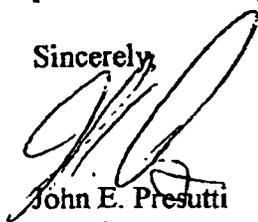
The purpose of this letter is to affirm our understanding and commitment to the following post-approval study regarding the above referenced NDAs.

We have agreed to conduct a 30 day toxicity study in dogs in order to comply with ICH Guidance (M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) under the following timelines:

Protocol Submission: Within 4 months of the date of NDA approval.
Study Start: Within 8 months of the date of NDA approval
Final Report Submission: Within 24 months of the date of NDA approval.

This topic has been discussed several times including a conference call on August 6, 2001, a May 14, 2002 submission of a protocol and a June 12, 2002 Agency letter accepting the protocol. It was again mentioned in the cover letter in our NDA submission on July 16, 2003.

Sincerely,



John E. Presutti
President

Chi, Christina H

From: Chi, Christina H
Sent: Monday, May 17, 2004 2:47 PM
To: 'Presind@aol.com'
Cc: Roeder, David L; Cox, Edward M; Albrecht, Renata; Sacks, Leonard V; Hundley, Stephen G; Miller, Kristen; Molinaro, Ellen F; Chi, Christina H
Subject: Letter of understanding regarding the Phase 4 commitment of Tindamax

Dear Mr. Presutti:

This communication is about the need of a Letter of Understanding regarding the Phase 4 commitment of NDAs 21-618, 21-681 and 21-682 for Tindamax (tinidazole) tablets.

Since most of the communications that we reference are over 2 years old, and were submitted or faxed to you during the IND phase (IND 2,292), we are asking you to resubmit your concurrence with the Post Marketing Commitment and the timeline.

Please send me a letter of understanding **dated today, May 17, 2004**. We will then reference today's submission in the AP letter. Please fax to 301-827-2326 as soon as the document is ready.

The letter should contain the following items.

1. that we have discussed the matter as evidenced in:
 - our teleconference dated August 6, 2001,
 - your IND 62,292 submission dated January 30, 2002,
 - the FDA fax of March 22, 2002,
 - your submission dated May 14, 2002
 - the FDA fax of June 12, 2002.

2. that we have discussed with you and that you have agreed on the post marketing study commitment as listed below:
 - a 30-day toxicity study in dogs in order to comply with ICH Guidance (M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals).

3. that we have discussed with you and that you have agreed on the postmarketing study commitment timeline:

• Protocol Submission:	Within 4 months of the date of this letter
• Study Start:	Within 8 months of the date of this letter
• Final Report Submission:	Within 24 months of the date of this letter

Thanks,
Christina Chi

Deputy Office Director Review

APPLICANT: Presutti Laboratories, Inc.
DRUG: tinidazole
TRADE NAME: Tindamax™
NDA: 21-618, 21-681, 21-682, _____
DATE OF SUBMISSION: July 17, 2003
PDUFA GOAL DATE: May 17, 2004
FORMULATION: tablet (250 mg and 500 mg)
INDICATIONS: Treatment of trichomoniasis
Treatment of giardiasis
Treatment of amebiasis (intestinal amebiasis and amebic liver abscess)

Recommended Regulatory Actions

NDA 21-618, 21-681, and 21-682 - Approval

- Treatment of trichomoniasis (NDA 21-618)
- Treatment of giardiasis (NDA 21-681)
- Treatment of amebiasis (intestinal amebiasis and amebic liver abscess) (NDA 21-682)

Background

Tinidazole, a nitroimidazole antimicrobial agent, has been approved for marketing for over two decades in a number of countries other than the United States. These countries include the United Kingdom, Australia, Belgium, Costa Rica, El Salvador, Finland, France, Germany, Guatemala, Honduras, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, South Africa, Spain, Sweden, and Switzerland.

