CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

CHEMISTRY REVIEW(S)

Division of Anti-Infective Drug Products (HFD-520)
Chemist's Review #1

NDA 20-010 November 26, 1990

Applicant:

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Contact:

Douglas B. Given, M.D., Ph.D

Date of Submission:

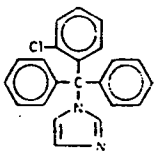
August 31,1989

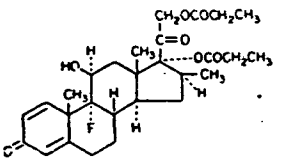
Proprietary Name:
Lotrisone (clotrimazole,1%/bethamethasone dipropionate,.05%)

Dosage Form / Route of Administration:
Lotion/topical
Pharmacological Category / Principal Indication:

—

Structural Formula / Chemical Name:





1-(o-chloro-α,α-diphenylbenzyl)imidazole and
9-Flouro-11β,17,21-trihydroxy-16β-methylpregna-diene-3,20-dione 17,21-dipropionate

Related NDA's, IND's and DMF's:

Lotrimin Solution	—	NDA 17-613
Lotrimin Cream	—	NDA 17-619
Lotrimin Lotion	—	NDA 18-813
Lotrisone Cream	—	, NDA 18-827
Lotrisone Lotion	—	
Diprosone Cream	—	NDA 17-536
Diprosone Ointment	—	, NDA 17-619
Diprosone Lotion	—	NDA 17-781
Diprosone Aerosol	—	, NDA 17-829
Lotrimin Aerosol		NDA 19-984
Lotrimin Powder		NDA 20-009

Amendments: Compliance Response dated 12/4/90

Remarks:

Conclusions:

The application is **APPROVABLE** under Section 505 of the Act. Specific items which are pending are identified under the following headings: Samples and Results, and Establishment Inspection.

/S/

David B. Katague, Ph. D.
Chemist, HFD-520

cc: Orig: NDA 20-010
HFD-100/Kumkumian
HFD-520
HFD-520/DBK
Init:WHDeCamp/ /S/ 12/26/90
HFD-520/MO/Bostwick
HFD-520/Pharm/Osterberg
HFD-520/CSO/Cook
DBK:11/26/90

(D)

Number of Pages Redacted 74

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Confidential,
Commercial Information

(D)

DEC 15 1994

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 18-827 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 15-DEC-94
20-010

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Correspondence (to both NDA's)	01-DEC-94	05-DEC-94	15-DEC-94

NAME & ADDRESS OF APPLICANT: Schering Corporation
Galloping Hill Road
Kenilworth, NJ 07033

DRUG PRODUCT NAME

Proprietary:	Lotrisone Cream (18-827) Lotrisone Lotion (20-010)
Nonproprietary/USAN:	clotrimazole / betamethasone dipropionate
Code Names/#'s:	n/a
Chemical Type/ Therapeutic Class:	4 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: cream (18-827); lotion (20-010)

STRENGTHS: 10 mg/g clotrimazole, 0.64 mg/g betamethasone dipropionate

ROUTE OF ADMINISTRATION: topical
DISPENSED: XX Rx _____ OTC

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

see USP/USAN

REMARKS/COMMENTS:

The report submitted here is in response to an ad hoc discussion on May 20, 1992. The data presented show that, in the absence of an appropriate microscopic method, [redacted] is an appropriate method of separating suspended solids from a topical semi-solid product. In addition, the resulting solid can be studied by [redacted] to achieve identification of the substances

present. The results are sufficient to demonstrate both that the drug substances are present in the product as a solid suspension and that the crystalline form is consistent from batch to batch. Clearly, polymorphic stability could also be monitored by this method.

CONCLUSIONS & RECOMMENDATIONS:

No action is indicated. However, for future reference, the regulatory implications of the study should be recognized, namely, that [redacted] represents an analytical method with potential regulatory use in identifying components of topical semi-solid products, as well as demonstrating their stability as a crystalline form. This may be true for other products as well.

/S/ 12/15/94
Wilson H. De Camp, Ph. D.
Supervisory Chemist

cc: Orig: NDA 18-827
Orig: NDA 20-010
HFD-540/Division File
HFD-540/Wilkin
HFD-540/Chambers
HFD-540/Slifman
HFD-540/Mainigi
HFD-540/Higgins
HFD-540/Cook

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF TOPICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-010 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 5-APR-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-AUG-89	05-SEP-89	Chem Rev # 1
AMENDMENT/NC	03-JUL-90	05-JUL-90	
AMENDMENT/NC	20-JUL-90	25-JUL-90	
AMENDMENT/BC	01-DEC-91	11-DEC-91	
AMENDMENT/NC	14-JAN-91	22-JAN-91	
AMENDMENT/A,M	19-MAR-91	25-MAR-91	
AMENDMENT/NC	31-MAY-91	04-JUN-91	
AMENDMENT/NC	06-AUG-91	09-AUG-91	
AMENDMENT/BL	30-AUG-91	03-SEP-91	
AMENDMENT/BL	16-SEP-91	18-SEP-91	
AMENDMENT/NC	26-MAR-92	31-MAR-92	
AMENDMENT/NC	06-MAY-92	07-MAY-91	
AMENDMENT/NC	06-JUN-94	13-JUN-94	
AMENDMENT/NC	25-AUG-94	29-AUG-94	
AMENDMENT/NC	16-SEP-94	23-SEP-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	21-OCT-94	24-OCT-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	01-DEC-94	05-DEC-94	15-DEC-1994*
AMENDMENT/NC	05-JAN-99	06-JAN-99	
AMENDMENT/AZ	07-OCT-99	13-OCT-99	10-NOV-99
AMENDMENT/BC	26-OCT-99	28-OCT-99	10-NOV-99
AMENDMENT/BC	03-MAR-00	06-MAR-00	10-MAR-00
AMENDMENT/BC	03-MAR-00	06-MAR-00	10-MAR-00
AMENDMENT/BC	13-MAR-00	15-MAR-00	16-MAR-00

