

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-555/S-008

19-555/S-016

ADMINISTRATIVE DOCUMENTS

(DIPROLENE Pediatric Exclusivity)

**Claim for PEDIATRIC Exclusivity based on DIPROLENE AND
DIPROSONE Pediatric Study**

1. Pursuant to the provisions of Sections 505A(c)(1)(A)(ii), (c)(2)(A) and (c)(2)(B) of the Food, Drug and Cosmetic Act (hereinafter "FDCA"), as amended by Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997, applicant claims that its **DIPROLENE** (BETAMETHASONE DIPROPIONATE) products for all of the approved indications is eligible to have an additional six (6) months added to the period during which an application may not be approved that contains a certification submitted under Section 505(b)(2)(A)(iii) or 505(j)(2)(A)(vii)(III) against the following U.S. Patent Nos. listed in the Orange Book for each of the following NDAs:

1. NDA # 19-408 DIPROLENE (BETAMETHASONE DIPROPIONATE) Gel

U. S. Patent No.	Expiration Date:
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4,489,070	May 13, 2003
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NDA Approval Date: November 22, 1991

**2. NDA # 19-555 DIPROLENE AF (BETAMETHASONE DIPROPIONATE)
Augmented Cream**

U. S. Patent No.	Expiration Date:
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4,489,071	December 9, 2003
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NDA Approval Date: April 27, 1987

**3. NDA # 19-716 DIPROLENE (BETAMETHASONE DIPROPIONATE)
Augmented Lotion**

U. S. Patent No.	Expiration Date:
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4,775,529	May 21, 2007
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NDA Approval Date: August 1, 1988

(LOTRISONE Pediatric Exclusivity)

Claim for PEDIATRIC Exclusivity based on LOTRISONE Pediatric Study

1. Pursuant to the provisions of Sections 505A(c)(1)(A)(ii), (c)(2)(A) and (c)(2)(B) of the Food, Drug and Cosmetic Act (hereinafter "FDCA"), as amended by Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997, applicant claims that its **LOTRISONE** (BETAMETHASONE DIPROPIONATE & CLOTRIMAZOLE) product for all of the approved indications is eligible to have an additional six (6) months added to the period during which an application may not be approved that contains a certification submitted under Section 505(b)(2)(A)(iii) or 505(j)(2)(A)(vii)(III) against the following U.S. Patent listed in the Orange Book for the following NDA:

1. **NDA # 18-827** **LOTRISONE (BETAMETHASONE DIPROPIONATE & CLOTRIMAZOLE) CREAM**

U. S. Patent No.

Expiration Date:

4,298,604

October 6, 2000

NDA Approval Date: July 10, 1984

Trade Name: Diprolene AF Cream, 0.05%

Generic Name: betamethasone dipropionate

Applicant Name: Schering Corporation

HFD # 540

Approval Date If Known: _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/___/NO/_X_/

b) Is it an effectiveness supplement?

YES/_X_/NO/___/

If yes, what type? (SE1, SE2, etc.) SE5(pediatric studies)_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES/___/NO/_X_/ N/A **Note: The Applicant conducted an open label safety study in pediatric patients 12 years of age down to 3 months of age. The Agency recommended that Diprolene AF Cream continue not to be recommended for use in pediatric patients 12 years of age and younger. The labeling was revised to reflect the new safety information that supports this restriction. (Efficacy was not requested as the efficacy of this drug product in adults can be extrapolated to pediatric patients.)**

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / (pediatric exclusivity) / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months

e) Has pediatric exclusivity been granted for this Active Moiety? **Pediatric Exclusivity not granted.**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES / / NO / /

If yes, NDA # _____ Drug Name _____ See below _____.

NDA 72-536 Betamethasone dipropionate Topical Cream, 0.05%, Clay Park

NDA 19-136 Betamethasone dipropionate Topical Cream, 0.05%, Pharmaderm

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation # 3 YES /___/ NO/___/

If you have answered "yes" for one or more investigations, identify

each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

IND # YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / ___ /

If yes, explain: _____

Signature: Date: Title:

/S/

9/27/01

Signature of ~~Office~~ Division Director

Signature: Date

/S/

10/2/01

cc: Original NDA 19-555
HFD-540 Division File
HFD-93 Mary Ann Holovac



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 019555
Trade Name: DIPROLENE AF CREAM, 0.05%
Generic Name: BETAMETHASONE DIPROPIONATE
Supplement Number: 016 **Supplement Type:** SE5
Dosage Form: Cream
Regulatory Action: OP **Action Date:** 10/5/00
COMIS Indication: CORTICOSTEROID

Indication #1: For the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Label Adequacy: Adequate for ~~some~~ ²⁻³ pediatric age groups

Formulation Needed: No new formulation is needed

Comments (if any) Pediatric studies have been conducted to determine the safety of Diprolene AF cream, 0.05%, in patients 12 years of age and younger. Upon review, it is recommended that Diprolene AF Cream continue not to be used in pediatric patients 12 years of age and younger.