The proposed indications in NDAs 21-618, _____ include treatment of trichomoniasis _____, treatment of giardiasis _____ and treatment of amebiasis (intestinal

amebiasis and amebic liver abscess). The applicant has previously requested and received orphan drug designation for the indications of giardiasis and amebiasis. For the three indications that are the subject of this application, the treatment of trichomoniasis, giardiasis, and amebiasis, there are limited FDA approved therapeutic options.

The data submitted to support the safety and efficacy for the proposed indications are derived from the published literature. The sponsor also provides data from a clinical pharmacology study to evaluate the bioequivalence of the applicant's formulation to Fasigyn (tinidazole) (Pfizer, UK) the formulation used in most of the clinical studies. In addition the applicant also conducted and submitted the report for a reproductive toxicology study that evaluated the effects of tinidazole on male rat fertility. Postmarketing adverse event data from Australia and the United Kingdom have also been provided.

For a detailed review of the elements within the NDA submission, the reader is referred to the discipline specific reviews. The reader is also referred to the Team Leader review. A brief summary of some of the discipline specific points is provided in the sections that follow.

Chemistry

The Chemist's review of NDA 21-618 recommends approval. The manufacturing facilities were found to be acceptable on April 1, 2004.

Pharmacology / Toxicology

The applicant provided data from the published literature and a reproductive toxicology study that evaluated the effects of tinidazole on male rat fertility that was conducted by the applicant. The Pharmacology/Toxicology review notes that in the embryo-fetal developmental toxicity studies an elevated incidence of embryo-fetal mortality was observed in rats at the 500 and 2,000 mg/kg dose levels. The 500 mg/kg dose in rats is 2.5 fold the highest human therapeutic dose based upon body surface area conversion. The final draft labeling for Tindamax™ lists tinidazole as a pregnancy category C agent. Prior to the submission of the NDA, through discussion with the sponsor and the division the agreement was reached to include the information on carcinogenicity in a Boxed WARNING based upon what is known about another member of the nitroimidazole class (metronidazole). The sponsor has committed to performing a 30-day toxicity study in beagle dogs as a phase 4 commitment.

Microbiology

Tinidazole, a 5-nitroimidazole compound, is an antimicrobial agent with antiprotozoal activity. The Applicant submitted a considerable number of reports from the published literature evaluating the microbiological activity of tinidazole. Of note is that, standardized methods for *in vitro* susceptibility testing for antiprotozoal agents have not

been established. Studies showed *in vitro* activity of tinidazole against *Trichomonas vaginalis*, *Giardia lamblia*, and *Entamoeba histolytica* comparable to metronidazole. *In vitro* MICs (minimal inhibitory concentrations) and MLCs (minimum lethal concentrations) showed a correlation between tinidazole and metronidazole for *T. vaginalis* suggesting cross-resistance for metronidazole and tinidazole. Experimental *in vivo* animal models of infection demonstrated activity against *Trichomonas vaginalis* and a *Trichomonas foetus*. Evidence was also presented demonstrating the activity of tinidazole in experimental animal models of infection for *G. lamblia* and *E. histolytica*.

Clinical Pharmacology

The Applicant performed a bioavailability study in healthy volunteers to investigate the bioavailability of the Applicant's tinidazole formulation to Fasigyn™ (tinidazole) (Pfizer, UK), the formulation used in most of the published literature reports that are submitted in the NDAs. The two formulations were found to be bioequivalent. The label provides information on drug interactions based upon what is known about drug interactions for metronidazole, a chemically-related nitroimidazole.

Efficacy - Clinical and Statistical

The Applicant submitted reports from the published literature on studies evaluating the efficacy of tinidazole in the treatment of trichomoniasis, giardiasis and amebiasis (intestinal amebiasis and amebic liver abscess). The number of studies from the published literature by indication included in the submission was 34 for trichomoniasis (including 14 comparative studies), 24 for giardiasis (including 15 comparative studies), 20 for intestinal amebiasis (including 9 comparative studies), and 15 for amebic liver abscess (including 9 comparative studies). The studies by indication, collectively provide sufficient evidence of efficacy for the proposed indications for the treatment of trichomoniasis, giardiasis, and amebiasis (intestinal amebiasis and amebic liver abscess) utilizing the proposed dosages and durations. Tabulations of the individual study data and statistical approaches to the analyses of the data are provided in the individual reviews.

