

metronidazole label was used in the tinidazole label in lieu of such carcinogenicity studies with tinidazole. The large experience with this drug in humans militated against the need for repeating such carcinogenicity studies in animals.

Unlike the pregnancy labeling for metronidazole, tinidazole was designated a category C based on a published study in rats showing fetal lethality at doses that were not toxic to the mothers. A similar study in mice was negative. Tinidazole is contraindicated during the first trimester of pregnancy.

Drug interactions that were characterized for metronidazole have been included in the tinidazole label where such data for tinidazole are unavailable. Some of these interactions ascribed to metronidazole do not yet appear in the existing metronidazole label but will be updated according to today's standards.

Warnings and precautions characteristic of nitroimidazoles that were listed in the metronidazole label have been included in the tinidazole label. These include a warning on the risk of convulsions and peripheral neuropathy and precautions on the use of tinidazole in patients with blood dyscrasia and severe hepatic disease.

Reviews by medical officers

For more detail see independent medical officer reviews for:

1. Trichomoniasis
2. Giardiasis
3. Amebiasis
4. Safety

Phase 4 studies:

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)

Leonard Sacks
Acting medical team leader

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

/s/

Leonard Sacks
5/17/04 03:03:31 PM
MEDICAL OFFICER

Renata Albrecht
5/17/04 05:26:59 PM
MEDICAL OFFICER

Edward Cox
5/17/04 07:10:24 PM
MEDICAL OFFICER

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

(b4)

Chi, Christina H

From: Presind@aol.com

Sent: Thursday, May 06, 2004 5:02 PM) *latest*

To: albrechtr@cder.fda.gov; chic@cder.fda.gov; colangelop@cder.fda.gov; delosreyesg@cder.fda.gov; higginskar@cder.fda.gov; hundleys@cder.fda.gov; krausc@cder.fda.gov; MATECKAD@cder.fda.gov; molenaroe@cder.fda.gov; sacksl@cder.fda.gov; suvarnak@cder.fda.gov; tracyl@cder.fda.gov; sainis@cder.fda.gov; coxe@cder.fda.gov

Cc: JRHead1@aol.com; fmradz@yahoo.com

Subject: 5/6/04-3:00pm tinidazole labeling revision

Hello everyone,

Attached is the revised labeling reflecting our telephone conference on wednesday, 5/5/04 and subsequent telephone conference with Dr. Colangelo on 5/6/04. Also attached are the notes reflecting the non-obvious changes in the labeling. Areas that were changed from the last version are underlined.

Informal feedback would be appreciated so that we may more quickly finalize the labeling.

Sincerely,
john presutti
847-359-7801 (we will be back in our office on friday)

5/7/2004

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



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: April ²⁹~~27~~, 2004

To: John Presutti	From: Christina H. Chi, Ph.D.
Company: Presutti Laboratory 1607 N. Douglas Ave. Arlington Heights, IL 60004	Division of Special Pathogen and Immunologic Drug Products.
Fax number: (847) 398-0198/359-7878 ²⁸⁵¹	Fax number: 301- 827-2326
Phone number: 847-359-7800	Phone number: 301- 827-2127

Subject: FDA's request for additional Chemistry information.

Total no. of pages including cover: 2

Comments: Please review the following request. Please submit your response in writing.

Document to be mailed: YES NO

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Memorandum

TELEPHONE FACSIMILE

Date: April ²⁹ 27, 2004

From: Christina H. Chi, Ph.D., Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

To: John Presutti
Presutti Laboratory
1607 N. Douglas Ave. Arlington Heights, IL 60004

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

Drug: Tindamax (tinidazole) tablets

Subject: FDA's request for additional Chemistry information.

Please provide, as soon as possible, a revised specification for tinidazole drug substance that reflects changes made via the 12-Apr-2004 amendment to the related substances acceptance criteria of the drug product specification and includes a revised acceptance criterion for "any individual unknown impurity (NMT ~~—~~)" as per ICH Q3A recommendations (Impurities in New Drug Substances).

Chi, Christina H

From: Chi, Christina H
Sent: Tuesday, April 27, 2004 12:01 PM
To: 'Presind@aol.com'
Subject: Faxed DSPIDP's labeling
Importance: High
Follow Up Flag: Follow up
Flag Status: Flagged
Mr.. Presutti :

*Attached:
FDA fax of suggested
labeling draft 1. doc (206 KB)*

The attached document is the electronic version of yesterday's official fax. I just noticed that it it supposed to be 20 pages with the fax cover page (instead of 19); sorry. I also put the two notations (! and a flag) on this e-mail as an example. Could you find it near the subject line or "envelope"?

Christina Chi

4/27/2004



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV**

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2004

To: Mr. John Presutti	From: Christina H. Chi, Ph.D.
Company: Presutti Laboratories	Division of Special Pathogen and Immunologic Drug Products (DSPIDP)
Fax number: 847-398-0198	Fax number: 301-827-2326
Phone number: 847-359-7800	Phone number: 301-827-2127
Subject: FDA suggested labeling (with markup) dated 4/26/2004	

Total no. of pages including cover: 19

Comments: The following document is the DSPIDP's proposed labeling of NDAs 21-618, 21-681, and 21-682 for  (or Tindamax?), tinidazole tablets. Please note that the labeling insert is bearing the name of  and the labeling for the carton and the bottle is Tindamax.

Document to be mailed: YES NO

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

Chi, Christina H

From: Presind@aol.com
Sent: Friday, April 16, 2004 9:10 AM
To: chic@cder.fda.gov
Subject: status report

Hi Dr. Chi,

I just faxed a copy of the completed form 3542a. we will send it in formally with the next amendment.

Regarding the _____ DMF revision, it now appears that the document will be at the agency on next tuesday, April 20th. It took a full week to move from _____ after being held up in customs in 2 countries. Sorry for the delay.

john presutti

4/16/2004

Chi, Christina H

From: Presind@aol.com
Sent: Wednesday, April 14, 2004 6:50 PM
To: chic@cder.fda.gov
Subject: tinidazole amebiasis document

Hi Dr. Chi,

FYI, a copy of the letter granting orphan status for amebiasis was in Amendment #1, sent on 9/15/03.

do you need more than this info?

john presutti

Note:

Please see next tab

ISI

4/15/2004

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

A-1b



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 29, 2004

To: John Presutti

From: Christina H. Chi, Ph.D.

