CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-618

21-681

21-682

CHEMISTRY REVIEW(S)

NDAs 21-618; 21-681; 21-682

TINDAMAX (tinidazole tablets)

Presutti Laboratories, Inc.

Dorota Matecka
Division of Special Pathogen and Immunologic Drug Products, HFD-590

Table of Contents

Chemistry Review Data Sheet

1. NDAs 21-618; 21-681; 21-682

2. REVIEW # 1

3. REVIEW DATE: 11-May-2004

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	16-Jul-2003
BC	23-Mar-2004
IR letter	29-Mar-2004
BC	12-Apr-2004
BC	6-May-2004 (received by fax)

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Original	16-Jul-2003
BC	23-Mar-2004
BC	12-Apr-2004
BC	6-May-2004 (received by fax)

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Presutti Laboratories, Inc.
Address:	1607 N. Douglas Ave.
Representative:	John E. Presutti, President
Telephone:	847-359-7800

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TINDAMAX
b) Non-Proprietary Name (USAN): tinidazole tablets
c) Code Name/#: N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: antiprotozoal

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 250 mg and 500 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

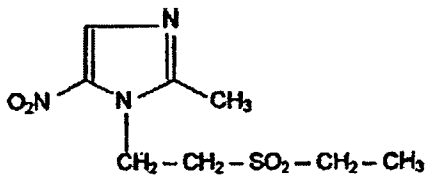
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[2-(ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole; MW = 247.27; $C_8H_{13}N_3O_4S$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Tinidazole	1	Adequate	10-May-2004	
	IV			1	Adequate	28-Mar-2004	
	III			3 and 4	Adequate (1996)	N/A	
	III			3 and 4	Adequate (1999)	N/A	
	III			3	Adequate (1999)	N/A	
	III			3	Adequate (1999)	N/A	
	III			3	Adequate (2000)	N/A	
	III			3	Adequate (2004)	N/A	
	III			3	Adequate (2003)	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

N/A

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	1-Apr-2004	Shrinette Ferguson
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
DMETS	Acceptable	26-Apr-2004	Jinhee L. Jahng, Pharm.D.
EA	Categorical exclusion	N/A	N/A
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-618

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

TINDAMAX (tinidazole tablets) have been developed as immediate release oral tablets in two strengths: 500-mg and 250-mg.

500-mg tablets are pink, caplet shaped, film-coated, scored tablets with P L debossed on one side and 500 on the other.

250-mg tablets are pink, round, film-coated, scored tablets with P L debossed on one side and 250 on the other.

TINDAMAX (tinidazole tablets) contain 500 mg or 250 mg of tinidazole, and the inactive ingredients include croscarmellose sodium, FD&C Red 40 lake, FD&C Yellow 6 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized corn starch, titanium dioxide, and triacetin.

Tinidazole tablets are quite stable at both, room temperature and accelerated conditions. The stability data submitted for the drug product in the original submission and the amendment dated 23-Mar-2004 support the proposed by the applicant expiration dating of 24 months.

The drug substance, tinidazole, is a synthetic antiprotozoal agent, which, similarly to metronidazole, is a derivative of 2-methyl-5-ntroimidazole.

Tinidazole is considered a new chemical entity (NCE). Although there is a USP monograph for tinidazole drug substance, it has not been yet marketed in the USA. However, tinidazole is available in a number of products outside of the USA.

Tinidazole drug substance for this NDA is manufactured by [redacted]. For the majority of chemistry, manufacturing and controls information regarding tinidazole, the reference is made to DMF Type [redacted] held by the manufacturer. The DMF was reviewed with reference to this NDA and several deficiencies were identified via the review # 1 (dated 2-Feb-2004). These deficiencies were subsequently addressed by the DMF holder and the DMF was found acceptable via review # 2 dated 10-May-2004.

Tinidazole drug substance is a white to pale yellow crystalline powder with only one [redacted] identified and manufactured by [redacted]

There are two impurities that have been specified for tinidazole, both in its USP monograph and the drug substance specification. These are: impurity [redacted] a starting material; and impurity [redacted] a tinidazole isomer. However, tinidazole drug substance is quite stable at both room temperature and accelerated conditions, and very little degradation is observed on storage even under accelerated conditions. Under prolonged exposure to [redacted] but there is no significant chemical degradation detected. It should be noted that the drug substance specification for this NDA includes a HPLC procedure for the assay and the detection of impurities, whereas the USP monograph utilizes the TLC procedure for that purpose.

The stability information provided for tinidazole drug substance in DMF [redacted] supports its proposed retest date o[redacted]

B. Description of How the Drug Product is Intended to be Used

TINDAMAX (tinidazole) tablets (500-mg and 250-mg) are indicated for the treatment of trichomoniasis (NDA 21-1618), giardiasis (NDA 21-681) and amebiasis (NDA 21-682). The initial three NDAs reflecting these different indications (for the administrative purpose) will eventually become one NDA (NDA 21-618).

The 250-mg tablets are packaged in HDPE bottles with child-resistant closures in the following configurations: [redacted]

The 500-mg tablets are packaged in HDPE bottles with child-resistant closures in the following configurations: [redacted]

Both, 250-mg tablets packaged in [redacted] and 500-mg tablets packaged in [redacted] are professional samples and not for sale.

The recommended expiration dating for tinidazole tablets is 24 months. The storage conditions statement recommends the following storage : "Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP]. Protect contents from light."

The labeling allows for using an oral suspension (of crushed tablets in the artificial cherry Humco® syrup) for those unable to swallow tablets (including the pediatric population). The procedure for extemporaneous compounding of the oral suspension that was used in the

pharmacokinetics study of tinidazole tablets is provided in the labeling. The labeling states that the suspension is stable for 7 days and should be shaken well before each administration.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of tinidazole tablets. During the review a number of issues, including the following were resolved.