[Redacted content]

Safety

The applicant provided 93 studies from the literature. Seventy-six of these published reports were evaluable for safety. These reports included approximately 3500 subjects. Adverse event rates for events occurring at frequencies of $\geq 1\%$ were tabulated from the data from the published reports. In addition postmarketing adverse event data from Australia and the United Kingdom were also submitted and evaluated. The observed adverse events were similar to what is known for metronidazole (a similar nitroimidazole agent) and to what is described in foreign product labels for tinidazole. Overall the safety data from the published literature, along with the data from the postmarketing experience with tinidazole provide a satisfactory characterization of the safety of tinidazole. In addition, information on the safety of nitroimidazole class antimicrobial agents (ie metronidazole) provides nitroimidazole class safety information for tinidazole (a nitroimidazole class antimicrobial agent).

Risk-Benefit

The overall assessment of the risk-benefit ratio for tinidazole based upon the data submitted is satisfactory for the indications of:

- Treatment of trichomoniasis
- Treatment of giardiasis
- Treatment of amebiasis (intestinal amebiasis and amebic liver abscess)

at their respective proposed dosing and durations as described in the final labeling.

Conclusions

This application presents a somewhat unique situation because of the following considerations that are specific to tinidazole:

- tinidazole has been marketed in a number of countries around the world since the 1970's
- postmarketing safety data is available for the use of tinidazole outside of the US. The application includes postmarketing adverse event data from Australia and the United Kingdom. A survey of the approved foreign labels shows that the approved indications, dosage, and duration are similar with regards to trichomoniasis, giardiasis, and amebiasis. Hence the postmarketing adverse event data is relevant to the proposed indications for trichomoniasis, giardiasis, and amebiasis.
- Two of the indications being sought have received orphan drug designation (giardiasis and amebiasis)
- Tinidazole would add a new therapeutic option to the existing antimicrobial armamentarium for the proposed indications for the treatment of protozoal organisms in the three proposed indications, infectious diseases for which there is a limited number of FDA approved therapeutic options.

Adequate evidence to support the safety and efficacy for the treatment of trichomoniasis, giardiasis, and amebiasis as in the final version of the proposed Tindamax™ (tinidazole) product labeling has been provided within NDA 21-618.

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/s/

Edward Cox
5/17/04 07:30:22 PM
MEDICAL OFFICER

TEAM LEADER REVIEW

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

Application number: NDA 21-618, NDA 21-681, NDA 21-682, _____

Generic Name: Tinidazole

Proposed Trade Name: _____

Pharmacologic Category: 2-methyl-5-nitroimidazole

Dosage Form: 250 and 500 mg Tablets

Route of Administration: Oral

Date of Submission: July 15, 2003

CDER Stamp Date: July 17, 2003

PDUFA goal date: May 17 2004

Recommendations regarding approval

The indications that the applicant seeks include a) trichomoniasis _____
_____ c) giardiasis, _____ e) amebiasis
(intestinal) and f) amebic liver abscess.

Based on published literature as outlined below, the Division has determined that the product is both safe and effective at the recommended dosing regimen for the indications of trichomoniasis, giardiasis, amebiasis (intestinal) and amebic liver abscess. There are no outstanding deficiencies in this application.

Background

Presutti laboratories, the applicant for this NDA 21-618, has requested approval to market tinidazole in the US. They have submitted a 505(b)(2) application where the entire body of clinical information is derived from published literature. They have no right of reference to innovator data supporting the development of tinidazole in the rest of the world. The product has been demonstrated in a clinical pharmacology study to be bioequivalent to Fasigyn, the brand of tinidazole used in most of the literature studies that are cited in support of this application.

Orphan drug status has been granted for the indications of giardiasis and amebiasis. In both of these conditions, the number of cases in the US is less than 200,000 per year.