Company: Presutti Laboratory
1607 N. Douglas Ave. Arlington
Heights, IL 60004

Division of Special Pathogen and
Immunologic Drug Products.

Fax number: 847-359-7878

Fax number: 301- 827-2326

Phone number: 847-359-7800

Phone number: 301- 827-2127

Subject: FDA's request for additional Chemistry information.

Total no. of pages including cover: 2

Comments: Please review the following request. Please submit your response in writing.

Document to be mailed:

YES

NO

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Memorandum

TELEPHONE FACSIMILE

Date: March 29, 2004

From: Christina H. Chi, Ph.D., Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

To: John Presutti
Presutti Laboratory
1607 N. Douglas Ave. Arlington Heights, IL 60004

NDA: 21-618

Drug: Tinidazole tablets

Subject: FDA's request for additional Chemistry information.

1. Please include an additional identity test in the drug product specification.
2. Please include test and acceptance criteria for microbial limits in tinidazole tablets specification or provide a scientific justification for not proposing a microbial limits test for the drug product.
3. Please provide results of microbial limits testing of the crushed tablets suspension in artificial cherry syrup after storage for 10 days at 25°C/60% RH.
4. Please revise (tighten) the acceptance criteria for related substances in the drug product specification based on available batch release and stability data.
5. Please provide available data on dissolution method development [redacted]
6. Please clarify the chemical name and structure of the impurity [redacted] (validation report; page 7-321).
7. Please revise the stability commitment to include stability testing on the first [redacted] production-scale batches of each of the two tablet's strength.

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

/s/

Christina Chi
3/29/04 03:01:25 PM
CSO

Norman Schmuff
3/30/04 12:39:02 PM
CHEMIST

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

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA#s: 21-618, 21-681 & 21-682 (original)		Efficacy Supplement Type SE-	Supplement Number
Drug: Tindamax (tinidazole) tablets, 250 and 500 mg		Applicant: Presutti Laboratories	
RPM: Christina H. Chi, Ph.D.		HFD- 590	Phone # 301-827-2127
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): None	
❖ Application Classifications:			
<ul style="list-style-type: none"> • Review priority 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 		1	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		Orphan status for amebiasis and giardiasis; New Molecular Entity	
❖ User Fee Goal Dates		May 17, 2004	
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
<ul style="list-style-type: none"> • User Fee 		<input type="checkbox"/> Paid	
<ul style="list-style-type: none"> • User Fee waiver 		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other: first human NDA	
<ul style="list-style-type: none"> • User Fee exception 		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)			
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<ul style="list-style-type: none"> • This application is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 		N/A	
<ul style="list-style-type: none"> • OC clearance for approval 		N/A	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified	
❖ Patent			
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted. 		<input checked="" type="checkbox"/> Verified	
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify type of certifications submitted. 		21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
<ul style="list-style-type: none"> • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). 		<input checked="" type="checkbox"/> Verified	

❖ Exclusivity (approvals only)	
• Exclusivity summary	(To be done)
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	=Regulatory Filing Review 4/15/04
Regulatory Information	
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (x) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	()
• Most recent applicant-proposed labeling	(x) April 27, 2004
• Original applicant-proposed labeling	()
• Labeling reviews (including DDMAC, DMETS, DSRCs) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS consults: 9/9/03; 4/6/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Flagyl tablets
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	()
• Applicant proposed	(x) April 27, 2004
• Reviews	(x) see each discipline's reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	(x) Approval letter May 17, 2004
• Documentation of discussions and/or agreements relating to post-marketing commitments	(x) Presutti's fax of May 17, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Letters and e-mails: 9-29-03 (2), 12-17-03, 3-29-04, 4-26-04, 4-27-04, 4-29-04, 5-10-04, 5-14-04
❖ Memoranda and Telecons	505(b)(2) & history: 3-31-04
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	May 27, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Dep. Office Director: May 17, 2004 Med. Team Leader: May 17, 2004
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i> Trichomoniasis and Metronidazole-Resistant Trichomoniasis Indication Amebiasis Indication Giardiasis Indication	May 17, 2004 May 17, 2004 May 17, 2004
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	May 14, 2004
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	May 17, 2004
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	See clinical reviews
❖ Demographic Worksheet <i>(NME approvals only)</i>	
❖ Statistical review(s) <i>(indicate date for each review)</i>	April 21, 2004
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	May 17, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	March 30, 2004
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	May 13, 2004
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	Requested by sponsor
• Review & FONSI <i>(indicate date of review)</i>	Requested by sponsor
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	Requested by sponsor
• Review of DMF	March 23, 2004
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	(x) March 16, 2004 Acceptable () Withhold recommendation
❖ Methods validation	() Completed N/A () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	April 26, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
CAC/ECAC report	N/A

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 02/21/04 DATE OF DOCUMENT: 01/16/04	DESIRED COMPLETION DATE: 04/1/04	ODS CONSULT #: 04-0110
TO: Renata Albrecht, M.D. Director, Division of Special Pathogen and Immunologic Drug Products HFD-590		
THROUGH: Christine H. Chi, Ph.D. Project Manager HFD-590		
PRODUCT NAME: _____ (Primary name) Tindamax (Alternate name) (Tinidazole Tablets, USP) 250 mg, 500 mg	NDA's SPONSOR: Presutti Laboratories, Inc.	
NDA's #: 21-618, 21-681, 21-682		
SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.		
RECOMMENDATIONS:		
<p>1. DMETS does not recommend the use of the proprietary name, _____. The sponsor has failed to submit persuasive evidence for DMETS to reverse its initial decision on the acceptability of the proprietary name _____. However, DMETS has no objections to the use of the proprietary name Tindamax. This decision is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.</p> <p>2. DDMAC finds the proprietary names _____ and Tindamax acceptable from a promotional perspective.</p>		
Carol Holquist, R.Ph. Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	Jerry Phillips, R.Ph. Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration	

