CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

CHEMISTRY REVIEW(S)

11 Page(s) Withheld

NDA 21-385

Sertaconazole Nitrate Cream, 2%

Mylan Pharmaceuticals, Inc.

J. S. Hathaway, Ph. D.

Division of Dermatologic and Dental Drug Products

HFD-540

Review #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-385

2. REVIEW #: 2

3. REVIEW DATE: 25-NOV-2003

4. REVIEWER: J. S. Hathaway, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original N-000	12-NOV-2002
Amendment N-000(BZ)	12-NOV-2002
Correspondence N-000(C)	24-APR-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-000(AZ)	09-OCT-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals, Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	Frank R. Sisto, V.P., Regulatory Affairs
Telephone:	(304) 599-2595

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ERTACZO

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

- Chem. Type: 1
- **Submission Priority**: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __X__Rx _____OTC

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

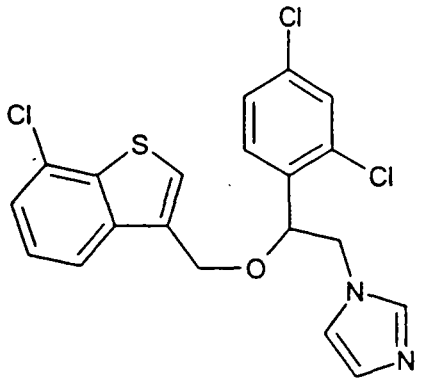
_____SPOTS product – Form Completed

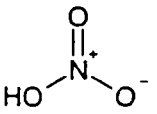
__X__Not a SPOTS product

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

Chemical Name: (±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[b]thien-3-yl) methoxy]phenethyl]imidazole nitrate
Molecular Formula: $C_{20}H_{15}Cl_3N_2OS \cdot HNO_3$

Molecular Weight: 500.8 (as nitrate salt)
—— (as free base)





17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]		3	Current	01-JUL-2002	Adequate
[redacted]	III	[redacted]		3	Current	27-JUN-2002	Adequate
[redacted]	IV	[redacted]		3	Current	01-JUL-2002	Adequate
[redacted]	IV	[redacted]		3	Current	01-JUL-2002	Adequate
[redacted]	II	[redacted]		1	Current	25-NOV-2003	Adequate

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	50,726	Sertaconazole nitrate cream

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	05-NOV-2003	J. D'Ambrogio (HFD-324)
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	Ertaczo acceptable	30-JUN-2002	C. Hoppes (HFD-420)
Methods Validation	Pending		
EA	Categorical Exclusion Acceptable		J. Hathaway (HFD-540)
Microbiology	Acceptable	15-FEB-2002	N. Sweeney (HFD-805)
ODS/DMETS	Pending		sent 11/12/03
DDMAC	Acceptable	18-NOV-2003	M. Brony (HFD-42)

The Chemistry Review for NDA 21-385

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

For the chemistry, manufacturing and controls of this application, the recommendation of this reviewer is for an APPROVAL action.

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

None.

II. Summary of Chemistry Assessments

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

(1) Drug Substance

Sertaconazole nitrate is an active pharmaceutical ingredient under review for use in the USA, and used in a number of drug product formulations marketed outside the USA. Sertaconazole nitrate is an organic salt having a single chiral center, and is manufactured as the racemic mixture via a — synthetic process.

— impurities have been identified and are controlled by the drug substance specification:

— Impurities are specified to be less than — (w/w) of the active, and were observed at lower levels in the analyses of production lots of the drug substance.

(2) Drug Product

Ertaczo™ (sertaconazole) Cream, [redacted] is a dispersion of the solid active ingredient in an oil-in-water cream base. The cream contains 17.5mg of sertaconazole per gram (as sertaconazole nitrate, 20mg), and its inactive formula consists of the compendial ingredients light mineral oil, sorbic acid, methylparaben, purified water, and the non-compendial ingredients ethylene glycol and polyethylene glycol palmitostearates, polyoxyethylened and glycolized saturated glycerides, and glyceryl isostearate.

The manufacturing process used to produce the cream base is a [redacted]

[redacted] The product is packaged in blind-end aluminum tubes lined with [redacted] capped with a [redacted] cap with a piercing tip. The proposed package sizes are a 2g sample, and 15g and 30g sizes for commercial distribution.

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

Ertaczo™ (sertaconazole) Cream, [redacted] is indicated for [redacted] (see labeling). Dosing frequency and duration is twice daily for four weeks. This drug product is a cream formulation of a new molecular entity, sertaconazole nitrate, which is structurally related to other approved imidazole antifungal compounds.

The recommended expiration date for Ertaczo™ (sertaconazole) Cream, [redacted] is 24 months. Labeled storage conditions for the cream in the collapsible aluminum tube are recommended to be 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The proposed formulation is based on a drug product formulation currently marketed in a number of countries in Europe and South America. The applicant provided the results of an in-vitro release rate study performed according to the protocol described in SUPAC-SS.