Tinidazole (a nitroimidazole product closely related to metronidazole) was developed by Pfizer. For reasons that have not been clarified, Pfizer did not develop tinidazole for licensing in the US. However tinidazole has been approved and extensively marketed since the 1970's in Europe (UK, Austria, Belgium, Spain, Finland, France, Germany,

Italy, Netherlands, Spain, Sweden, Switzerland), India, Australia, central America and South Africa. Approved indications in these countries include trichomoniasis, giardiasis, intestinal amebiasis and amebic liver abscess, non-specific vaginitis, prevention of post-operative infections, treatment of anaerobic infections, ulcerative gingivitis, and *Helicobacter pylori* infections causing duodenal ulceration.

Tinidazole has a spectrum of clinical and microbiological activity that covers various protozoa including *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia intestinalis*. Pharmacokinetic differences between tinidazole and metronidazole include a longer plasma half-life (12-14 hours for tinidazole versus 8 hours for metronidazole) and later peak concentrations.

A large body of published material representing over 30 years of clinical use has provided an understanding of the safety of tinidazole as well as efficacy for the requested indications. Published articles cover a range of tested doses using a variety of study designs and the results confirm the safety and the efficacy of the product. The drug has been used in many parts of the world including Canada, Europe, Africa and Asia. As a member of a known class of drugs (nitroimidazoles) the understanding of the safety and efficacy of tinidazole is enhanced by existing knowledge of related drugs. Two of the sought indications qualify for orphan drug status, emphasizing the importance of tinidazole for the treatment of diseases with limited therapeutic options. Many of these options include drugs that are no longer marketed and drugs that are not approved in the US. Tinidazole has the advantage of a shorter duration of therapy compared with available agents for several of the proposed indications.

Since the Division has not had access to the source data for this material, the assessment of safety has been based on corroborative findings as reflected in published articles, foreign labeling and foreign post-marketing adverse event reporting. Evidence supporting the efficacy of tinidazole for the proposed indications is derived from published literature alone as detailed below.

Contents of submission

The submission included 3 original studies, a toxicology study in male rats to investigate the effects of tinidazole on spermatogenesis, and two biopharmaceutic studies, one to demonstrate bioequivalence between the Presutti tinidazole, and Fasigyn, the brand of tinidazole used in most of the reference literature and the second to investigate inhibition of P450 enzymes by tinidazole. The bioavailability of crushed tablets in cherry syrup, and the effects of food were also addressed in these studies.

The balance of the submission included an extensive compendium of published articles on tinidazole dating back to the 1970's, copies of foreign labels in the countries where tinidazole is approved, and a collection of post-marketing adverse event reports from Australia and the United Kingdom.

Synopsis of efficacy by indication

a) Trichomoniasis

Efficacy in women:

Metronidazole, either given as a single 2gm dose or at a dose of 250mg tid for 7 days, is the only treatment for trichomoniasis currently approved in the US. Cases are recognized where repeat courses of metronidazole fail to eradicate the infection.

The applicant identified 34 publications where a 1 or 2 gram single dose of tinidazole was used to treat trichomoniasis. It was confirmed that the literature search was comprehensive and unbiased. Nine of the studies (summarized in the table below) were blinded, comparative studies using the single 2 gram dose. All were considered randomized, controlled trials of the 2 gm single dose of tinidazole by their respective authors. Five hundred eighty-six females 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 (see medical officer review).

Among the nine published comparative blinded studies utilizing a single 2 gm dose of tinidazole, comparators were metronidazole, ornidazole, carnidazole or placebo.

Inclusion criteria included a positive wet mount and/or culture.

Follow-up was performed between 6 and 30 days after initiation of therapy.

In total 425 evaluable women in these trials were treated with a single 2 gm dose of tinidazole.

Cure rates as determined by culture or wet mount were $\geq 80\%$ in each of these trials (see table below).

Tinidazole for trichomoniasis in women

Study	# TNZ pts evaluable	Partner Treat- ment	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

A further 25 published studies of less scientific rigor (either open label or non-randomized) confirmed efficacy rates for tinidazole of 80-100%, when women with trichomoniasis were treated with a single 2 gm dose of tinidazole. No pediatric data on women less than 16 years of age were provided in this submission, although young females post menarche may be affected by this condition.