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 6, 2004

NDA #: 21-618, 21-681, 21-682

NAME OF DRUG: _____ (Primary name)
Tindamax (Alternate name)
(Tinidazole Tablets, USP)
250 mg, 500 mg

NDA HOLDER: Presutti Laboratories, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), to reconsider the proposed proprietary name _____ regarding potential name confusion with other proprietary or established names. In a review dated September 9, 2003, (ODS Consult #03-0219), DMETS recommended against the use of the proposed proprietary name, _____ due to the potential orthographic similarities with Trimox and Tenormin. The sponsor disagreed with FDA's opinion on the acceptability of _____ and provided an independent analysis of the name to support its use. Additionally, the sponsor submitted information to support a request for reconsideration of _____ including a point-by-point rebuttal to comments from the DMETS review. Furthermore, the sponsor noted that they agreed with DMETS' decision on the unacceptability of _____ which was another name for consideration in the first review.

In addition, the sponsor submitted an alternative name, Tindamax, for review only if and after DMETS and the Division have concluded that _____ is unacceptable. Labels and labeling were not provided for review and comment at this time.

PRODUCT INFORMATION

_____ Tindamax (tinidazole) is a synthetic antiprotozoal and antibacterial agent indicated for trichomoniasis, giardiasis, and amebiasis. Patients take a single 2 gram dose but may require an extended course of treatment if treating amebiasis

_____ Tindamax will be available as 250 mg and 500 mg tablets.

II. RECONSIDERATION OF _____

In a letter dated, January 16, 2004, the sponsor has requested re-consideration of the proprietary name _____. The sponsor believes the potential for confusion between _____ and Trimox or Tenormin is negligible for the following reasons.

A. Trimox

1. New Information Summary

- a. **Sponsor's Comment:** *The "Trimox" brand of amoxicillin is rarely used by physicians when prescribing amoxicillin.*

DMETS Response: The sponsor noted that the Trimox brand of amoxicillin is rarely used by physicians, and yet their independent study demonstrates that 13% of the pharmacists interviewed recall seeing a Trimox prescription in the last 6 months. Although this number may seem small, it may indicate a higher number when extrapolated to the general U.S. population.

- b. **Sponsor's Comment:** *A 2 gram stat dose of amoxicillin is an uncommon dose (the most common prescription size for _____ for trichomoniasis and giardiasis will be a 2 gram stat dose). If a 2 gram stat dose is written for amoxicillin, it is usually written by a dentist with instructions to take the capsules just prior to the next visit.*

DMETS Response: The sponsor notes that the 2 gram stat dose of amoxicillin is an uncommon dose, however, various medical references list amoxicillin as the drug of choice for bacterial endocarditis prophylaxis in patients undergoing dental procedures, oral or upper respiratory tract surgery, or minor gastrointestinal or genitourinary tract procedures. Therefore, dentists are not the only specialty prescribing a 2 gram stat dose of amoxicillin.

- c. **Sponsor's Comment:** *The probability of a combination of a _____ prescription a) written to resemble Trimox and b) that prescription having other than a 2 gram dose and c) being received by a pharmacist who routinely sees Trimox prescriptions and d) who is not aware of _____ is very remote.*

DMETS Response: The DMETS prescription analysis studies demonstrated that Trimox and _____ can look similar when scripted. The overlapping orthographic characteristics in conjunction with identical dosage regimens (2 grams daily or 1 gram twice daily), increase the potential for a dispensing error to occur. The sponsor's internal analysis studies provide evidence that pharmacists still dispense Trimox. Additionally, the potential for confusion may increase if a practitioner is unfamiliar with _____ (e.g. during launch).

2. Pharmacist Survey Details

- a. **Sponsor's Comment:** *It comes in 250 mg and 500 mg capsule forms. _____ comes in tablet form. Trimox also come in liquid forms of 125 mg/5 mL and 250 mg/5 mL.*

DMETS Response: Post-marketing experience has shown confusion between different dosage forms, regardless of route of administration. This confusion exists, but is not exclusive to, capsules and tablets, which are often confused with one another because the dosage form is not always written in a prescription order.

- b. **Sponsor's Comment:** *The Trimox brand is rarely prescribed (actually written) by physicians....Only 13% of pharmacists had seen a Trimox prescription within the last six months.*

DMETS Response: See comment under New Information Summary (A.1.a.).

- c. **Sponsor's Comment:** *Most amoxicillin prescriptions are written as "amoxicillin" or "amox" with some using the brand name Amoxil or other non-Trimox brands.*

DMETS Response: See comment under New Information Summary (A.1.a.).

- d. **Sponsor's Comment:** *A significant portion of amoxicillin (29%) prescriptions are for liquid. Tinidazole does not come in liquid form.*

DMETS Response: According to the sponsor's study results, 29% of amoxicillin prescriptions are for the liquid form, however, this study result neglects to recognize the fact that 71% of the prescriptions are not in liquid form. Confusion may still exist between different dosage forms, especially if the same dosage route is utilized.

- e. **Sponsor's Comment:** *The most common prescription size for _____ will be the 2 gram stat dose (standard dose for trichomoniasis and giardiasis). This 2 gram stat dose is rarely written for amoxicillin...*

DMETS Response: See comments under New Information Summary (A.1.b.).

- f. **Sponsor's Comment:** *Amoxicillin is rarely prescribed in the hospital since it is not available in injectable form.*

DMETS Response: Amoxicillin is indicated for use in bacterial endocarditis prophylaxis in patients undergoing dental procedures, oral or upper respiratory tract surgery, or minor gastrointestinal or genitourinary tract procedures. As such, it would not be uncommon to see a prescription order for a patient admitted for one of the aforementioned procedures. Oral medications are not exclusive to outpatient use and are often used in the hospital setting. It would not be uncommon to see a prescription for amoxicillin tablets/capsules. Also, DMETS questions the validity and value of this statement since _____ is available only in oral form.