APR 5 2000

* Chemistry review # 1 for NDA 18-827

NAME & ADDRESS OF APPLICANT:

Schering Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
(908)298-2628

DRUG PRODUCT NAME

Proprietary:	Lotrisone Lotion
Nonproprietary/USAN:	Clotrimazole/Betamethasone Dipropionate
Code Names/#'s:	SCH 370
Chemical Type	Imidazole + Fluorinated Glucocorticoid
Therapeutic Class:	4 S

Patent Status: (Lotrisone) U.S. Patent Number 4,289,604 (expiration date: 6 October 2000)

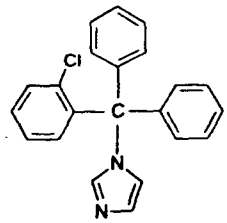
PHARMACOLOGICAL CATEGORY/INDICATION: [redacted]

DOSAGE FORM:	Lotion
STRENGTHS:	Clotrimazole 1%; Betamethasone dipropionate 0.05%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS NUMBER:

(i) CLOTRIMAZOLE:

- 1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole
- 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole
- Diphenyl-(2-chlorophenyl)-1-imidazolylmethane
- 1-(*o*-Chloro-trityl)imidazole



TRADE NAME: Lotrimin (for products containing clotrimazole only)

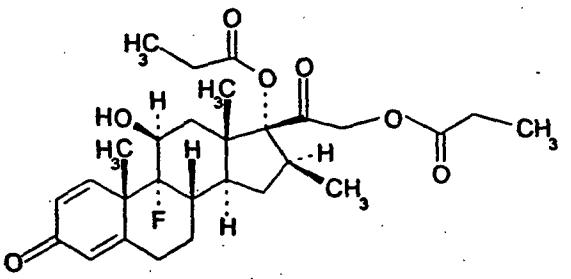
MOLECULAR FORMULA: $C_{22}H_{17}ClN_2$

MOLECULAR WEIGHT: 344.84

CAS NUMBER: 23593-75-1

(ii) BETAMETHASONE DIPROPIONATE:

- 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11β,16β)-9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11β,16β)-9-Fluoro-11-hydroxy-16-methyl-17,21-*bis*(1-oxopropoxy)-pregna-1,4-diene-3,20-dione



TRADE NAME: Diprosone, Diprolene (for drug products containing the betamethasone dipropionate only)

MOLECULAR FORMULA: $C_{28}H_{37}FO_7$

MOLECULAR WEIGHT: 504.59

CAS NUMBER: 5593-20-4

SUPPORTING DOCUMENTS:

- NDA 18-813, Lotrimin Lotion as a central repository for clotrimazole drug substance (S-019); submitted 3/12/98; approved 5/18/98.
- NDA 19-716, Diprolene Lotion as a central repository for betamethasone dipropionate drug substance (S-008; submitted 12/12/97; approved 6/15/98.
- [redacted] Type II DMF; [redacted] Letter of authorization for FDA access dated 2/25/99. Last update of DMF: 3/30/99. Last review of DMF by Mamta Gautam-Basak in 10/7/99; acceptable.
- [redacted] Type II DMF; [redacted] Letter of authorization for FDA access dated November 24, 1997. Last update of DMF: 3/6/96. Last review of DMF by Eric Duffy in 5/1992; acceptable, after correction of deficiencies.
- [redacted] Type III DMF, [redacted] Letter of authorization for FDA access dated July 1, 1999. The DMF was reviewed by Donald Klein on 12/21/99 and found inadequate. The DMF holder responded to the agency IR letter dated 12/21/99 with a package dated 1/5/00. The package was not reviewed.
- [redacted] Type I DMF, but incorrectly identified by the applicant as a Type III DMF for [redacted] Letter of authorization for FDA access dated June 24,

1999. The confusion concerning the Type of DMF and the information needed by FDA for [redacted] was clarified in a teleconference with the applicant and the DMF holder on 3/9/00 (see page 34 under [redacted] for details). No review is needed.

- [redacted] Type III DMF, [redacted]. Letter of authorization for FDA access dated June 24, 1999. Requested DMF 1/28/00.
- [redacted] Type III DMF, [redacted] Limited letter of authorization for FDA access dated January 20, 1999. [redacted] Limited letter of authorization for FDA access dated June 24, 1999. Requested DMF 1/28/00.
- [redacted] Type III DMF, [redacted]. Letter of authorization for FDA access dated July 20, 1999. Reviewed by Su C. Tso on 12/13/99 and found to be current and adequate (only the subject [redacted] was reviewed).

RELATED DOCUMENTS:

- NDA 17-613, Lotrimin Solution
- NDA 17-619, Lotrimin Cream
- NDA 18-827, Lotrimin Cream
- [redacted]
- NDA 17,536, Diprosone Cream
- NDA 17,619, Diprosone Ointment
- NDA 17,781, Diprosone Lotion
- NDA 17,829, Diprosone Aerosol
- NDA 19-984, Lotrimin Aerosol
- NDA 20-009, Lotrimin Powder

CONSULTS:

CMC microbiology was consulted on March 6, 2000, concerning the determination of microbial limits using the pre-enrichment media specified by the AOAC Bacteriological Analytical Manual (as opposed to following USP protocols). The applicant was requested to provide more details about the media and precise references. CMC microbiology was also consulted on March 13, 2000, the reduction below specifications of the amount of benzyl alcohol, the preservative in the drug product, and whether there was a need for testing for microbial limits at that temperature (i.e. ICH: 30°C/60%RH). There were no concerns. See Attachment 2.