The recommended expiration dating period for Ertaczo™ (sertaconazole) Cream, [redacted] is 24 months, based on the reviewed data. The labeled storage condition for the cream in the collapsible aluminum tube is "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]". Alternatively, "Store at 25°C (77°F)" can be substituted with [redacted] or, if space is limited, the [redacted] can be omitted.

The submission also included an adequate master batch manufacturing procedure, a finished drug product specification, carton, container, and package insert labeling.

Inspections of the manufacturing facilities were judged to be acceptable by the Office of Compliance on 05-NOV-2003.

III. Administrative

A. Reviewer's Signature

(see attached electronic signature page)

B. Endorsement Block

Chemist/JSHathaway/Date:
ChemistryTeamLeader/WHDeCamp/
ProjectManager/FHCross/

C. CC Block

15 Page(s) Withheld

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

/s/

Steve Hathaway
11/25/03 03:16:19 PM
CHEMIST
AP recommended; MV pending

Wilson H. DeCamp
11/25/03 03:27:55 PM
CHEMIST
concur with review; approval action recommended

NDA 21-385

Sertaconazole Nitrate Cream, 2%

Mylan Pharmaceuticals, Inc.

J. S. Hathaway, Ph. D.

Division of Dermatologic and Dental Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-385

2. REVIEW #: 1

3. REVIEW DATE: 03-JUL-2002

4. REVIEWER: J. S. Hathaway, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-SEP-2002
Amendment	12-NOV-2002
Correspondence	24-APR-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals, Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	Frank R. Sisto, V.P., Regulatory Affairs
Telephone:	(304) 599-2595

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 1
- **Submission Priority**: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __X__Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note28]:

_____SPOTS product – Form Completed

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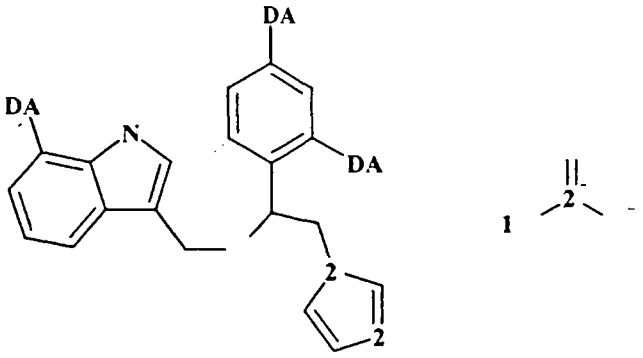
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[b]thien-3-yl) methoxy]phenethyl]imidazole nitrate
Molecular Formula: $C_{20}H_{15}Cl_3N_2OS \cdot HNO_3$

Molecular Weight: 500.8



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[redacted]	IV	[redacted]		1	Current	01-JUL-2002	Adequate
[redacted]	IV	[redacted]		1	Current	01-JUL-2002	Adequate
[redacted]	II	[redacted]		1	Current	01-JUL-2002	Adequate

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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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	50,726	Sertaconazole nitrate cream

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-MAY-2002	S. Adams (HFD-324)
Pharm/Tox	N/A		
Biopharm	N/A		
LNC/ODS	Ertaczo acceptable	30-JUN-2002	C. Hoppes (HFD-420)
Methods Validation	Pending		
OPDRA	N/A		
EA	Categorical Exclusion Acceptable		J. Hathaway (HFD-540)
Microbiology	Acceptable	15-FEB-2002	N. Sweeney (HFD-805)

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-385

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

For the chemistry, manufacturing and controls of this application, the recommendation of this reviewer is for an APPROVABLE action.

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

None.

II. Summary of Chemistry Assessments

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

(1) Drug Substance

Sertaconazole nitrate is an active pharmaceutical ingredient under review for use in the USA, and used in a number of drug product formulations marketed outside the USA. Sertaconazole nitrate is an organic salt having a single chiral center, and is manufactured as the racemic mixture via a [redacted] synthetic process.

[redacted]

[redacted] impurities have been identified and are controlled by the drug substance specification: [redacted]

[redacted] impurities are specified to be less than [redacted] (w/w) of the active, and are generally less than that in the analyses of production lots of the drug substance.

(2) Drug Product

Sertaconazole nitrate cream, 2%, is a dispersion of the solid active ingredient in an oil-in-water cream base. The cream contains 20mg of sertaconazole nitrate per gram, and its inactive formula consists of the compendial ingredients [redacted] light mineral oil NF, sorbic acid NF, methylparaben NF, purified water NF, and the non-compendial ingredients ethylene glycol and polyethylene glycol palmitostearates, polyoxyethylened and glycolized saturated glycerides, and glyceryl isostearate.