3. Medical Risks of a Mix-up

- a. **Sponsor's Comment:** *This is amoxicillin, a semi-synthetic penicillin derivative, employing capsule presentations as well as liquid forms. In the case of a substitution of Trimox capsules for _____ tablets in error, the worst consequence appears to be failure to treat the trichomonas or giardiasis infection on the first try. The side effects of amoxicillin are generally mild. Oral drugs are very much less likely to produce an allergic reaction than injectable forms, but a rash is possible. In the case for the infection targeted for amoxicillin treatment. This is unlikely to be a*

serious infection because an I.V. or IM anti-infective form would be used for serious cases and there is no I.V. or I.M. of amoxicillin or _____

DMETS Response: A patient inadvertently receiving Trimox instead of _____ is not only of receiving suboptimal therapy to eradicate microorganisms which _____ is specifically indicated for but also may be subject to severe allergic reactions (contraindicated in patients with a known allergy to any penicillin), resulting in a severe adverse event. The same holds true if _____ was inadvertently dispensed instead of Trimox. _____ is contraindicated in patients with a known hypersensitivity to tinidazole or other 5-nitroimidazole derivatives. We consider all drug misadventures to be serious in nature and should be prevented if possible.

- b. **Sponsor's Comment:** *The Agency fax mentions the case of amoxicillin treatment of H. pylori as part of triple therapy as an area where therapeutic failure due to substitution of tinidazole may ensue...We do not believe there to be a therapeutic concern since there are numerous publications showing that replacement of amoxicillin by tinidazole as part of triple therapy is at least effective as when amoxicillin is used.*

DMETS Response:

B. Tenormin

1. New Information Summary

- a. **Sponsor's Comment:** *Most atenolol prescriptions are written as atenolol, not Tenormin.*

DMETS Response: The sponsor notes that the Tenormin brand of atenolol is rarely used by physicians, and yet their independent study demonstrates that 30% of the prescriptions are written as Tenormin. Because this study has a small sample size (100 pharmacists), it does not accurately reflect the magnitude of prescriptions written for Tenormin vs. atenolol. Thirty percent of atenolol prescriptions is still a significant number when extrapolated to the general U.S. population. Any medication error should be prevented if possible.

- b. **Sponsor's Comment:** _____ and Tenormin come in different tablet sizes (250 and 500 mg for _____ vs. 25, 50, and 100 mg for atenolol). Tenormin tablets are small and white. _____ tablets are pink and larger.

DMETS Response: DMETS acknowledges that the differences in the products physical attributes may help prevent a medication error occurrence, especially for patients who are receiving prescription refills. However, if the error is detected at this stage of the prescription order process, the concern about the variance in

product physical appearance is moot. The error would most likely take place in the interpretation stage, when the prescription is first received. Also, despite differences in the tablet sizes, post-marketing experience has shown medication errors occurring as a result of a numerical similarity in strengths (250 mg and 500 mg vs. 25 mg and 50 mg). Moreover, the products share a numerically similar daily dosage (200 mg vs. 2000 mg) and a dosing schedule of once daily, which may increase the likelihood for a dispensing error to occur (see below).

Tenormin 200mg QD x 30 days
_____ 200mg QD x 30 days

- c. **Sponsor's Comment:** Most atenolol prescriptions are written as 50 mg QD x 30 tablets with 5-11 refills. The tablet size, number of tablets, and number of refills will not match a typical acute therapy with _____ (2 gram stat) or even an extended acute therapy (1 gram BID x 14 days).

DMETS Response: Tenormin may have an optimal effect at doses as high as 200 mg daily. Although the majority of patients may receive a 50 mg daily dose, it does not account for the patients who receive doses other than 50 mg daily. Also, prescriptions are often written for quantities sufficient for less than a month's supply, especially in a hospital setting.

- d. **Sponsor's Comment:** Pharmacists routinely match the tablet strength and dosing to the product name to check for errors.

DMETS Response: DMETS agrees that this "checking" takes place in the pharmacy. However, the FDA receives many medication error reports despite this practiced "checking" procedure. Additionally, generic substitutions are often made in the pharmacy without updating their respective computer systems to accurately reflect this change. Moreover, the argument presented above is moot, since the error would most likely take place in the interpretation stage (i.e. the name is mistaken for the other and vice versa), when the prescription is first received. The similarities in dosage strength (200 mg vs. 2000mg), dosage schedule (daily), route of administration (oral), and orthographic characteristics, increase the potential for _____ to be mistaken for Tenormin.

2. Pharmacist Survey Details

- a. **Sponsor's Comment:** Tenormin prescriptions are received as either Tenormin or atenolol (30% written as Tenormin, 70% written as atenolol in retail pharmacies). The few hospital pharmacists contacted indicated similar numbers.

DMETS Response: See comment under New Information Summary (B.1.a.).

- b. **Sponsor's Comment:** Dosing is chronic and prescriptions written for a short term care are rare. None saw a 2 gram stat dose of Tenormin and the most common prescription is for a 50 mg tablet single daily dose for 30-60 tablets with

5-11 refills. _____ prescriptions will generally be for acute dosing of one 2 gram dose with minimal prescriptions written for two weeks of therapy... It is very unlikely that a _____ prescription will be written for 30 tablets... Only 4% of Tenormin/atenolol prescriptions are written for less than one month's worth of pills.

DMETS Response: While there is some validity to the sponsor's comment, prescriptions are often written for quantities sufficient for less than a month's supply, especially in the hospital setting. Because patient's conditions are in flux and often changing, acute therapies are often ordered by prescribers. A Tenormin prescription written for "Tenormin 200 mg x1" could potentially be misinterpreted for _____ and vice versa. See comment under New Information Summary (B.1.b.). Additionally, discontinuation orders written in the hospital setting oftentimes include the proprietary or established name only, and do not include dosage strengths and schedules (ex. D/C Tenormin or _____).