REMARKS/COMMENTS:

An approvable letter was issued on July 31, 1991. The agency letter included a request for twelve copies of the final printed labeling for the drug product "that are identical to the enclosed revised version of the draft labeling submitted on August 31, 1989." The agency letter also included a request for the advertising copy (in duplicate) which the applicant intended to use in their proposed introductory and/or advertising campaign. The applicant was also informed that the drug application could not be approved until satisfactory Establishment Inspection Reports for all facilities involved in the manufacture and packaging of the drug substances and the drug product were received. There no other CMC issues.

At a teleconference on February 24, 1999, the applicant agreed to provide the following as part of their amendment (resubmission):

- A updated label that satisfies current standards.
- A complete Chemistry Manufacturing and Controls section in accordance with current standards.
- Deletion of —— overcharge for betamethasone dipropionate.
- Complete addresses for all manufacturing, packaging and control sites for the drug substances and the drug product.
- A statement that the manufacturing and testing sites for drug substances and drug product are ready for FDA inspection. Dates of the last inspection and inspection results for each site should be included.
- Available stability data from the first three batches of Lotrisone Lotion, manufactured at the new manufacturing site in Kenilworth, NJ, and placed on stability studies under ICH conditions.

The agency agreed to accept information on the drug substances by cross reference: to Diprolene Lotion (NDA 19-716) as the repository for betamethasone dipropionate (S-008; submitted 12/12/97; approved 6/15/98) and Lotrimin Lotion (NDA 18-813) as the repository for Clotrimazole (S-019; submitted 3/12/97; approved 5/18/98). The agency also agreed to respond to this resubmission within 180 days from the date of receipt of the amendment.

It is noted that the applicant makes an incorrect statement concerning the difference between Lotrisone Cream and Lotrisone Lotion (vol. 6.2, page 250). Under the heading "Development Summary" the applicant states that "*the formulations for these two products differ only by the amount of water present*". The formulations of the two products, however, differ by much more than the amount of water present, as shown in Table I below. Table I only highlights the differences between the two drug products and is not intended to be complete.

Table I. Excipient Differences between Lotrisone Cream and Lotrisone Lotion

Component	Lotrisone Cream mg/g (percent)	Lotrisone Lotion mg/g (percent)
Ceteareth-30		
Cetearyl Alcohol 70/30		
[redacted]		
Propylene Glycol		
Mineral Oil		
White Petrolatum		
Water		

The formulation of Lotrisone Lotion is provided in vol. 6.1, page 75 of the present resubmission and in Table II on page 14 of this review. The composition of Lotrisone Cream is provided in vol. 6.1, page 205 of the present resubmission, and was also provided on March 3, 2000 in response to an information request by the agency (see Attachment 3).

Other deficiencies are listed in the body of the review. None of the deficiencies constitute CMC approvability issues, but they do require post approval surveillance (phase 4 commitments as noted in the review).

CONCLUSIONS & RECOMMENDATIONS:

The application is **APPROVABLE** for manufacturing and controls under section 505 pending a phase 4 commitment and the receipt of missing and requested information from the applicant. Specific items which are missing and/or requested are identified under the following headings: Drug Product [Manufacturing and Packaging Methods, Container/Closure, Microbiology, Stability], Investigational Formulations, Labeling, and Establishment Inspections. A phase 4 commitment is requested to put the first three commercial batches, and at least one commercial batch per year for the following three years in a stability program under ICH conditions to determine the following:

- Whether the drug product remains within specifications for 24 months at 30°C, the requested excursion temperature (new storage condition, not in the original 1989 submission) —
- The amounts impurities identified in the present submission, but not in the original 1989 submission.

betamethasone

[redacted]

- Whether there is a change of particle size of the active ingredients over the shelf life of the drug product.
- Whether there is a change in the homogeneity of the drug product over its shelf life.

/S/ 1/5/00

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 20-010
HFD-540/Division File
HFD-540/SATurujman/4/5/00
HFD-540/MO/MLuke
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/FCross
HFD-540/ChemTmLdr/WHDeCamp /S/ 1/5/00
C:\DATA\TURUJMAN\REVIEWS\NDA\20010REV#2 APRIL 5, 2000.DOC

/S/ 4/18/00

APPEARS THIS WAY
ON ORIGINAL

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

61

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20010/000
Stamp: 05-SEP-1989
Regulatory Due:
Applicant: SCHERING
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033
Priority: 3AS
Org Code: 540

Action Goal:
District Goal:
Brand Name: LOTRISONE TOPICAL LOTION
Estab. Name:
Generic Name: CLOTRIMAZOLE/BETAMETHASONE DIPROPIONATE

Dosage Form: (LOTION)
Strength: 10 MG/0.5 MG

Application Comment:
FDA Contacts: F. CROSS JR (HFD-540) 301-827-2023 , Project Manager
S. TURUJMAN (HFD-540) 301-827-2085 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:
Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE
Estab. Comment: [redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-JUL-1991				EES_CONV
OC RECOMMENDATION	05-AUG-1991			ACCEPTABLE BASED ON PROFILE	EES_CONV
SUBMITTED TO OC	23-JAN-1992				EES_CONV
OC RECOMMENDATION	28-JAN-1992			ACCEPTABLE BASED ON PROFILE	EES_CONV
SUBMITTED TO OC	06-JAN-2000				TURUJMANS
OC RECOMMENDATION	06-JAN-2000			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	06-JAN-2000				TIMMERW
OC RECOMMENDATION	10-JAN-2000			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JAN-2000				TURUJMANS
OC RECOMMENDATION	06-JAN-2000			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	06-JAN-2000				TIMMERW
OC RECOMMENDATION					

