

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

PHARMACOLOGY REVIEW(S)

NOV 29, 1989

Review and Evaluation of Pharmacology/Toxicology Data

NDA 20-010 (Original Submission 9-5-89)

Date Assigned: 9-11-89

Date Review Completed: 11-29-89

Sponsor/Applicant: Schering Corporation
Kenilworth, N.J.

Drug: Lotrisone (Clotrimazole, USP 1%/Betamethasone Dipropionate,
USP 0.5%) Lotion

Category: Antifungal (Topical)

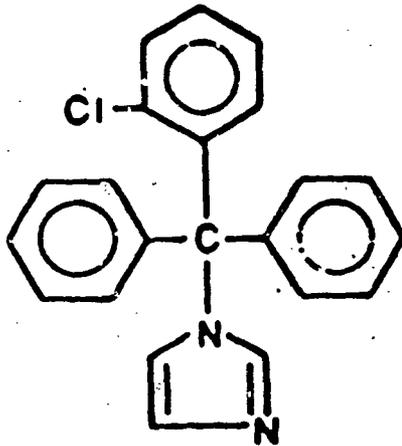
Code Name: SCH 370

Chemical Name:

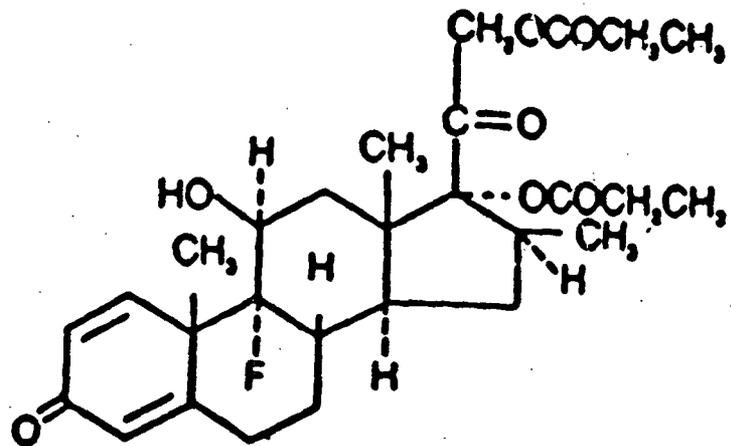
Clotrimazole: 1)-[(2-chlorophenyl) diphenylmethyl]-1H-imidazole
2) 1-(0-chloro- α,α -diphenylbenzyl) imidazole

Betamethasone dipropionate: 9-Fluoro-11 β ,17,21-trihydroxy-16- β -
methylpregna-1,4-diene-3,20-dione 17,21-
dipropionate

Chemical Structure



Clotrimazole



Betamethasone

Composition

<u>Component</u>	<u>Mg/g</u>
Betamethasone Dipropionate, USP,	0.643*
Clotrimazole, USP,	10.00
White Petrolatum, USP	
Mineral Oil, USP	
Cetearyl Alcohol 70/30	
Ceteareth-30	
Benzyl Alcohol, NF	
Na-Phosphate, USP Monohydrate	
Phosphoric Acid, NF	
Propylene Glycol, USP	
Purified Water, USP	
NqOH, NF (

* Equivalent to 0.5 mg/g of betamethasone

Clinical Indication

**APPEARS THIS WAY
ON ORIGINAL**

Related Submissions

<u>Formulation</u>	<u>IND</u>	<u>NDA</u>
Lotrimin Solution		17-613
Lotrimin Cream		17-619
Lotrimin Lotion		18-813
Lotrisone Cream		18-827
Lotrisone Lotion		--
Diprosone Cream		—
Diprosone Ointment		—
Diprosone Lotion		17-781
Diprosone Aerosol		—

Preclinical Studies

Acute Ocular Irritation Study of SCH 370 (clotrimazole 1%/Betamethasone dipropionate 0.06%)* Lotion in Rabbits [P-5348]

*Equivalent to 0.05% betamethasone base

Study Objective/Design/Observations

The ocular irritation potential of SCH 370 lotion and vehicle was assessed in 6 young male adult (3.7-4.7 kg) NZW rabbits. Animals (3/group) received ocular instillations of 2 drops of lotion or vehicle in the right-eye. The left eye served as an untreated control. Signs of ocular irritation were scored prior to dosing and at 0.5, 6, 24, 48, and 72 hours after dosing.