- c. **Sponsor's Comment:** *Pharmacists are taught to scan the product name, the dose, and prescribing information and then re-scan the product name.*

DMETS Response: This method of "checking" is not common practice, especially in the retail setting. Also, if the sponsor is referring to the recent approved barcoding rule, many institutions are in the process of implementing this kind of practice, but are yet to be compliant. In the retail setting, the pharmacist would more likely "scan" the prescription label at the final "checking" stage to review the accuracy of the filled medication with the ordered medication on the prescription.

- d. **Sponsor's Comment:** *If there ever was written confusion over the brand name (_____ vs. Tenormin) the tablet size, tablet strength, dosing, number of tablets, and number of refills are too different to allow a mix-up.*

DMETS Response: See comment under New Information Summary (B.1.b. and B.1.d).

3. Medical Risks of a Mix-up

- a. **Sponsor's Comment:** *This is atenolol, a cardioselective beta-blocker for treating angina, hypertension, and arrhythmia. In general, populations prescribed this drug will be older than those prescribed _____ will primarily be used in younger, healthier patients.*

DMETS Response: Tenormin is indicated in the treatment of hypertension, angina pectoris, and acute myocardial infarction. It would be misleading to assume that this product would primarily be used exclusively in an "older" population, as the aforementioned disease states can be present in any age group. A potential for overlap in patient population exists for Tenormin and _____.

- b. **Sponsor's Comment:** *Short-term administration of atenolol by mistake is not likely to cause significant medical concerns.*

DMETS Response: Adverse effects resulting from an inadvertent administration of atenolol may not always “cause significant medical concerns”, however, the possibility still exists that an adverse event may occur. The predominant symptoms reported following Tenormin overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in Tenormin overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycemia. All drug misadventures are serious in nature and should be prevented if possible.

- c. **Sponsor’s Comment:** *It is highly unlikely that a pharmacist will dispense four 50 mg atenolol tablets for one-time consumption since this is such an unusual dose. This mis-interpretation of the trade name would generate a call to the physician.*

DMETS Response: DMETS agrees that dispensing four 50 mg atenolol tablets may be “unusual”, but in some cases (e.g. titration/cost), prescribers write/call in prescriptions asking for lower strengths, with the intention of adjusting the dose as needed. The Tenormin package insert lists 200 mg as an acceptable dose in certain indications. Therefore, it would not necessarily generate a “call to the physician”, since this dose (Tenormin 200 mg or Tenormin 50 mg – 4 tablets) would fall within an acceptable dosage range.

- d. **Sponsor’s Comment:** *In the event that an acute dose of _____ is dispensed to a first time user of Tenormin, there is little likelihood of serious complications and most likely the patient will question a why only a few tablets have been dispensed for their chronic condition.*

DMETS Comment: See comment under Medical Risks of Mix-up (B.3.b.).

- e. **Sponsor’s Comment:** *It is unlikely that a patient already established on Tenormin therapy would be inadvertently switched to _____ in the case of a pharmacy mix-up given the pharmacy computer systems. However, should it happen, the size, shape, color, and markings of the _____ tablet will be very different from the Tenormin tablet. The patient will detect an inappropriate change.*

DMETS Response: DMETS agrees that some patients are aware of their medication regimen and would recognize changes in their medications. However, not all patients are astute, and many may continue to take the medication undetected. In some instances, patients assume they are receiving a generic version or an alternate generic version of their prescribed medication, and do not question the “change” in drug appearance. All drug misadventures, whether or not a serious outcome results, are serious in nature and should be prevented if possible.

III. RISK ASSESSMENT OF TINDAMAX:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Tindamax to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Tindamax. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified several names that were thought to have the potential for confusion with the name Tindamax. These products are listed in Table 1 (see page 10) along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC finds the proprietary name Tindamax acceptable from a promotional perspective.

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Tindamax	Tinidazole Tablets 250 mg, 500 mg	Trichomoniasis: 2 g to be taken with food. For female patients with documented metronidazole resistant trichomoniasis: 1 g twice daily for 14 days. Giardiasis: 2 g to be taken with food. For patients with metronidazole resistance: 1 g twice daily for seven days. Amebiasis: 2 g daily for 3– 5 days.	
Trimox	Amoxicillin Capsules 250 mg and 500 mg Amoxicillin Suspension 125 mg/5 mL, 250 mg/5 mL	Depending on indication and severity of infection, 250 mg three times daily, 500mg every 12 hours, 875 mg every 12 hours, 500 mg three times daily have been recommended; a single 3 gram dose for treating gonorrhoea. For duodenal ulcer due to H. pylori, amoxicillin 1 g bid is given for 14 days in conjunction with clarithromycin and lansoprazole. For Dual therapy, amoxicillin is given 1 g tid for 14 days with lansoprazole.	LA
Inomax	Nitric Oxide Gas 100 ppm, 800 ppm	For the treatment of respiratory failure in neonates with pulmonary hypertension, the recommended dose is 20 ppm (parts per million). In patients with adult respiratory distress syndrome, concentrations less than 1 ppm have been effective.	LA
Fosamax	Alendronate Sodium Tablets 5 mg, 10 mg, 35 mg, 40 mg, 70 mg	Treatment of osteoporosis in postmenopausal women: One 70 mg tablet once weekly or one 10 mg tablet once daily. Prevention of osteoporosis in postmenopausal women: One 35 mg tablet once weekly or one 5 mg tablet once daily. Treatment of glucocorticoid-induced osteoporosis in men and women: One 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily. Paget's disease of bone in men and women: The recommended treatment regimen is 40 mg once a day for six months.	LA
Tenormin	Atenolol Tablets 25 mg, 50 mg, 100 mg Atenolol Injection 0.5 mg/mL	Hypertension: 50 mg – 100 mg po daily Angina Pectoris: 50 – 200 mg po daily Acute Myocardial Infarction: 5 mg IV over 5 min then 5 mg 10 min later. In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day.	LA
ClindaMax	Clindamycin Gel, 1%	Apply to affected area once of twice daily.	LA/SA
ClindaMax Lotion	Clindamycin Topical Suspension, 1%		
Topamax Topamax Sprinkle Capsules	Topiramate Tablets 25 mg, 100 mg, 200 mg Topiramate Capsules 15 mg, 25 mg	400 mg/day in two divided doses.	LA/SA
*Frequently used, not all-inclusive **LA (look-alike), SA (sound-alike)			