BASED ON PROFILE

Establishment: 2210048
SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
Profile: OIN OAI Status: OAI ALERT
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	06-JAN-2000				TIMMERW
SUBMITTED TO DO	07-JAN-2000	10D			FERGUSONS
DO RECOMMENDATION	19-JAN-2000			WITHHOLD	RBROWN4
				PEND REG ACTION - WARNING LTR	

NWJ-DO HAS BEEN NOTIFIED BY CDER AND ATTENDED MEETINGS ABOUT SYSTEMATIC PROBLEMS WITH SUBMISSIONS BY THIS FIRM. COMPLIANCE STATUS IS CURRENTLY UNDER ASSESSMENT.

Establishment: 2211256
SCHERING CORP
1011 MORRIS AVE
UNION, NJ 07083

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CRU OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-JUL-1991				EES_CONV
OC RECOMMENDATION	05-AUG-1991			ACCEPTABLE	EES_CONV
				BASED ON PROFILE	

Profile: CTL OAI Status: NONE
Estab. Comment: TESTING (on 24-AUG-1996 by EES_CONV)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-JUL-1991				EES_CONV
OC RECOMMENDATION	05-AUG-1991			ACCEPTABLE	EES_CONV
				BASED ON PROFILE	
SUBMITTED TO OC	06-JAN-2000				TURUJMANS
SUBMITTED TO DO	06-JAN-2000	GMP			FERGUSONS
SUBMITTED TO OC	06-JAN-2000				TIMMERW
SUBMITTED TO DO	07-JAN-2000	GMP			FERGUSONS
DO RECOMMENDATION	19-JAN-2000			WITHHOLD	RBROWN4
				PEND REG ACTION - WARNING LTR	

NWJ-DO HAS ATTENDED MEETINGS AND BEEN NOTIFIED BY CDER THAT THERE ARE SYSTEMATIC PROBLEMS WITH SUBMISSIONS BY THIS FIRM. COMPLIANCE STATUS IS UNDER CURRENT ASSESSMENT.

Profile: LIO OAI Status: NONE

Estab. Comment: APPROVED PER FAX FROM NWK-DD - The above address is correct. The facility is manufacturer, packager and labelerof drug product (on 24-AUG-1996 by EES_CONV)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-NOV-1990				EES_CONV
OC RECOMMENDATION	05-FEB-1991			ACCEPTABLE BASED ON PROFILE	EES_CONV
SUBMITTED TO OC	26-JUL-1991				EES_CONV
SUBMITTED TO DO	13-AUG-1991	10D			EES_CONV
OC RECOMMENDATION	25-SEP-1991				EES_CONV
No OC recommendation in historical data					
SUBMITTED TO OC	23-JAN-1992				EES_CONV
SUBMITTED TO DO	29-JAN-1992	10D			EES_CONV
OC RECOMMENDATION	10-FEB-1992				EES_CONV
No OC recommendation in historical data					

Profile: OIN OAI Status: OAI ALERT

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
DO RECOMMENDATION	13-SEP-1991			ACCEPTABLE	EES_CONV
BASED ON PREVIOUS EI OF 1/4/91 & REVIEW OF FIRM'S CURRENT REGULATORY STATUS, NWK-DO RECOMMENDS APPROVAL OF THIS APPLICATION.....An addition request from HFD-320 on 1/29/92.... Continue to recommend approve.....					
OC RECOMMENDATION	13-SEP-1991			ACCEPTABLE	EES_CONV
ADMINISTRATIVE ACTION FOR HISTORICAL DATA MIGRAION PURPOSE					

Establishment: 2650149
SCHERING PLOUGH PRODUCTS INC
CARRETERA ESTATAL NUMBER 686 KILO METRO
MANATI, PR 00701

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: Facility is manufacturer of bulk drug, betamethasone dipropionate The above address is correct. (on 24-AUG-1996 by EES_CONV)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-JUL-1991				EES_CONV
OC RECOMMENDATION	05-AUG-1991			ACCEPTABLE BASED ON PROFILE	EES_CONV
SUBMITTED TO OC	23-JAN-1992				EES_CONV
OC RECOMMENDATION	28-JAN-1992			ACCEPTABLE BASED ON PROFILE	EES_CONV
SUBMITTED TO CC	06-JAN-2000				TURUJMANS
SUBMITTED TO DO	06-JAN-2000	GMP			FERGUSONS
SUBMITTED TO OC	06-JAN-2000				TIMMERW
SUBMITTED TO DO	07-JAN-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	21-JAN-2000	GMP			MTORRES
INSPECTION SCHEDULED	21-JAN-2000		24-FEB-2000		MTORRES