Ocular examination revealed a drug-related transient, mild conjunctival redness in one rabbit at 30 minute examination. No corneal lesions were observed.

Review of Safety Data and Recommendations

Except for the ocular irritation study reviewed above, no other pharmacology and toxicology studies were conducted for Lotion formulation. Reference is made to the studies conducted for other formulations containing clotrimazole. A topical cream formulation of Lotrisone (NDA 18-827) is currently sold in the U.S. market.

Lotrisone is a combination of a broad spectrum antifungal agent clotrimazole, and synthetic fluorinated corticosteroid betamethasone. Both compounds have been marketed individually, and are recognized to be clinically safe and effective. According to Dr. George w. James (Reviewer: _____) "The SCH-370 animals exhibit only the usual signs of corticosteroid exposure following continued treatment with SCH-370 Cream".

The proposed labeling for Lotrisone lotion is essentially similar to Lotrisone cream and includes all the information required under the federal law. From a safety point of view, I have no objection to the approval of this new drug application.

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Kumar D. Mainigi, Ph.D., DABT *11/28/89*

cc: NDA 20-010
HFD-340
HFD-502/Weissinger
HFD-520
HFD-520/Pharm/Mainigi
HFD-520/MO/Sanders
HFD-520/Chem/DeCamp
HFD-520/CSO/Bostwick
HFD-520/R/D init by: REOsterberg 11/10/89 *REC 11/29/89*
R/D 11/19/89 jpg F/T 11-29-89

Number of Pages in this review 4

mml 2/13/90

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: antifungal, glucocorticoid, label

Reviewer Name: Paul C. Brown

Division Name: Division of Dermatologic and Dental Drug Products

HFD#540

Review Completion Date: March 10, 2000

Review number: 2 (counting original review dated 11/28/89 as #1)

NDA number: 20-010

Serial number/date/type of submission: 7 October 1999 / AZ

Sponsor (or agent): Schering Corporation

Drug Product:

Trade Name: Lotrisone Lotion

This drug product contains a combination of two active ingredients: 1% clotrimazole and 0.0643% betamethasone dipropionate.

Drug substances:

a.

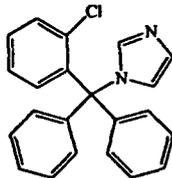
Generic Name: clotrimazole

Chemical Name: 1H-imidazole, 1-[(2-chlorophenyl)diphenyl-methyl]-

CAS Registry Number: 23593-75-1

Molecular Formula/ Molecular Weight: $C_{22}H_{17}ClN_2$ / MW=344.85

Structure:



b.

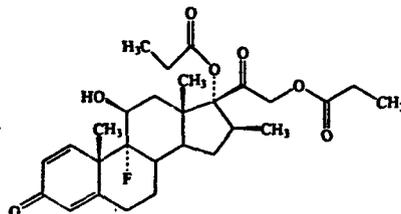
Generic Name: betamethasone dipropionate

Chemical Name: 9-fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene, 3,20-dione 17,21-dipropionate

CAS Registry Number: 5593-20-4

Molecular Formula/ Molecular Weight: $C_{28}H_{37}FO_7$ / MW=504.60

Structure:



Relevant INDs/NDAs/DMFs: NDA 18-827 (Lotrisone cream)

Drug Class: antifungal and corticosteroid

Indication: _____

Clinical formulation: lotion containing 1% clotrimazole and 0.0643% betamethasone dipropionate (equivalent to 0.05% betamethasone), inactive ingredients include white petrolatum, mineral oil, cetearyl alcohol 70/30, cetareth-30, benzyl alcohol, sodium phosphate monobasic, phosphoric acid, propylene glycol, water and sodium hydroxide

Route of administration: topical to the skin

Previous clinical experience:

Lotrisone lotion is similar to the previously approved Lotrisone cream. Both products contain the same concentrations of active ingredients and both contain the same inactive ingredients.