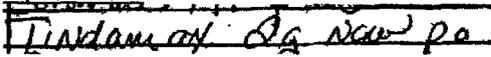
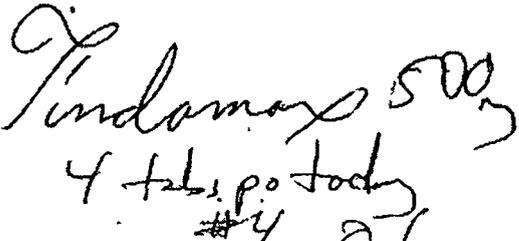
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Tindamax were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Tindamax with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses) for the Tindamax studies. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Tindamax (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Inpatient RX: </p>	<p>Tindamax 500 mg Take 4 tablets now. #4</p>
<p>Outpatient RX: </p>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. Many of the incorrect name interpretations were misspelled/phonetic variations of "Tindamax". See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Tindamax, the primary concerns related to look-alike and sound-alike confusion with Trimox, Inomax, Fosamax, Tenomin, ClindaMax, and Topamax.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Tindamax. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

1. Trimox and Tindamax may look-alike when scripted. Trimox is a penicillin antimicrobial agent available in capsule or suspension form and is typically given twice or thrice daily. Tindamax has eight letters versus Trimox's six and the prefix "Tin-" looks similar to "Tri-" as do the suffixes ("-max" vs. "-mox"). However, the "-da-" in Tindamax helps distinguish itself from Trimox because of its distinct upstroke characteristic, not to mention the additional letter, which elongates the name (see below). Trimox, when used to eradicate *H. pylori*, has a recommended dose of 1 gram twice daily, which is similar to Tindamax's twice daily dosing regimen. Trimox and Tindamax share other similarities, such as dosage form (capsule) and dosage strength (250 mg and 500 mg). Despite product similarities, the orthographic differences mentioned above minimize the risk of confusion between Trimox and Tindamax.

Tindamax Trimox

2. Inomax and Tindamax have potential for look-alike confusion. Inomax is nitric oxide gas indicated for treatment of respiratory failure in neonates with pulmonary hypertension and patients with adult respiratory conditions. Inomax and Tindamax have five overlapping letters (see below). Although the "I-" in Inomax resembles the "T-" in Tindamax and the suffix, "-max" is identical, the middle letters ("-inda-" vs. "-no-") help distinguish one name from the other. However, Inomax and Tindamax have many differences which minimize the potential for a medication error. The proposed names have different dosage forms (gas vs. tablets), indication, dosage schedule, and dosage strength. Also, the two drugs would be stored in two different areas in the pharmacy, minimizing the likelihood for confusion.

**I O M A X
T I N D A M A X**

Inomax Tindamax

3. Fosamax and Tindamax have potential for look-alike confusion. Fosamax is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Fosamax is indicated for prevention and treatment of osteoporosis in postmenopausal women, treatment of glucocorticoid-induced osteoporosis and Paget's disease in men and women. Fosamax and Tindamax have three syllables and share the suffix "-amax". The "Fo-" in Fosamax and the "Ti-" in Tindamax can look-alike when scripted (see page 13), especially if the "F-" is not crossed prominently and the "o-" is narrow in width.

However, the “-d-” in Tindamax helps distinguish itself from Fosamax because of its distinct upstroke characteristic. Fosamax is available as 5 mg, 10 mg, 35 mg, 40 mg, and 70 mg tablets and is usually administered once daily or once weekly. Tindamax can be given once or twice daily. Both Fosamax and Tindamax share a common route of administration (oral), dosage form (tablet), and dosage schedule (once daily). However, both Fosamax and Tindamax would need a specific dosage strength assigned when prescribed because of the multiple strengths that are available for each drug. Clarification with the physician will help minimize this type of misinterpretation. Therefore, DMETS believes that the likelihood for confusion between the two drug products is minimal.

FOS
TIND

Tindamax

Tindamax

Fosamax

Fosamax

4. Tenormin and Tindamax were found to have look-alike similarities. Tenormin is a long-acting, cardioselective beta-adrenergic blocking agent without membrane stabilizing or intrinsic sympathomimetic activities. Both Tenormin and Tindamax have eight letters, and begin and end with similar looking prefixes (“Ten-” vs. “Tin-”) and suffixes (“-min” vs. “-max”). The two names look similar when scripted (see below), however, the “-d-” in Tindamax helps distinguish itself from Tenormin because of its distinct upstroke characteristic. Tenormin is available as a 25 mg, 50 mg, and 100 mg tablet; Tindamax is available as a 250 mg and 500 mg tablet. Although Tenormin’s strength is 1/10 of Tindamax’s, post-marketing experience has shown medication errors occurring as a result of a numerical similarity in strengths (25 mg vs. 250 mg, 50 mg vs. 500 mg). They also share a numerically similar dosing regimen (200 mg once daily vs. 2000 mg once daily). Despite product similarities, the orthographic differences mentioned above minimize the likelihood for a dispensing error to occur, especially in the interpretation stage.

_____ *Tenormin*

5. ClindaMax was identified as a possible sound and look-alike name to _____ ClindaMax (clindamycin) is a lincosamide antimicrobial agent that is a semi-synthetic derivative of lincomycin. ClindaMax is a topical agent used for the treatment of acne vulgaris. It is available in gel and lotion form. If the “Max” in ClindaMax is written in lowercase, ClindaMax and Tindamax have the potential to look-alike (see page 14). ClindaMax has nine letters, whereas Tindamax has eight, however, they share the same letter combination except for the first few letters (“Cl-” vs. “T-”). Likewise, ClindaMax and _____ have the potential to sound-alike because each shares three syllables, rhyming characteristics, and identical middle (“-inda-”) and ending (“-max”) sounds. ClindaMax is usually applied to the affected area twice daily. Tindamax can also be administered twice daily. The two products variance in dosage form (gel/lotion vs. tablet), route of administration (topical vs. oral), and dosage strength (1% vs. 250 mg and 500 mg), minimize the potential for a medication error despite overlapping similarities.