Efficacy in men:

Four open label studies in men using a single 2gm dose of tinidazole were submitted where diagnosis was confirmed by parasitological examination of urine. Cure was confirmed by the absence of the organisms in urine, generally after 1 week. Among these studies (which included a total of 142 treated men who were microbiologically evaluable), cure rates ranged from 83% to 100% (see table below).

Tinidazole Treatment of Trichomoniasis in Males

Study, year	Country	Treatment	Study Design	Patients receiving 2 gm tinidazole	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 (9)	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)

b) Giardiasis

Giardiasis is an uncommon cause of diarrhea in the US. Annual numbers of cases reported to CDC between 1992 and 1996 ranged between 12,793 and 27,778, with the highest incidence in children aged 0-5 years. (MMWR Vol.49/No SS_7, August 2000). Nitazoxanide (given for 3 days) and furazolidone (100mg QID for 7-10 days) are approved in the US for this indication. Other agents used for treatment, but not approved by FDA include metronidazole (2gm daily for 3 days or 400mg TID for 5 days) Mepacrine (100mg TID for 5-7 days), quinacrine or paromomycin.

The applicant identified 24 studies in the literature which studied the effectiveness of tinidazole in the treatment of giardiasis. It was confirmed that the literature search was comprehensive and unbiased. There were approximately 2300 patients evaluated in these trials. Over 1600 subjects received tinidazole and close to half of these were children. Twenty of the studies utilized a single dose of tinidazole (or the pediatric equivalent of 50mg/kg). Sixteen of the twenty studies were comparative and nine of these 20 were both comparative and randomized. These nine studies involving 349 tinidazole treated subjects are shown in the table below.

Eight compared a single 2 gm dose or a single dose of 50mg/kg of tinidazole with metronidazole given according to various dosage regimens. (Metronidazole, while not approved for this indication in the US, represents the standard of care for giardiasis.) One compared a single dose of 1.5gm of tinidazole with the same dose of ornidazole (not approved in the US).

Inclusion criteria included presence of diarrheal symptoms and Giardia cysts or trophozoites in stool.

Cure rates from 12 days to 8 weeks after initiation of therapy, as determined by parasitological clearance in between 1 and 3 stool samples (depending on the individual study) are shown below.

Single dose studies of tinidazole in 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	

* pediatric studies

Cure rates were numerically higher for tinidazole when compared with single dose metronidazole therapy, and similar to cure rates achieved with repeat doses of metronidazole.

Five of the 9 studies included were performed in children (196 treated with tinidazole) between 3 and 12 years of age. Separate analyses comparing response by age were not performed. The response rates were 88.3% to 100%, similar to the response rates in the 4 adult studies which ranged from 80% to 97%. The substantial number of pediatric patients in the studies supported pediatric labeling for this indication.

Four of the largest non-randomized studies involving over 700 patients, (over 500 of whom received tinidazole) and using a variety of comparators, confirmed cure rates of 80-96%

c) Amebiasis

Intestinal amebiasis is predominantly a disease of the developing world with approximately 3000 US cases reported annually to CDC.

The applicant has proposed a tinidazole dose of 2gm or 50mg/kg daily, given for 3 days.

The applicant identified 26 published clinical reports on the use of tinidazole in the treatment of intestinal amebiasis. These trials included approximately 2200 patients and about 1400 were treated with tinidazole. Nine of the trials were randomized and eight of these used metronidazole as a comparative drug. Four of these trials utilized the proposed tinidazole dose of 2 grams once daily for 3 days. These four studies were considered the pivotal studies. One of these studies was single blind, the rest were not blinded. In common, all compared tinidazole with metronidazole at the same dose.

Inclusion criteria included symptomatic patients with trophozoites or cysts in the stool.

Some studies employed sigmoidoscopy in the initial patient evaluation.

Follow-up was performed between 4 and 30 days after initiation of therapy.