Introduction and drug history:

This NDA was originally submitted on August 31, 1989 and was issued an approvable letter on July 31, 1991. At the time of the approvable letter, there were no outstanding pharmacology/toxicology issues.

Labeling Review:

The labeling sections most relevant to the pharm/tox discipline proposed by the sponsor are listed below in normal font. My comments are written in *Italics*.

C _____

Comment: It is not clear that the chronic oral dosing study with clotrimazole in rats was a carcinogenicity study. If it was not, then it is not appropriate to state that this study has not revealed any carcinogenic effect.

Betamethasone was negative in the bacterial mutagenicity assay (Salmonella and Escherichia), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone, _____

Comment: Published studies have shown dexamethasone and hydrocortisone to be negative in bacterial mutagenicity studies but positive in other *in vitro* and *in vivo* genotoxicity studies. However, it is not clear that this is widely accepted as a "class

effect" of glucocorticoids. Describing these genotoxic effects as class effects may decrease the level of concern assigned to these effects. It is recommended that the final sentence of this paragraph be deleted or that it read: "This pattern of response is similar to that of dexamethasone and hydrocortisone."

In genotoxicity testing of clotrimazole, chromosomes of the spermatophores of Chinese hamsters which had been exposed to five daily oral clotrimazole doses of 100 mg/kg body weight were examined for structural changes during the metaphase.

Comment: These two paragraphs appear to be describing the same study. One of the paragraphs should be deleted. The first paragraph was the one that was listed in the approvable letter.

Comment: The label in the approvable letter included the following paragraphs in this section.

These paragraphs were deleted in the current version of the label. The sponsor states that these descriptions were deleted since they were inappropriately included in this section. Since this section includes fertility information, it is not clear why the sponsor believes this is not the appropriate section to include this information. Other labels of Schering betamethasone dipropionate products contain descriptions of intramuscular studies in rabbits, mice and rats such as the following sentence from the Diprolene label, "Studies in rabbits, mice and rats using intramuscular doses up to 1.0, 33 and 2.0 mg/kg, respectively, resulted in dose related increases in fetal resorptions in the rabbits and mice." The rabbit and mouse studies are probably the same as those described in the Lotrisone lotion label in the original approvable letter. It seems appropriate to include a description of these studies in the current label in the Carcinogenesis,

Mutagenesis and Impairment of Fertility section. The Segment I study in rats using oral dosing of clotrimazole that is described in the current label may be the same rat study referred to in the approvable letter. Therefore, the wording describing the oral clotrimazole rat study in the approvable letter could be deleted in favor of the more complete description now provided in the current label. However, the oral clotrimazole study in mice in which decreased litter size was observed does not appear to be described in the current label and so this information should be retained. An examination of the pharm/tox review of NDA 18-813 for Lotrimin lotion shows that the decreased litter size was observed in mice receiving oral clotrimazole at dose of 120 mg/kg and higher.

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Comment: The sponsor included two references to support this paragraph; however, the references do not seem to support this strong a restriction. The references submitted discuss the dangers of using solutions containing benzyl alcohol to rinse catheters being used in infants. One of the submitted references states that toxicity from benzyl alcohol appears to have been caused by large daily doses of benzyl alcohol per kilogram of body weight; daily intake in these cases ranged from 99-404 mg/kg/day. Lotrisone lotion contains 1% benzyl alcohol, which is 10 mg/g. The label states that no more than 45 ml of Lotrisone lotion should be used per week. This is approximately 6.4 g per day, which would be 64 mg benzyl alcohol/day. If all of the benzyl alcohol was absorbed and all of it was transferred to the infant via breast milk, the dose would still be less than the doses associated with toxicity. Published information indicates that benzyl alcohol can penetrate across the skin. For example, in one in vitro study, up to 33% of the applied dose of benzyl alcohol penetrated across human skin over 5 days. Benzyl alcohol is metabolized to benzoic acid in the liver, conjugated to glycine and excreted in the urine. Therefore, it seems unlikely that all of the applied benzyl alcohol would be absorbed and transferred to a nursing infant. This issue has been discussed with the medical officer, Dr. Markham Luke.