Tindamax

CL [REDACTED]

6. Topamax and Tindamax have the potential for sound-alike and look-alike confusion. Topamax is a sulfamate substituted monosaccharide, antiepileptic drug indicated as adjunctive therapy for the treatment of patients with partial onset seizures, generalized tonic-clonic seizures, or Lennox Gastaut syndrome. Both Topamax and Tindamax sound and look similar since both names begin with the letter "T-" and share the suffix "-amax". The two respective letters ("op" vs. "in") can resemble each other if not precisely scripted (see below), however, the additional letter, "-d-", in Tindamax distinguishes one name from the other. The "-op-" in Topamax phonetically distinguishes itself from the "-in-" in Tindamax. Topamax is available as 25 mg, 100 mg, and 200 mg tablets and also as 15 mg and 25 mg capsules. Tindamax is available as a 250 mg and 500 mg tablet. Post-marketing experience has shown medication errors occurring as a result of a numerical similarity in strength (25 mg vs. 250 mg). Although Topamax and Tindamax share a common route of administration (oral), dosage form (tablet) and dosing schedule (twice daily), the aforementioned sound and look-alike differences minimize the potential for a dispensing mishap.

topamax

tindamax

IV. COMMENTS TO THE SPONSOR

After consideration of the additional material submitted for reconsideration of the acceptability of the proposed name, ~~_____~~, DMETS continues to recommend against its use. Comments from the sponsor are addressed below. However, DMETS has no objections to the use of the proprietary name, Tindamax.

In a letter dated, January 16, 2004, the sponsor has requested a re-consideration of the proprietary name ~~_____~~. The sponsor believes the potential for confusion between ~~_____~~ and Trimox or Tenormin is negligible for the following reasons.

A. Trimox

1. New Information Summary

a. **Sponsor's Comment:** *The "Trimox" brand of amoxicillin is rarely used by physicians when prescribing amoxicillin.*

DMETS Response: The sponsor noted that the Trimox brand of amoxicillin is rarely used by physicians, and yet their independent study demonstrates that 13% of the pharmacists interviewed recall seeing a Trimox prescription in the last 6 months. Although this number may seem small, it may indicate a higher number when extrapolated to the general U.S. population.

b. **Sponsor's Comment:** *A 2 gram stat dose of amoxicillin is an uncommon dose (the most common prescription size for ~~_____~~ for trichomoniasis and giardiasis will be*

a 2 gram stat dose). If a 2 gram stat dose is written for amoxicillin, it is usually written by a dentist with instructions to take the capsules just prior to the next visit.

DMETS Response: The sponsor notes that the 2 gram stat dose of amoxicillin is an uncommon dose, however, various medical references list amoxicillin as the drug of choice for bacterial endocarditis prophylaxis in patients undergoing dental procedures, oral or upper respiratory tract surgery, or minor gastrointestinal or genitourinary tract procedures. Therefore, dentists are not the only specialty prescribing a 2 gram stat dose of amoxicillin.

- c. **Sponsor's Comment:** The probability of a combination of a _____ prescription a) written to resemble Trimox and b) that prescription having other than a 2 gram dose and c) being received by a pharmacist who routinely sees Trimox prescriptions and d) who is not aware of _____ is very remote.

DMETS Response: The DMETS prescription analysis studies demonstrated that Trimox and _____ can look similar when scripted. The overlapping orthographic characteristics in conjunction with identical dosage regimens (2 grams daily or 1 gram twice daily), increase the potential for a dispensing error to occur. The sponsor's internal analysis studies provide evidence that pharmacists still dispense Trimox. Additionally, the potential for confusion may increase if a practitioner is unfamiliar with _____ (e.g. during launch).

2. Pharmacist Survey Details

- a. **Sponsor's Comment:** It comes in 250 mg and 500 mg capsule forms. _____ comes in tablet form. Trimox also come in liquid forms of 125 mg/5 mL and 250 mg/5 mL.

DMETS Response: Post-marketing experience has shown confusion between different dosage forms, regardless of route of administration. This confusion exists, but is not exclusive to, capsules and tablets, which are often confused with one another because the dosage form is not always written in a prescription order.

- b. **Sponsor's Comment:** The Trimox brand is rarely prescribed (actually written) by physicians....Only 13% of pharmacists had seen a Trimox prescription within the last six months.

DMETS Response: See comment under New Information Summary (A.1.a.).

- c. **Sponsor's Comment:** Most amoxicillin prescriptions are written as "amoxicillin" or "amox" with some using the brand name Amoxil or other non-Trimox brands.

DMETS Response: See comment under New Information Summary (A.1.a.).

- d. **Sponsor's Comment:** A significant portion of amoxicillin (29%) prescriptions are for liquid. Tinidazole does not come in liquid form.

DMETS Response: According to the sponsor's study results, 29% of amoxicillin prescriptions are for the liquid form, however, this study result neglects to recognize

the fact that 71% of the prescriptions are not in liquid form. Confusion may still exist between different dosage forms, especially if the same dosage route is utilized.

- e. **Sponsor's Comment:** *The most common prescription size for _____ will be the 2 gram stat dose (standard dose for trichomoniasis and giardiasis). This 2 gram stat dose is rarely written for amoxicillin...*

DMETS Response: See comments under New Information Summary (A.1.b.).

- f. **Sponsor's Comment:** *Amoxicillin is rarely prescribed in the hospital since it is not available in injectable form.*

DMETS Response: Amoxicillin is indicated for use in bacterial endocarditis prophylaxis in patients undergoing dental procedures, oral or upper respiratory tract surgery, or minor gastrointestinal or genitourinary tract procedures. As such, it would not be uncommon to see a prescription order for a patient admitted for one of the aforementioned procedures. Oral medications are not exclusive to outpatient use and are often used in the hospital setting. It would not be uncommon to see a prescription for amoxicillin tablets/capsules. Also, DMETS questions the validity and value of this statement since _____ is available only in oral form.