The microbial limits testing of the suspension of crushed tinidazole tablets in the artificial cherry syrup (Humco®) stored for [redacted] days at room temperature was recommended to and conducted by the applicant to assure the microbiological stability of the suspension.

The specification for the drug product, specifically the acceptance criteria for impurities, was revised to include the sum of impurities [redacted] (as NMT [redacted]) and total unknown impurities (as NMT [redacted]). In addition, the second identity test and microbial limits test was added to the drug product specification.

The specification for the tinidazole drug substance, specifically the acceptance criteria for impurities were also revised to include the sum of impurities [redacted] (as NMT [redacted], total unknown impurities (as NMT [redacted]) and tightened acceptance criterion for any individual unknown impurity (from NMT [redacted] to NMT [redacted]).

The manufacturing facilities were found acceptable on 1-Apr-2004 (copy of the acceptable EER is attached in the end of this review).

The trade name "TINDAMAX" was found acceptable by DMETS and by the Division HFD-590. The established name was revised from the proposed "tinidazole" to "tinidazole tablets".

Several changes in the container labels were recommended to the applicant.

III. Administrative

A. Reviewer's Signature

DFS (electronic)

B. Endorsement Block

Chemist/DMatecka/
ChemistryTeamLeader/NSchmuff/
ProjectManager/CChi/

C. CC Block

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

(b4)

A-4

EER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21618/000
Org Code : 590
Priority : 1S

Sponsor: PRESUTTI LABS
1607 NORTH DOUGLAS AVE
ARLINGTON HEIGHTS, IL 60004

Stamp Date : 17-JUL-2003
PDUFA Date : 17-MAY-2004
Action Goal :
District Goal: 18-MAR-2004

Brand Name : [redacted] (TINIDAZOLE)
250MG/500MG TABLETS
Estab. Name
Generic Name: TINIDAZOLE
Dosage Form: (TABLET)
Strength : 250 MG, 500 MG

FDA Contacts:	C. CHI	Project Manager (HFD-590)	301-827-2166
	D. MATECKA	Review Chemist (HFD-590)	301-827-2398
	N. SCHMUFF	Team Leader (HFD-590)	301-827-2425

Overall Recommendation: ACCEPTABLE on 01-APR-2004by S. FERGUSON(HFD-322) 301-827-9009

Establishment : CFN : 1050658 FEI : 1050658
MIKART INC
MARIETTA BLVD NW/CHATTAHOOCHEE AVE
ATLANTA, GA 30318

CMF NO: ADR:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TCM CAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-APR-04
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Establishment : [redacted] FEI : [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

[redacted]

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-MAR-04		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

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

/s/

Dorota Matecka
5/12/04 07:48:55 PM
CHEMIST

Norman Schmuff
5/13/04 06:04:59 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21618/000	Action Goal:	
Stamp:	17-JUL-2003	District Goal:	18-MAR-2004
Regulatory Due:	17-MAY-2004	Brand Name:	[redacted] (TINIDAZOLE)
Applicant:	PRESUTTI LABS	Estab. Name:	250MG/500MG TABLETS
	1607 NORTH DOUGLAS AVE	Generic Name:	TINIDAZOLE
	ARLINGTON HEIGHTS, IL 60004		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	590	Strength:	250 MG, 500 MG

Application Comment: THIS IS NME (DRUG SUBSTANCE TINIDAZOLE IS MANUFACTURED BY [redacted]. THE DRUG PRODUCT ARE PINK FILMED-COATED TABLETS WITH DEBOSSED MARKINGS.
I WOULD BE INTERESTED IN PARTICIPATING IN THE INSPECTION OF DS FACILITY (IF SUCH INSPECTION IS GOING TO TAKE PLACE) [redacted] by D. MATECKA (HFD-590) 301-827-2398)

FDA Contacts:				
	C. CHI	(HFD-590)	301-827-2166	, Project Manager
	D. MATECKA	(HFD-590)	301-827-2398	, Review Chemist
	N. SCHMUFF	(HFD-590)	301-827-2425	, Team Leader

Overall Recommendation: ----------

Establishment: CFN 1050658 FEI 1050658
MIKART INC
MARIETTA BLVD NW/CHATTAHOOCHEE AVE
ATLANTA, GA 30318

DMF No: AADA:

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TCM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUL-2003				MATECKAD
S' TTED TO DO	30-JUL-2003	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	25-SEP-2003	PS			LANDREWS
INSPECTION SCHEDULED	26-SEP-2003		07-APR-2004		LANDREW1@OR

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: 10350 AADA:

Responsibilities. [redacted]

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUL-2003				MATECKAD
SUBMITTED TO DO	30-JUL-2003	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	04-AUG-2003	PS			DAMBROGIOJ
DO RECOMMENDATION	08-MAR-2004			WITHHOLD	ADAMSS
				FIRM NOT READY	

BASED ON EMAIL FROM [redacted] STATING THAT COMPANY NOT READY AT TIMES PROPOSED BY AGENCY DUE TO HOLIDAY AND US CUSTOMERS THAT PLAN TO FILE ANDA'S AS WELL. COMPANY WILL CONTACT AGENCY WHEN READY FOR INSPECTION.

OC RECOMMENDATION	08-MAR-2004			WITHHOLD	ADAMSS
				FIRM NOT READY	

SEE DO RECOMMENDATION

:COMMENDATION	16-MAR-2004			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	

BASED ON REVIEW OF GMP HISTORY OF FIRM. POST APPROVAL INSPECTION WILL OCCUR FOR THIS FIRM. LAST INSPECTION IN 1999.

OC RECOMMENDATION	16-MAR-2004			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	