

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-743

CHEMISTRY REVIEW(S)

SEP 17 1997

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-743 CHEM.REVIEW #: 03 REVIEW DATE: 03-SEPT-97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENT/NC	26-AUG-97	27-AUG-97	
AMENDMENT/BL	02-SEPT-97	03-SEPT-97	

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

<u>Proprietary:</u>	Noritrate®
<u>Nonproprietary/USAN:</u>	metronidazole
<u>Code Names/ #'s:</u>	PF004910 and 546201
<u>Chemical Type/</u>	
<u>Therapeutic Class:</u>	3 S

PHARMACOLOGICAL CATEGORY/INDICATION: Topical treatment of rosacea including inflammatory papules, pustules, and erythema

<u>DOSAGE FORM:</u>	Cream
<u>STRENGTHS:</u>	1%
<u>ROUTE OF ADMINISTRATION:</u>	Topical
<u>DISPENSED:</u>	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: 171.16

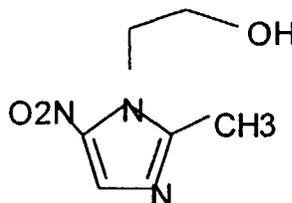
2-methyl-5-nitroimidazole-1-ethanol

C₆H₉N₃O₃

CAS#: 443-48-1

SUPPORTING DOCUMENTS:

DMF



DMF

DMF

CONSULTS:

EA Consult requested, reviewed and sent back. The FONSI was signed on 2/24/97.

Labeling and Nomenclature Consult requested and found acceptable on 2/5/97. It was noted that a look-alike/sound alike conflict was stated by the Labeling and Nomenclature Committee, Noritate: Norlutate.

EER consult requested 12/13/96, a recommendation of acceptable was received on August 6, 1997.

REMARKS/COMMENTS:

This amendment is in reference to the August 21, 1997 fax from Olga Cintron which contained a request from the chemistry reviewer for a post-approval commitment to evaluate globule size. Reference is also made to the August 22, 1997 telephone conversation with Olga Cintron and Janet Higgins and the August 26, 1997 telephone conversation with Dr. Peter Cooney, Microbiology Supervisor regarding expiration dating.

Dermik has committed to develop and validate a method to evaluate globule size. The first five stability batches packaged in 30 g tubes will be tested for globule size both at release and as a part of stability testing. The results of these measurements will be submitted in the next NDA annual report, and, if appropriate, a supplemental application will be submitted to propose a regulatory specification and method.

It should also be noted that during our August 22, 1997 telephone conversation with Dermik. We informed Dermik that only a 12 month expiry dating period would be permitted per the microbiologist. Dermik was confused by this statement since other products with a similar microbial profile were

permitted a longer expiry dating period in the past. This resulted with Dermik contacting Dr. Peter Conney.

On August 26, 1997, Dr. Peter Cooney sent a e-mail to me clarifying the wording in Neal Sweeney's Microbiologist's Review #3. He stated that, "there may have been some confusion due to the specific wording in the last sentence of Neal's List of Deficiencies and Comments. This sentence states that

Therefore, Dermik states that a report containing stability data up to 12 months at room temperature on June 20, 1997 was submitted and based upon that data, as well as the supportive stability data provided in the original NDA, Dermik proposed a 24 month expiration date under room temperature storage. Dermik will continue to conduct microbiological testing under room temperature conditions as indicated in the stability protocol submitted in the original NDA and the revised stability protocol in the amendment dated July 21, 1997. All results will be submitted to the NDA annual report. Thus, it is the recommendation of the chemistry, microbiology, and statistical staff that this product be approved for the proposed 24 month expiration dating period under room temperature storage conditions.

In the amendment dated September 2, 1997, the applicant has made all the necessary labeling changes on the carton and tube labels.

NDA 20-743
Noritate (metronidazole cream), 1%
Dermik Laboratories, Inc.

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CONCLUSIONS & RECOMMENDATIONS:

It is my recommendation that the Division of Dermatologic and Dental Drug Products issue an approval action from a chemistry point of view.

It should be noted that the agency is aware of the post-approval commitments that the applicant has stated in the amendment dated September 2, 1997.

Janet G. Higgins 9/3/97

Janet G. Higgins
Review Chemist

cc: Orig. NDA 20-743
HFD-540/Division File
HFD-540/Higgins
HFD-540/Ko
HFD-540/Alam
HFD-540/Cintron
HFD-540/Wilkin
R/D Init by: Decamp

WD 9/17/97

filename: N20743.r03

FW 9/25/97

AUG 29 1997

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-743 CHEM.REVIEW #: 02 REVIEW DATE: 19-AUG-97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENT/BC	20-JUN-97	23-JUN-97	30-JUN-97
AMENDMENT/BL	01-JUL-97	03-JUL-97	15-JUL-97
Amendment/BC	21-JUL-97	22-JUL-97	23-JUL-97
Amendment/BC	05-AUG-97	06-AUG-97	12-AUG-97