In addition to the above comments, the various doses used in the animal reproductive toxicity studies should also be expressed as the human dose multiple based on a mg/m² comparison.

Additional nonlabeling issues:

The reviewing chemist for this NDA has noted the possible presence of _____ as a degradation product of clotrimazole. Clotrimazole can breakdown into equimolar amounts of _____.

The specification for _____
There is no specification for _____
but it would be expected to be present at the same concentration as _____
These are not new impurities. For example, the
specification for _____ in Lotrisone cream is also _____
Because these impurities have been present in the previously approved product, they may be considered to be adequately qualified.

Conclusions:

The NDA remains approvable from a pharm/tox perspective with the suggested changes to the label.

Recommendations:

The following bullets summarize the suggested changes to the pharmacology and toxicology relevant sections of the label:

1. It is not appropriate to include the comment that the _____ . Therefore this statement should be deleted. The beginning of the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section should be reworded to reflect that

neither the combination of clotrimazole with betamethasone dipropionate nor the individual agents have been evaluated for carcinogenicity.

2. The description of the betamethasone genotoxicity should not refer to this as a class effect of glucocorticoids since it is not clear that this is true.
3. In the electronic version of the label available to the reviewer there were two similar paragraphs describing the *in vivo* Chinese hamster genotoxicity study. One of these paragraphs should be deleted.
4. The sponsor has deleted some impairment of fertility information from the label that should be restored.
5. In addition to the actual doses used in the reproductive toxicity studies, a human dose multiple based on a mg/m^2 comparison should be included for each study.

The following paragraphs provide suggested wording for the relevant label sections: **Carcinogenesis, Mutagenesis, Impairment of Fertility:** There are no laboratory animal studies with either the combination of clotrimazole and betamethasone dipropionate or with either component individually to evaluate carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (Salmonella and Escherichia), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone.

In genotoxicity testing of clotrimazole, chromosomes of the spermatophores of Chinese hamsters, which had been exposed to five daily oral clotrimazole doses of 100 mg/kg body weight, were examined for structural changes during the metaphase. The results of this study showed that clotrimazole had no mutagenic effect.

Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular route and in mice up to 33 mg/kg by the intramuscular route indicated no impairment of fertility except for dose-related increases in fetal resorption rates in both species. These doses are approximately 5 and 38 fold the human dose based on a mg/m^2 comparison, respectively.

Oral doses of clotrimazole in mice resulted in decreased litter size at doses of 120 mg/kg and higher. This dose is approximately 10 fold the human dose based on a mg/m^2 comparison.

A Segment I (fertility and general reproduction) study of clotrimazole was conducted in rats. Males and females were dosed orally (diet admixture) at doses of 5, 10, 25 or 50 mg/kg/day for 10 weeks prior to mating. At 50 mg/kg (approximately 8 times the human dose based on a mg/m^2 comparison), there was an adverse effect on maternal body weight gain and rearing of the offspring. Doses of 25 mg/kg (approximately 4 times the human dose based on a mg/m^2 comparison) and lower were well tolerated and produced no adverse effects on fertility or reproduction.

Pregnancy Category C: There have been no teratogenic studies performed in animals or humans with the combination of clotrimazole and betamethasone dipropionate.

A Segment II (teratology) study in pregnant rats with intravaginal doses up to 100 mg/kg clotrimazole have revealed no evidence of harm to the fetus. This dose is approximately 17 fold the human dose based on a mg/m² comparison.