The manufacturing process used to produce the cream base is a [redacted]

The product is packaged in blind-end aluminum tubes [redacted] capped with a [redacted] cap with a piercing tip. The proposed package sizes are a 2g sample, and 15g and 30g sizes for commercial distribution. A twenty-four month expiration dating period was proposed, and is acceptable.

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

Sertaconazole nitrate cream, 2%, is indicated for the treatment of interdigital tinea pedis caused by dermatophytes. This drug product is a cream formulation of a new molecular entity, sertaconazole nitrate, which is structurally related to other approved imidazole antifungal compounds.

The recommended expiration date for Sertaconazole Nitrate Cream, 2%, is 24 months. Labeled storage conditions for the cream in the collapsible aluminum tube are recommended to be [redacted]25°C [redacted]77°F) with excursions permitted to 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The proposed formulation is based on a drug product formulation currently marketed in a number of countries in Europe and South America. Different formulations were presented in the IND and NDA. The formulation studied under the IND was different from that proposed for US marketing, in that it did not contain the ingredient [redacted] This ingredient, [redacted]

was added late in development in order to [redacted], and the formulation containing [redacted] was the only formulation proposed for marketing and documented in the NDA. This ingredient was not present in the formulation studied in the pivotal clinical trials, safety trials or preclinical studies.

The applicant, applying to a pre-approval situation the guidance recommendations of the SUPAC-SS document for post-approval changes, provided an in-vitro release comparison study using the protocol described in to support the claim that the addition of [redacted] would have no impact on safety, efficacy or quality. Note that a change of this type, submitted for an approved drug product, would be classified as a Level 3 change, and would require submission of chemistry, in-vitro release and in-vivo bioequivalence documentation.

The applicant did not perform in-vivo bioequivalence studies, but did provide the results of an in-vitro release rate study performed according to the protocol described in SUPAC-SS. In-vitro release rates for the two formulations of the drug product were compared for lots manufactured at the DPT site as well as from the original manufacturing site at [redacted] and were found to be consistent with the recommendations in the SUPAC-SS guidance regarding in-vitro release testing.

A teleconference was conducted on 30-MAY-2002 between FDA and the applicant to discuss concerns regarding the incorporation of [redacted] into the formulation of the drug product. FDA's concerns, arising from the fact that the formulation proposed in the NDA has not been studied clinically, were outlined for the applicant and alternative proposals were discussed.

From this discussion, the applicant appears to have two options regarding the different formulations. The contents of the NDA's CMC section support the proposed commercial formulation containing [redacted]. However, this formulation is not supported by clinical studies to support efficacy or safety. Alternatively, the applicant could propose the formulation without [redacted] for marketing, and could amend the NDA to provide adequate CMC information to support the [redacted] formulation. The specific data necessary for the consideration of the [redacted] formulation are outlined below.

The following deficiencies should be communicated to the applicant with regard to the [redacted] product:

[redacted]

1 Page(s) Withheld

The recommended expiration dating period for Sertaconazole Nitrate Cream, 2%, is 24 months, based on the currently available data. The proposed labeled storage condition for the cream in the collapsible aluminum tube is not acceptable since there are no full shelf-life data at [redacted] to support long-term storage at this temperature. It is recommended that the labeled storage condition be changed to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]". Alternatively, "Store at 25°C (77°F)" can be substituted with [redacted] or, if space is limited, the [redacted] can be omitted.

If the applicant should choose to amend the CMC information in the NDA to support the [redacted] free formulation of Sertaconazole Nitrate Cream, the following additional information and data would be required to allow for review of this version of the drug product formulation:

A. a revised master batch manufacturing procedure, deleting the [redacted] from the formulation;

B. a revised finished drug product specification which omits the [redacted]. The recommended change to the specification for Related Compounds, noted in item 2. above, would also apply to the formulation without [redacted]

C. revisions to the carton, container, and package insert labeling to remove the reference to [redacted] in the list of ingredients. All other recommended changes noted in item 3. above would also apply to the formulation without [redacted]

D. revised qualitative and quantitative statements of composition;

E. a revision to indicate that the supporting stability data submitted in the NDA would be considered as the primary data, and the data derived from [redacted] containing lots would be considered supporting lots.

III. Administrative

A. Reviewer's Signature

(see attached electronic signature page)

B. Endorsement Block

Chemist/JSHathaway/Date: July 24, 2002
ChemistryTeamLeader/WHDeCamp/
ProjectManager/FHCross/

C. CC Block

37 Page(s) Withheld

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

/s/

Steve Hathaway
7/24/02 12:46:33 PM
CHEMIST
"AE" recommended
Absolutely the final version for your concurrence

Wilson H. DeCamp
7/24/02 12:55:59 PM
CHEMIST
concur with review; APPROVABLE letter may be issued