In these trials, a total 220 adults were treated with tinidazole.

Cure rates ~30 days after initiation of therapy, as determined by microscopy and symptom resolution are shown below.

Tinidazole trials in intestinal amebiasis

Study	TNZ Efficacy 2g/d x 3d	MTZ Efficacy 2g/d x 3d	Study Design	Measure of Cure	Sigmoid- oscopy	Follow-up Period
Swami (197)	25/29 86.2%	8/27 26.6%	OL,R,C	Complete resolution of symptoms; Stools -	"Wherever possible"	4,20,30 days
Singh (196)	25/27 92.6%	17/29 58.6%	OL,R,C	Complete resolution of symptoms; Stools -	"Wherever possible"	4,20,30 days
Misra	27/30	16/30	OL,R,C	Complete	All patients	5,20,30

(194)	90%	53.3%		resolution of symptoms; stools-		days
Bakshi (118)	123/134 91.7%	66/123 53.6%	DB,R,C	Near complete resolution of symptoms; Stools -	Not mentioned	4,20,30 days
Total	220	209				

Cure rates were numerically higher for tinidazole when compared with equivalent doses of metronidazole therapy.

One study provided information on the treatment of approximately 550 children in India, Bangladesh, Korea, the Philippines, and Indonesia with parasitological success rates of 95% and 96% respectively. A second open label study in Brazil described the treatment of children with mixed parasitic infections including giardia, necator, strongyloides and ascaris. The dose of tinidazole was described as 0.5ml/kg for 2 days and the corresponding mg/kg dose could not be ascertained. Parasitological cure was described in 63% of the tinidazole treated children and clinical improvement was described in 91% of the tinidazole treated children.

Amebic liver abscess

Amebic liver abscess is an uncommon complication of intestinal amebiasis, with a potentially fatal outcome. The diagnosis generally relies on the radiographic evidence of a hepatic abscess, positive amebic serology, an appropriate response on amebicidal therapy alone, and on occasions, parasitological confirmation of the organism in material from the abscess wall. Metronidazole (500mg or 750mg orally three times daily for 5 to 10 days) is the agent approved in the US for this condition. The proposed dose of tinidazole for this indication is 2gm or 50mg/kg for 3-5 days.

Eighteen trials were identified by the applicant in the literature, evaluating the use of tinidazole in the treatment of amebic liver abscess. Nine studies were randomized trials comparing tinidazole with metronidazole. Seven of these trials used the tinidazole dose of 2g/day for 2-5 days and were regarded by the division as pivotal in support of this indication. These seven trials, conducted in India, Bangladesh and South Africa were published between 1977 and 1985. All participants were adults and all were treated with tinidazole 2g/day for 2-5 days. The diagnosis was made on clinical grounds with aspiration of typical pus in 5/7 studies. One study reported serological confirmation of the diagnosis, and radiological evidence was recorded in some of the studies. Among 134 patients treated with tinidazole (2gm/day for 2-5 days) and followed up for periods ranging from 30 to 56 days, clinical cure rates in individual studies ranged from 80-100%. Comparative response rates for 138 metronidazole-treated patients ranged from 33% to 93% (see table).

Tinidazole trials in amebic liver abscess

Study	TNZ Dose	TNZ Efficacy	MTZ Dose	MTZ Efficacy	Diagnosis Anchovy Pus Required	Response Measurement

Kundu (297)	2g/d x 3d	8/9 (88%)	2g/d x 3d	3/9 (33%)	Yes	Excellent, good, fair, poor- excellent or good considered cure
Islam (296)	2g/d x 3d	15/16 (94%)	2g/d x 3d	12/15 (80%)	No	Not clearly stated
Kokhani (119)	2g/d x 2d	10/10 (100%)	2g/d x 2d	5/9 (56%)	Yes	Clinical and radiological improvement
Mather (198)	2g/d x 2d	11/12 (91.7%)	2g/d x 2d	10/11 (91%)	Yes	Same as Kundu
Bakshi (118)	2g/d x 2d	48/50 (96%)	2g/d x 2d	37/49 (76%)	Yes	Complete versus incomplete
Simjee (302)	2g/d x 5d	17/21 (80%)	2g/d x 5d	25/27 (93%)	Yes (also serology)	Not clearly stated
Mendis (299)	2g/d x 3d	16/16 (100%)	400mg tidx5d	14/18 (77.8%)	No	Rapid, intermediate, slow
Total		134		138		