Segment II (teratology) studies of clotrimazole were conducted by the oral (gavage) route in rats, mice, and rabbits. In rats administered 25, 50, 100, or 200 mg/kg/day, no increase in malformations was seen at doses up to 200 mg/kg. Doses of 100 and 200 mg/kg were embryotoxic (increased resorptions) as well as maternally toxic, while doses of 25 and 50 mg/kg were well tolerated by both the dams and the fetuses. These doses are approximately 4, 8, 17 and 34 fold the human dose based on a mg/m² comparison, respectively.

In pregnant mice, clotrimazole at oral doses of 25, 50, 100, or 200 mg/kg/day was not teratogenic and was well tolerated by both the dams and the fetuses. These doses are approximately 2, 4, 8 and 17 fold the human dose based on a mg/m² comparison, respectively. No evidence of maternal toxicity or embryotoxicity was seen in pregnant rabbits dosed orally with 60, 120, or 180 mg/kg/day. These doses are approximately 20, 40 and 61 fold the human dose based on a mg/m² comparison, respectively.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately the human dose based on a mg/m² comparison. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

one ✓
S. & W.
/S/

Betamethasone dipropionate has not been tested for teratogenic potential by the dermal route of administration. Other corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroids production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to product detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOTRISONE Lotion is administered to a nursing woman.

~~_____~~
~~_____~~

Note: These recommendations and suggested wording may be conveyed to the sponsor or incorporated into the label at the time of the Division labeling meeting.

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3/10/00

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:
NDA 20-010
HFD-340
HFD-540
HFD-540/Pharm/Brown
HFD-540/TL/Jacobs
HFD-540/MO/Luke
HFD-540/Chem/Turujman
HFD-540/PM/Cross

Concurrence Only:
HFD-540/DD/Wilkin

HFD-540/TL/Jacobs a.g. INDFS 3/13/00

Draft date (# of drafts): March 10, 2000 (1st draft)

Appendix/attachments:
Appendix 1: Dose multiple calculations.

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3/30/00
A minor change on p.7 to
facilitate rapid comprehension
does not alter the
meaning of the original.
DFG ✓

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 1: Dose multiple calculations.

Maximum human dose:

$$\frac{45 \text{ ml lotion / week}}{7 \text{ days / week}} = 6.4 \text{ g lotion / day (assumes density of 1 g/ml)}$$

For betamethasone dipropionate:

$$6.4 \text{ g lotion / day} \times 0.0643\% = 4.1 \text{ mg betamethasone dipropionate / day}$$

$$\frac{4.1 \text{ mg / day}}{60 \text{ kg}} = 0.07 \text{ mg / kg / day (assumes 60 kg human)}$$

$$0.07 \text{ mg / kg / day} \times 37 = 2.59 \text{ mg / m}^2 \text{ / day (km = 37)}$$

Human to animal dose comparison based on body surface area.

Dose in mg/kg	Dose in mg/m ² (mg/kg × km)	Multiple of human dose (mg/m ² ÷ 2.59 mg/m ²)
Mouse (km = 3)		
33	99	38.22
Rabbit (km = 12)		
0.05	0.6	0.23
1.0	12.0	4.63

For clotrimazole:

$$6.4 \text{ g lotion / day} \times 1.0\% = 64 \text{ mg clotrimazole / day}$$

$$\frac{64 \text{ mg / day}}{60 \text{ kg}} = 1.07 \text{ mg / kg / day (assumes 60 kg human)}$$

$$1.07 \text{ mg / kg / day} \times 37 = 39.59 \text{ mg / m}^2 \text{ / day (km = 37)}$$

Human to animal dose comparison based on body surface area.

Dose in mg/kg	Dose in mg/m ² (mg/kg × km)	Multiple of human dose (mg/m ² ÷ 35.59 mg/m ²)
Mouse (km = 3)		
25	75	2.11
50	150	4.21
100	300	8.43
120	360	10.11
200	600	16.86
Rat (km = 6)		

5	30	0.84
10	60	1.69
25	150	4.21
50	300	8.43
100	600	16.86
200	1200	33.72
Rabbit ($km = 12$)		
60	720	20.23
120	1440	40.46
180	2160	60.69

**APPEARS THIS WAY
ON ORIGINAL**