DIVISION OF TOPICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-010 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 24-AUGUST-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-AUG-89	05-SEP-89	Chem Rev # 1
AMENDMENT/NC	03-JUL-90	05-JUL-90	
AMENDMENT/NC	20-JUL-90	25-JUL-90	
AMENDMENT/BC	01-DEC-91	11-DEC-91	
AMENDMENT/NC	14-JAN-91	22-JAN-91	
AMENDMENT/A,M	19-MAR-91	25-MAR-91	AUG 2 5 2000
AMENDMENT/NC	31-MAY-91	04-JUN-91	
AMENDMENT/NC	06-AUG-91	09-AUG-91	
AMENDMENT/BL	30-AUG-91	03-SEP-91	
AMENDMENT/BL	16-SEP-91	18-SEP-91	
AMENDMENT/NC	26-MAR-92	31-MAR-92	
AMENDMENT/NC	06-MAY-92	07-MAY-91	
AMENDMENT/NC	06-JUN-94	13-JUN-94	
AMENDMENT/NC	25-AUG-94	29-AUG-94	
AMENDMENT/NC	16-SEP-94	23-SEP-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	21-OCT-94	24-OCT-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	01-DEC-94	05-DEC-94	15-DEC-1994*
AMENDMENT/NC	05-JAN-99	06-JAN-99	
AMENDMENT/AZ	07-OCT-99	13-OCT-99	Chem Rev # 2
AMENDMENT/BC	26-OCT-99	28-OCT-99	Chem Rev # 2
AMENDMENT/BC	03-MAR-00	06-MAR-00	Chem Rev # 2
AMENDMENT/BC	03-MAR-00	06-MAR-00	Chem Rev # 2
AMENDMENT/BC	13-MAR-00	15-MAR-00	Chem Rev # 2
AMENDMENT/BC	05-APR-00	07-APR-00	11-APR-00
AMENDMENT/BC	13-APR-00	14-APR-00	20-APR-00
AMENDMENT/BC	13-APR-00	14-APR-00	20-APR-00
AMENDMENT/BC	05-MAY-00	09-MAY-00	15-MAY-00
AMENDMENT/BC	30-JUN-00	05-JUL-00	10-JUL-00
AMENDMENT/BC	21-JUL-00	25-JUL-00	1-AUG-00
AMENDMENT/BC	27-JUL-00	31-JUL-00	1-AUG-00

* Chemistry review # 1 for NDA 18-827

NAME & ADDRESS OF APPLICANT:

Schering Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
(908)298-2628

DRUG PRODUCT NAME

Proprietary: Lotrisone Lotion
Nonproprietary/USAN: Clotrimazole/Betamethasone Dipropionate
Code Names/#'s: SCH 370

Chemical Type Therapeutic Class:	Imidazole + Fluorinated Glucocorticoid 4 S
Patent Status: (Lotrisone)	U.S. Patent Number 4,289,604 (expiration date: 6 October 2000)

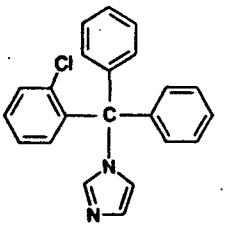
PHARMACOLOGICAL CATEGORY/INDICATION: [redacted]

DOSAGE FORM:	Lotion
STRENGTHS:	Clotrimazole 1%; Betamethasone dipropionate 0.05%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS NUMBER:

(i) CLOTRIMAZOLE:

- 1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole
- 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole
- Diphenyl-(2-chlorophenyl)-1-imidazolylmethane
- 1-(*o*-Chloro-trityl)imidazole



TRADE NAME: Lotrimin (for products containing clotrimazole only)

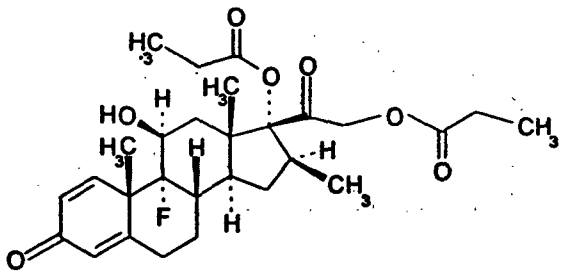
MOLECULAR FORMULA: $C_{22}H_{17}ClN_2$

MOLECULAR WEIGHT: 344.84

CAS NUMBER: 23593-75-1

(ii) BETAMETHASONE DIPROPIONATE:

- 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11β,16β)-9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11β,16β)-9-Fluoro-11-hydroxy-16-methyl-17,21-*bis*(1-oxopropoxy)-pregna-1,4-diene-3,20-dione



TRADE NAME: Diprosone, Diprolene (for drug products containing the betamethasone dipropionate only)

MOLECULAR FORMULA: $C_{28}H_{37}FO_7$

MOLECULAR WEIGHT: 504.59

CAS NUMBER: 5593-20-4

SUPPORTING DOCUMENTS:

See review # 2

RELATED DOCUMENTS:

See review # 2

CONSULTS:

No new consults.

REMARKS/COMMENTS:

The original NDA, dated August 31, 1989, was issued an approvable letter on July 31, 1991. The applicant responded with a resubmission dated October 7, 1999. Chemistry review # 2, dated April 5, 2000, rated the resubmission "Approvable" for manufacturing and controls under section 505 pending a Phase 4 commitment and the receipt of missing and requested information from the applicant. The applicant provided adequate responses to the agency questions and stated that 12 month stability data will be provided on September 29, 2000.

Subsequent to review # 2, a warning letter was issued to the sponsor on May 8, 2000 by the Office of Compliance. The response and corrective actions by the sponsor were discussed during a meeting with the District Office held on May 25, 2000. These were found to adequately address the deficiencies identified. The sites are therefore currently in GMP compliance (see Appendix 2).

CONCLUSIONS & RECOMMENDATIONS:

The applicant's responses are acceptable. (See Chemistry reviewer's comments).