Lower Range	Upper Range	Status	Date
13 years	Adult	Completed	10/4/01

This page was last edited on 7/28/01

Signature / S / Date 9/24/01

Signature / S / Date ~ 10/2/01

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: July 25, 2001.

NDA's: 19-555/S-016/Diprolene AF Cream
18-827/S-022/S-020/Lotrisone Cream
17-536/S-024/Diprosone Cream
17-691/S-024/Diprosone Ointment
17-781/S-022/Diprosone Lotion

APPLICANT: Elin Krhoun, Manager, Regulatory Affairs
Schering Corporation

FDA: Jonathan Wilkin, M.D., Director, DDDDP, HFD-540
Olga Cintron, R.Ph., Project Manager, DDDDP, HFD-540

Subject: Pediatric Efficacy Supplements - Labeling

The Division contacted the Applicant to provide an update regarding the Agency's thinking with respect to the new pediatric safety information and the impact on labeling for the above mentioned drug products. The Division indicated that this issue has been shared with the Office and is planning to forward this information to the CDER Pediatric Group. The Division further indicated that the Agency believes that in conjunction with the Applicant, a plan to develop constructive ways as to how to share the new safety information with physicians and dermatologists in a timely manner needs to be performed. The option of an Advisory Committee can be further discussed at a meeting.

The Applicant expressed appreciation for this call and indicated that they were willing to work together with the Agency to address this issue.

Signature, minutes preparer: _____

Concurrence, Chair: _____



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 20, 2001. Number of Pages (including cover sheet) – 1
TO: Elin Krhoun, Manager, Regulatory Affairs
COMPANY: Schering Corporation
FAX#: 908-740-6500

MESSAGE: RE: NDA supplements 17-536/S-024, 17-691/S-024, 17-781/S-022, 19-555/S-016
(Pediatric efficacy supplements)

Please find comments and request or information from the chemistry reviewer:

The efficacy supplements did not contain the following information:

- (1) The proposed changes in the efficacy supplement do not affect the CMCs as submitted in the NDA.
- (2) An environmental assessment statement should be submitted for the efficacy supplement, claiming categorical exclusion as required by 21 CFR 25.31 (a).

The Applicant should provide the information mentioned above.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

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TO: Elin Krhoun, Manager, Regulatory Affairs
COMPANY: Schering Corporation
FAX#: 908-740-6500

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(Pediatric efficacy supplements)

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- (2) An environmental assessment statement should be submitted for the efficacy supplement, claiming categorical exclusion as required by 21 CFR 25.31 (a).

The Applicant should provide the information mentioned above.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 19, 2001.

Number of Pages (including cover sheet) – 1

TO: Dr. Todd Paporello, Regulatory Affairs

COMPANY: Schering Corporation

FAX#: 908-740-6500

MESSAGE: RE: NDA supplements 17-536/S-024; 17-691/S-024; 17-781/S-022; 19-555/S-016
(Pediatric Efficacy Supplements)

Please find informational request from the medical officer:

Concerning study P1260:

1. Please provide the line listings for facial atrophy for center 0006. This information is missing from the table in section 16.2.9.2.1. That center has 6 patients.
2. Please provide CRFs for subjects 04/05, 05/03, 07/01, 07/02, 07/09.
3. Were there any 9-12 year olds treated on the face with Diprolene AF Cream, 0.05%? If so, please submit CRFs. Please describe where in the submission we could find which patients were treated on the face. This information is needed for all 4 studies.

FROM: Olga Cintron, R.Ph.

TITLE: Project Manager

PHONE #: 301-827-2020

FAX #: 301-827-2075/2091

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FDA Fax Memo

Date: February 5, 2001

Subject: NDA supplements 17-536/S-024, 17-691/S-024, 17-781/S-022 and 19-555/S-016

Information Request for Betamethasone dipropionate pediatric study submission

1. Please provide the line listing of the date of enrollment and termination for each patient in each topical steroid study. If already provided, please identify location in submission.
2. Please provide follow-up results of all patients who had end of treatment post Cortrosyn stimulaiton of less than 18ug/dL serum cortisol. If this was not done, please provide the case report form of each of those patients where it is lacking.

Thank you.