3. Medical Risks of a Mix-up

- a. **Sponsor's Comment:** *This is amoxicillin, a semi-synthetic penicillin derivative, employing capsule presentations as well as liquid forms. In the case of a substitution of Trimox capsules for _____ tablets in error, the worst consequence appears to be failure to treat the trichomonas or giardiasis infection on the first try. The side effects of amoxicillin are generally mild. Oral drugs are very much less likely to produce an allergic reaction than injectable forms, but a rash is possible. In the case for the infection targeted for amoxicillin treatment. This is unlikely to be a serious infection because an I.V. or IM anti-infective form would be used for serious cases and there is no I.V. or I.M. of amoxicillin or _____*

DMETS Response: A patient inadvertently receiving Trimox instead of _____ is not only of receiving suboptimal therapy to eradicate microorganisms which _____ is specifically indicated for but also may be subject to severe allergic reactions (contraindicated in patients with a known allergy to any penicillin), resulting in a severe adverse event. The same holds true if _____ was inadvertently dispensed instead of Trimox. _____ is contraindicated in patients with a known hypersensitivity to tinidazole or other 5-nitroimidazole derivatives. We consider all drug misadventures to be serious in nature and should be prevented if possible.

- b. **Sponsor's Comment:** *The Agency fax mentions the case of amoxicillin treatment of H. pylori as part of triple therapy as an area where therapeutic failure due to substitution of tinidazole may ensue...We do not believe there to be a therapeutic concern since there are numerous publications showing that replacement of amoxicillin by tinidazole as part of triple therapy is at least effective as when amoxicillin is used.*

DMETS Response: _____

B. Tenormin

1. New Information Summary

- a. **Sponsor's Comment:** *Most atenolol prescriptions are written as atenolol, not Tenormin.*

DMETS Response: The sponsor notes that the Tenormin brand of atenolol is rarely used by physicians, and yet their independent study demonstrates that 30% of the prescriptions are written as Tenormin. Because this study has a small sample size (100 pharmacists), it does not accurately reflect the magnitude of prescriptions written for Tenormin vs. atenolol. Thirty percent of atenolol prescriptions is still a significant number when extrapolated to the general U.S. population. Any medication error should be prevented if possible.

- b. **Sponsor's Comment:** ~~_____~~ and Tenormin come in different tablet sizes (250 and 500 mg for _____ vs. 25, 50, and 100 mg for atenolol). Tenormin tablets are small and white. _____ tablets are pink and larger.

DMETS Response: DMETS acknowledges that the differences in the products physical attributes may help prevent a medication error occurrence, especially for patients who are receiving prescription refills. However, if the error is detected at this stage of the prescription order process, the concern about the variance in product physical appearance is moot. The error would most likely take place in the interpretation stage, when the prescription is first received. Also, despite differences in the tablet sizes, post-marketing experience has shown medication errors occurring as a result of a numerical similarity in strengths (250 mg and 500 mg vs. 25 mg and 50 mg). Moreover, the products share a numerically similar daily dosage (200 mg vs. 2000 mg) and a dosing schedule of once daily, which may increase the likelihood for a dispensing error to occur (see below).

~~_____~~ 200mg QD x 30 days
_____ 200mg QD x 30 days

- c. **Sponsor's Comment:** *Most atenolol prescriptions are written as 50 mg QD x 30 tablets with 5-11 refills. The tablet size, number of tablets, and number of refills will not match a typical acute therapy with _____ (2 gram stat) or even an extended acute therapy (1 gram BID x 14 days).*

DMETS Response: Tenormin may have an optimal effect at doses as high as 200 mg daily. Although the majority of patients may receive a 50 mg daily dose, it does not account for the patients who receive doses other than 50 mg daily. Also, prescriptions are often written for quantities sufficient for less than a month's supply, especially in a hospital setting.

- d. **Sponsor's Comment:** *Pharmacists routinely match the tablet strength and dosing to the product name to check for errors.*

DMETS Response: DMETS agrees that this "checking" takes place in the pharmacy. However, the FDA receives many medication error reports despite this practiced "checking" procedure. Additionally, generic substitutions are often made in the pharmacy without updating their respective computer systems to accurately reflect this change. Moreover, the argument presented above is moot, since the error would most likely take place in the interpretation stage (i.e. the name is mistaken for the other and vice versa), when the prescription is first received. The similarities in dosage strength (200 mg vs. 2000mg), dosage schedule (daily), route of administration (oral), and orthographic characteristics, increase the potential for _____ to be mistaken for Tenormin.

2. Pharmacist Survey Details

- a. **Sponsor's Comment:** *Tenormin prescriptions are received as either Tenormin or atenolol (30% written as Tenormin, 70% written as atenolol in retail pharmacies). The few hospital pharmacists contacted indicated similar numbers.*

DMETS Response: See comment under New Information Summary (B.1.a.).

- d. **Sponsor's Comment:** *Dosing is chronic and prescriptions written for a short term care are rare. None saw a 2 gram stat dose of Tenormin and the most common prescription is for a 50 mg tablet single daily dose for 30-60 tablets with 5-11 refills. _____ prescriptions will generally be for acute dosing of one 2 gram dose with minimal prescriptions written for two weeks of therapy... It is very unlikely that a _____ prescription will be written for 30 tablets... Only 4% of Tenormin/atenolol prescriptions are written for less than one month's worth of pills.*

DMETS Response: While there is some validity to the sponsor's comment, prescriptions are often written for quantities sufficient for less than a month's supply, especially in the hospital setting. Because patient's conditions are in flux and often changing, acute therapies are often ordered by prescribers. A Tenormin prescription written for "Tenormin 200 mg x1" could potentially be misinterpreted for _____" and vice versa. See comment under New Information Summary (B.1.b.). Additionally, discontinuation orders written in the hospital setting oftentimes include the proprietary or established name only, and do not include dosage strengths and schedules (_____).

- e. **Sponsor's Comment:** *Pharmacists are taught to scan the product name, the dose, and prescribing information and then re-scan the product name.*