/S/ 8/24/00

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 20-010
HFD-540/Division File
HFD-540/SATurujman/8/24/00
HFD-540/MO/MLuke
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/FCross
HFD-540/ChemTmLdr/WHDeCamp S 8/25/00 /S/ 9/7/00

C:\DATA\TURUJMAN\REVIEWS\NDA\20010\20010 REV # 3 AUGUST 24, 2000.DOC archival only

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

9

(E)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20010/000
Stamp: 05-SEP-1989 Regulatory Due:
Applicant: SCHERING
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033

Priority: 3S Org Code: 540
Action Goal: District Goal:
Brand Name: LOTRISONE TOPICAL LOTION
Established Name:
Generic Name: CLOTRIMAZOLE/BETAMETHASONE DIPROPIONATE
Dosage Form: LOT (LOTION)
Strength: 10 MG/0.5 MG

FDA Contacts:

F. CROSS JR	(HFD-540)	301-827-2023	, Project Manager
S. TURUJMAN	(HFD-540)	301-827-2085	, Review Chemist
W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation:

ACCEPTABLE on 12-JUN-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: [redacted]
AADA N..

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-JAN-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-JAN-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: 2210048
SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033

DMF No:
AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-APR-2000

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

FINISHED DOSAGE PACKAGER

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2211256**
SCHERING CORP
1011 MORRIS AVE
UNION, NJ 07083

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-AUG-1991**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-FEB-1992**

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-SEP-1991**
Decision: **ACCEPTABLE**
Reason:

Establishment: **2650149**
SCHERING PLOUGH PRODUCTS INC
CARRETERA ESTATAL KM 686
MANATI, PR 00701

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-JUN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

SEP 15 2000

SENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: September 12, 2000

To: NDA 20-010

From: Saleh A. Turujman, Ph.D.
Review Chemist, HFD-540

Through: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540

Subject: Addendum to Chemistry Rev # 3

In concurrence with the clinical recommendation, the applicant should be requested to modify the labeling (carton, container label and patient insert) to include the following:

LOTRISONE® LOTION

[redacted]

FOR TOPICAL USE ONLY

NOT RECOMMENDED FOR PATIENTS UNDER THE AGE OF 12 YEARS AND NOT RECOMMENDED FOR DIAPER DERMATITIS

For consistency, this modification may also be needed for Lotrisone Cream (NDA 18-827).

/S/

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig [redacted]
NDA 18-827
HFD-540/Division File
HFD-540/DivDir/JWilkin
HFD-540/SATurujman/9/12/00
HFD-540/MO/Mluke
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/FCross
HFD-540/ChemTmLdr/WHDeCamp WD 9/15/00

12/8/00

/S/ for Jonathan K. WILKIN

C:\DATA\TURUJMAN\REVIEWS\NDA\20010\20010 ADDENDUM TO REV # 3.DOC

OCT 27 2000

DIVISION OF TOPICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-010 **CHEM. REVIEW #:** 4 **REVIEW DATE:** 26-OCT-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-AUG-89	05-SEP-89	Chem Rev # 1
AMENDMENT/NC	03-JUL-90	05-JUL-90	
AMENDMENT/NC	20-JUL-90	25-JUL-90	
AMENDMENT/BC	01-DEC-91	11-DEC-91	
AMENDMENT/NC	14-JAN-91	22-JAN-91	
AMENDMENT/A,M	19-MAR-91	25-MAR-91	
AMENDMENT/NC	31-MAY-91	04-JUN-91	
AMENDMENT/NC	06-AUG-91	09-AUG-91	
AMENDMENT/BL	30-AUG-91	03-SEP-91	
AMENDMENT/BL	16-SEP-91	18-SEP-91	
AMENDMENT/NC	26-MAR-92	31-MAR-92	
AMENDMENT/NC	06-MAY-92	07-MAY-91	
AMENDMENT/NC	06-JUN-94	13-JUN-94	
AMENDMENT/NC	25-AUG-94	29-AUG-94	
AMENDMENT/NC	16-SEP-94	23-SEP-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	21-OCT-94	24-OCT-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	01-DEC-94	05-DEC-94	15-DEC-1994*
AMENDMENT/NC	05-JAN-99	06-JAN-99	
AMENDMENT/AZ	07-OCT-99	13-OCT-99	Chem Rev # 2
AMENDMENT/BC	26-OCT-99	28-OCT-99	Chem Rev # 2
AMENDMENT/BC	03-MAR-00	06-MAR-00	Chem Rev # 2
AMENDMENT/BC	03-MAR-00	06-MAR-00	Chem Rev # 2
AMENDMENT/BC	13-MAR-00	15-MAR-00	Chem Rev # 2
AMENDMENT/BC	05-APR-00	07-APR-00	Chem Rev # 3
AMENDMENT/BC	13-APR-00	14-APR-00	Chem Rev # 3
AMENDMENT/BC	13-APR-00	14-APR-00	Chem Rev # 3
AMENDMENT/BC	05-MAY-00	09-MAY-00	Chem Rev # 3
AMENDMENT/BC	30-JUN-00	05-JUL-00	Chem Rev # 3
AMENDMENT/BC	21-JUL-00	25-JUL-00	Chem Rev # 3
AMENDMENT/BC	27-JUL-00	31-JUL-00	Chem Rev # 3
AMENDMENT/NC	30-AUG-00	01-SEP-00	14-SEP-00
AMENDMENT/BL	27-SEP-00	29-SEP-00	29-SEP-00
AMENDMENT/BC	29-SEP-00	03-OCT-00	17-OCT-00
AMENDMENT/BL	13-OCT-00	16-OCT-00	23-OCT-00

* Chemistry review # 1 for NDA 18-827

NAME & ADDRESS OF APPLICANT:

Schering Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
(908)298-2628

DRUG PRODUCT NAME

Proprietary:	Lotrisone Lotion
Nonproprietary/USAN:	Clotrimazole/Betamethasone Dipropionate
Code Names/#'s:	SCH 370
Chemical Type	4S
Therapeutic Class:	Imidazole + Fluorinated Glucocorticoid