Response rates were numerically higher for 3-5 days of tinidazole compared to 3-5 days of metronidazole in 5/6 of the studies. Only one small study (Mendis) compared tinidazole to a longer courses but lower dose of metronidazole therapy

Three supportive studies on 65 adults treated with doses of tinidazole \leq to the proposed dose of 2gm daily for for 3-5 days showed response rates between 93 and 100%. A single uncontrolled study in children compared tinidazole doses of 50-60mg/kg given either for 3 or for 5 days. Of 25 children, 23 (92%) were cured over a follow up period of 6 months.

Synopsis of Safety:

Safety was evaluated from 4 sources; a) published literature references, b) post marketing adverse event reports from the UK and Australia, c) a review of foreign labeling and d) safety evaluation of the participants in the original bioequivalence study.

a) published literature

Seventy-six published references covering 3515 treated subjects were identified where safety data was provided. Given the diversity of study indications and study design, the adverse event reports showed considerable variability.

Exposure

Doses in the literature ranged from 50mg/kg to 2 gm for duration of 1 to 7 days. Safety data was available for durations of exposure up to 3 days. Safety data was not reported in studies with longer exposures.

Populations

- Pediatrics

Eleven pediatric studies were identified where 417 pediatric patients were treated with tinidazole and 24 adverse events were documented. Most were treated with single doses. Ninety children were treated for 3 days and tolerance of therapy was similar to that seen

for adults. Limited available data among children treated for 5 days did not identify toxicity.

- **Pregnancy**

Three literature reports on the use of tinidazole beyond the first trimester in pregnant women did not identify adverse effects on the mother or fetus.

- **Geriatric**

Geriatric information was not provided

Serious adverse events

No deaths were reported that were attributed to the drug. Three serious adverse reactions were identified in the submitted literature, two cases of congenital anomalies where drug association was "possible", a case of Bell's palsy and a patient with convulsions

Frequent adverse events

The most frequently reported adverse events involved the gastrointestinal and neurological systems, most commonly taste change, nausea, anorexia and vomiting, weakness, dizziness and headache. The safety profile appears similar to that for metronidazole.

Laboratory abnormalities

Sporadic reports of various abnormal laboratory results did not point to any systematic toxicity from tinidazole

b) post marketing adverse event reports from the UK and Australia

Three hundred and fifty post-marketing adverse events were reported to the Australian regulatory authority and 48 to the UK regulatory authority. As an indication of the utilization of tinidazole in these countries, the applicant reports marketing research information showing that during the 1996-1997 time frame, sales of tinidazole tablets in the UK totaled approximately 500mg tablets/year and in Australia, approximately 500mg tablets/year.

c) review of foreign labeling

A review of 12 submitted foreign labels indicated consistency in the reporting of neurologic adverse events, (incoordination, convulsions, peripheral neuropathy, vertigo, dizziness, headache, ataxia) gastrointestinal adverse events, (abdominal pain, taste change, diarrhea, anorexia, vomiting and nausea), allergic events and leucopenia. Consistency was also found in the listing of contraindications (organic CNS disease, hypersensitivity, use in 1st trimester of pregnancy, blood dyscrazia, and breastfeeding.)

d) Safety evaluation of the participants in the original bioequivalence study

Among 18 healthy volunteers participating in a bioequivalence study, nausea, headaches and dysgeusia were the most commonly reported adverse events. None were serious.

Labeling

In developing a label for this product, considerable reliance was placed on the existing label for metronidazole which shares many of the chemical and toxicological features of Tinidazole. Specifically, a black box warning for carcinogenicity in mice and rats in the