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

Proprietary: Noritate®
Nonproprietary/USAN: metronidazole
Code Names/ #'s: PF004910 and 546201
Chemical Type/
Therapeutic Class: 3 S

PHARMACOLOGICAL CATEGORY/INDICATION: Topical treatment of rosacea including inflammatory papules, pustules, and erythema

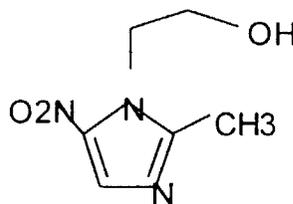
DOSAGE FORM: Cream
STRENGTHS: 1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: xx Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: 171.16

2-methyl-5-nitroimidazole-1-ethanol

C₆H₉N₃O₃

CAS#: 443-48-1



SUPPORTING DOCUMENTS:

DMF

NDA 20-743
Noritate (metronidazole cream), 1%
Dermik Laboratories, Inc.

Page 2

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DMF

CONSULTS:

EA Consult requested, reviewed and sent back. The FONSI was signed on 2/24/97.

Labeling and Nomenclature Consult requested and found acceptable on 2/5/97. It was noted that a look-alike/sound alike conflict was stated by the Labeling and Nomenclature Committee, Noritate: Norlutate.

EER consult requested 12/13/96, sent to the Office of Compliance; consult received, currently still pending evaluation of CGMPs.

REMARKS/COMMENTS:

The amendment dated July 1, 1997 is a copy of the revised package insert. This package insert was reviewed and revised at a team labeling meeting on July 9, 1997. All necessary modifications were made to the label and the team agreed on the revisions to request to the applicant. The amendment dated June 20, 1997 includes the following updates to the CMC section of this NDA:

1. The UV-VIS Absorbance Spectrum Scan for Noritate
2. Revised Manufacturing Master Document
3. Revised Test Method for Determination of Particle Size of Metronidazole
4. 12-month Stability Report

The amendment dated July 21, 1997 addresses the information request letter dated June 20, 1997 which was sent to the applicant so that the chemistry review could be completed. The amendment dated August 5, 1997 was submitted as a result of July 31, 1997 and August 1, 1997 telephone conversations. This submission consists of clarifications of the chemistry, manufacturing and controls information and methods validation information included in the July 21, 1997 submission. In addition, revised mock-up copies of the tube and carton labels are included.

Noritrate (metronidazole cream), 1%
Dermik Laboratories, Inc.

CONCLUSIONS & RECOMMENDATIONS:

It is my recommendation that the Division of Dermatologic and Dental Drug Products issue an approval action from a chemistry point of view.

A post approval commitment regarding the globule size testing is requested along with some minor modifications of the carton and tube label. It should also be noted that only a 12 month expiration date will be considered. ✓
✓

Janet A. Higgins 8/20/97

Janet G. Higgins
Review Chemist

cc: Orig. NDA 20-743
HFD-540/Division File
HFD-540/Higgins
HFD-540/Ko
HFD-540/Alam
HFD-540/Cintron
HFD-540/Wilkin
R/D Init by: Decamp

ws 8/29/97

filename: N20743.r02

929197

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

MAY 13 1997

NDA #: 20-743 CHEM.REVIEW #: 01, REVIEW DATE: 09-MAY-97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL/	30-SEPT-96	04-OCT-96	26-NOV-96
AMENDMENT/BC	14-NOV-96	15-NOV-96	26-NOV-96
Amendment/BC	19-DEC-96	20-DEC-96	17-JAN-97

NAME & ADDRESS OF APPLICANT: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

DRUG PRODUCT NAME

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MOL.WT: 171.16

2-methyl-5-nitroimidazole-1-ethanol

C₆H₉N₃O₃

CAS#: 443-48-1

Refer to the current Merck Index for the chemical structure
of this compound.

SUPPORTING DOCUMENTS:

DMF

NDA 20-743
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Dermik Laboratories, Inc.

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EER consult requested 12/13/96, sent to the Office of Compliance; consult received, currently still pending evaluation of CGMPs.

REMARKS/COMMENTS:

There exist many portions of this NDA which are not acceptable and require additional revisions. Under the drug product section the following information is inadequately described: methods of manufacturing and packaging, reprocessing operations, specifications and methods, methods validation, stability and labeling. The following section of this review that is still pending is the establishment inspections.

NDA 20-743
Noritate (metronidazole cream), 1%
Dermik Laboratories, Inc.

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CONCLUSIONS & RECOMMENDATIONS:

At this point in the review process, it is my recommendation
The Division of Dermatologic and Dental Drug Products issue
an information request letter. For more details regarding
the requested information, please refer to the draft of the
information request letter.

Janet G. Higgins 5/12/97

Janet G. Higgins
Review Chemist

cc: Orig. NDA 20-743
HFD-540/Division File
HFD-540/Higgins
HFD-540/Ko
HFD-540/Alam
HFD-540/Cintron
HFD-540/Wilkin
R/D Init by: Decamp

ws 5/12/97

filename: N20743.org

gw 6/9/97