Patent Status: (Lotrisone) U.S. Patent Number 4,289,604 (expiration date: 6 October 2000)

PHARMACOLOGICAL CATEGORY/INDICATION:

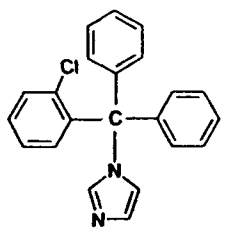
DOSAGE FORM: Lotion
STRENGTHS: Clotrimazole 1%; Betamethasone dipropionate 0.05%

ROUTE OF ADMINISTRATION: Topical
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS NUMBER:

(i) **CLOTRIMAZOLE:**

- 1-(*o*-Chloro-□,□-diphenylbenzyl)imidazole
- 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole
- Diphenyl-(2-chlorophenyl)-1-imidazolylmethane
- 1-(*o*-Chloro-trityl)imidazole



TRADE NAME: Lotrimin (for products containing clotrimazole only)

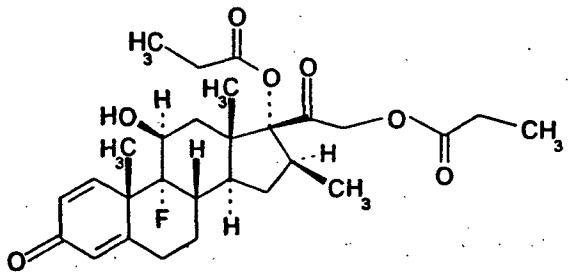
MOLECULAR FORMULA: $C_{22}H_{17}ClN_2$

MOLECULAR WEIGHT: 344.84

CAS NUMBER: 23593-75-1

(ii) **BETAMETHASONE DIPROPIONATE:**

- 9-Fluoro-11*β*,17,21-trihydroxy-16*β*-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11*β*,16*β*)-9-Fluoro-11β,17,21-trihydroxy-16*β*-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11*β*,16*β*)-9-Fluoro-11-hydroxy-16-methyl-17,21-*bis*(1-oxopropoxy)-pregna-1,4-diene-3,20-dione



TRADE NAME: Diprosone, Diprolene (for drug products containing the betamethasone dipropionate only)

MOLECULAR FORMULA: $C_{28}H_{37}FO_7$

MOLECULAR WEIGHT: 504.59

CAS NUMBER: 5593-20-4

SUPPORTING DOCUMENTS:

See review # 2

RELATED DOCUMENTS:

See review # 2

CONSULTS:

No new consults.

REMARKS/COMMENTS:

The original NDA, dated August 31, 1989, was issued an approvable letter on July 31, 1991. The applicant responded with a resubmission dated October 7, 1999. Chemistry review # 2, dated April 5, 2000, rated the resubmission "Approvable" for manufacturing and controls under section 505 pending a Phase 4 commitment and the receipt of missing and requested information from the applicant. Review # 3 concluded that the applicant had provided adequate responses to the agency questions. All sites were also in GMP compliance (see Review # 3, Appendix 2).

The current review covers the 12-month stability data, communications with the Applicant, and the Applicant's responses to Agency requests concerning stability and labeling issues,).

The only remaining issues concern labeling: the pediatric warning , including the logo, and the carton labeling of the 10 mL bottle (see chemistry reviewer's comments under "F. LABELING", page 7).

CONCLUSIONS & RECOMMENDATIONS:

The applicant's responses are acceptable. (See Chemistry reviewer's comments).

/S/ 10/26/00

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 20-010
HFD-540/Division File
HFD-540/SATurujman/10/26/00
HFD-540/MO/MLuke
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/FCross
HFD-540/ChemTmLdr/WHDeCamp /S/ 10/27/00

✓Not entered into DFS

/S/ 11/2/00

C:\MY DOCUMENTS\TURUJMAN\REVIEWS\NDA\20010\20010_REV#4.DOC

APPEARS THIS WAY
ON ORIGINAL

F

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5

F

DIVISION OF TOPICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-010 **CHEM. REVIEW #**: 5 **REVIEW DATE**: 1-DEC-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-AUG-89	05-SEP-89	Chem Rev # 1
AMENDMENT/NC	03-JUL-90	05-JUL-90	
AMENDMENT/NC	20-JUL-90	25-JUL-90	
AMENDMENT/BC	01-DEC-91	11-DEC-91	
AMENDMENT/NC	14-JAN-91	22-JAN-91	
AMENDMENT/A,M	19-MAR-91	25-MAR-91	
AMENDMENT/NC	31-MAY-91	04-JUN-91	
AMENDMENT/NC	06-AUG-91	09-AUG-91	
AMENDMENT/BL	30-AUG-91	03-SEP-91	
AMENDMENT/BL	16-SEP-91	18-SEP-91	
AMENDMENT/NC	26-MAR-92	31-MAR-92	
AMENDMENT/NC	06-MAY-92	07-MAY-91	
AMENDMENT/NC	06-JUN-94	13-JUN-94	
AMENDMENT/NC	25-AUG-94	29-AUG-94	
AMENDMENT/NC	16-SEP-94	23-SEP-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	21-OCT-94	24-OCT-94	
AMENDMENT/NC	20-OCT-94	24-OCT-94	
AMENDMENT/NC	01-DEC-94	05-DEC-94	15-DEC-1994*
AMENDMENT/NC	05-JAN-99	06-JAN-99	
AMENDMENT/AZ	07-OCT-99	13-OCT-99	Chem Rev # 2
AMENDMENT/BC	26-OCT-99	28-OCT-99	Chem Rev # 2
AMENDMENT/BC	03-MAR-00	06-MAR-00	Chem Rev # 2
AMENDMENT/BC	03-MAR-00	06-MAR-00	Chem Rev # 2
AMENDMENT/BC	13-MAR-00	15-MAR-00	Chem Rev # 2
AMENDMENT/BC	05-APR-00	07-APR-00	Chem Rev # 3
AMENDMENT/BC	13-APR-00	14-APR-00	Chem Rev # 3
AMENDMENT/BC	13-APR-00	14-APR-00	Chem Rev # 3
AMENDMENT/BC	05-MAY-00	09-MAY-00	Chem Rev # 3
AMENDMENT/BC	30-JUN-00	05-JUL-00	Chem Rev # 3
AMENDMENT/BC	21-JUL-00	25-JUL-00	Chem Rev # 3
AMENDMENT/BC	27-JUL-00	31-JUL-00	Chem Rev # 3
AMENDMENT/NC	30-AUG-00	01-SEP-00	Chem Rev # 4
AMENDMENT/BL	27-SEP-00	29-SEP-00	Chem Rev # 4
AMENDMENT/BC	29-SEP-00	03-OCT-00	Chem Rev # 4
AMENDMENT/BL	13-OCT-00	16-OCT-00	Chem Rev # 4
AMENDMENT/BC*	29-NOV-00	29-NOV-00	30-NOV-00

* via Fax

* Chemistry review # 1 for NDA 18-827

NAME & ADDRESS OF APPLICANT:

Schering Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
(908)298-2628

DRUG PRODUCT NAME

Proprietary:	Lotrisone Lotion
Nonproprietary/USAN:	Clotrimazole/Betamethasone Dipropionate
Code Names/#'s:	SCH 370
Chemical Type	4S
Therapeutic Class:	Imidazole + Fluorinated Glucocorticoid

Patent Status: (Lotrisone) U.S. Patent Number 4,289,604 (expiration date: 6 October 2000)

PHARMACOLOGICAL CATEGORY/INDICATION: [redacted]

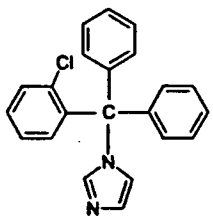
DOSAGE FORM: Lotion
STRENGTHS: Clotrimazole 1%; Betamethasone dipropionate 0.05%

ROUTE OF ADMINISTRATION: Topical
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS NUMBER:

(i) **CLOTRIMAZOLE:**

- 1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole
- 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole
- Diphenyl-(2-chlorophenyl)-1-imidazolylmethane
- 1-(*o*-Chloro-trityl)imidazole



TRADE NAME: Lotrimin (for products containing clotrimazole only)

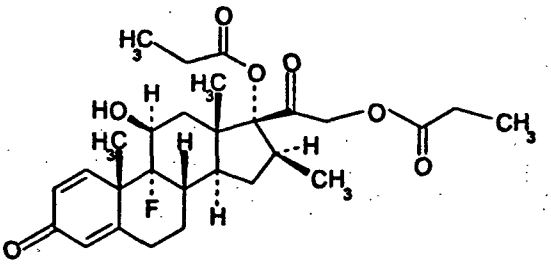
MOLECULAR FORMULA: $C_{22}H_{17}ClN_2$

MOLECULAR WEIGHT: 344.84

CAS NUMBER: 23593-75-1

(ii) **BETAMETHASONE DIPROPIONATE:**

- 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11β,16β)-9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate;
- (11β,16β)-9-Fluoro-11-hydroxy-16-methyl-17,21-*bis*(1-oxopropoxy)-pregna-1,4-diene-3,20-dione



TRADE NAME: Diprosone, Diprolene (for drug products containing the betamethasone dipropionate only)

MOLECULAR FORMULA: $C_{28}H_{37}FO_7$

MOLECULAR WEIGHT: 504.59

CAS NUMBER: 5593-20-4

SUPPORTING DOCUMENTS:

See review # 2

RELATED DOCUMENTS:

See review # 2

CONSULTS:

No new consults.

REMARKS/COMMENTS:

The original NDA, dated August 31, 1989, was issued an approvable letter on July 31, 1991. The applicant responded with a resubmission dated October 7, 1999. Chemistry review # 2, dated April 5, 2000, rated the resubmission "Approvable" for manufacturing and controls under section 505 pending a Phase 4 commitment and the receipt of missing and requested information from the applicant. Review # 3, dated August 24, 2000, concluded that the applicant had provided adequate responses to the agency questions. All sites were also in GMP compliance (see Review # 3, Appendix 2). Review # 4, dated October 26, 2000, concluded that the 12 month stability data were acceptable, and that the Applicant had provided adequate responses to the agency questions.

The current review covers communications with the Applicant, and the Applicant's responses to Agency requests concerning the Applicants Phase 4 commitment (see under "6. Stability", page 6), and the changes in labeling: the pediatric warning editorial changes, a draft carton labeling of the 10 mL bottle etc. (see under "F. Labeling", page 6).

CONCLUSIONS & RECOMMENDATIONS:

The applicant's responses are acceptable. The recommendation for this application is **APPROVAL** for manufacturing and controls under section 505 of the Act.

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 20-010
HFD-540/Division File
HFD-540/SATurujman/11/30/00
HFD-540/MO/MLuke
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/FCross
HFD-540/ChemTmLdr/WHDeCamp

Not entered into DFS

C:\MY DOCUMENTS\TURUJMAN\REVIEWS\NDA\20010\20010 REV # 5.DOC

APPEARS THIS WAY
ON ORIGINAL

/s/

Saleh Turujman
12/1/00 12:32:25 PM
CHEMIST

Wilson H. DeCamp
12/1/00 12:36:06 PM
CHEMIST
concur with review

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

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(G)