CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-691/S-019

17-691/S-024

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

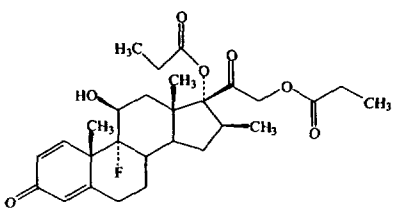
NDA number: 17-691
Serial number/date/type of submission: SE8-024 / 4 October 2000 /
SE5-024 / 31 May 2001 / BZ
000/ 21 May 2001 / NC

Information to sponsor: Yes
Sponsor (or agent): Schering Corporation

Reviewer Name: Paul C. Brown
Division Name: Division of Dermatologic and Dental Drug Products
HFD#540
Review Completion Date: August 2, 2001

Drug:

Code Name: SCH11460
Generic Name: betamethasone dipropionate
Trade Name: Diprosone® Ointment
Chemical Name: 9-fluoro-11 beta, 17, 21-trihydroxy-16 beta-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=504.59
Structure:



Related NDAs: NDA 16-322, NDA 16-740, NDA 16-932, NDA 17-536, NDA 17-781, NDA 17-829, NDA 19-408, NDA 19-716, NDA 18-741, NDA 19-555

Drug Class: corticosteroid

Indication: Corticosteroid responsive dermatoses

Clinical formulation: 0.05% ointment

Route of administration: topical

Introduction and drug history:
This NDA is for an approved drug product. The sponsor has conducted several clinical studies in pediatric patients and the submissions dated 10/4/00 and 5/31/01 are a labeling supplement to include information from these studies in a revised label.

A pharm/tox review for this NDA was written, dated 8 April 1999, in which revisions to the Carcinogenesis, Mutagenesis and Impairment of Fertility section of the label were recommended. The sponsor had conducted three genotoxicity studies and submitted the reports of these studies to this and several other NDA's for betamethasone containing products. It was recommended at that time that the sponsor revise future versions of labels for products containing betamethasone to include the specific genotoxicity information about betamethasone. The submission dated 5/21/01 contains updated wording for the Carcinogenesis, Mutagenesis and Impairment of Fertility section of the label which now incorporates information about the genotoxic assays conducted with betamethasone.

Discussion:
In the 5/21/01 submission, the sponsor has proposed the following changes in the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the label. Deletions are marked with strikeout text and additions are highlighted.

> Long term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.
>
> ~~Studies to determine mutagenicity with prednisolone have revealed negative results.~~ Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), 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.

These changes add the genotoxicity information about betamethasone to the label. However, there are fertility data about betamethasone that should also be incorporated into this section of the label. Changes in the first sentence of this section are also recommended. Below are suggested changes for the first sentence of the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the label and an additional sentence about the effects of betamethasone on fertility that should be added immediately after the description of the genotoxicity assays. Additions are highlighted and deletions are indicated by strikeout text.

> Long-term animal studies have not been performed to evaluate the carcinogenic potential ~~or the effect on fertility~~ of ~~topical corticosteroids~~ betamethasone dipropionate.
>
> Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0~~m~~g/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 0.5 and 4 fold the estimated maximum human dose based on a mg/m^2 comparison, respectively.

The sentences used to describe the genotoxicity and fertility information are similar to those recently found acceptable for Lotrisone Lotion (Letter signed 12/8/00, NDA 20-010), which is another Schering product that contains betamethasone dipropionate. These modifications are also consistent with changes recommended for other Schering betamethasone containing products. The primary difference from the Lotrisone label is the dose multiple calculation for the fertility

data. For Lotrisone the dose multiples were calculated based on the limit for the maximum amount of drug to be used as described in the label (45 g or ml per week). For Diprosone Ointment no limit on the amount of drug to be used is included in the label. Therefore, the maximum use was assumed to be whole body application twice per day (see appendix for dose multiple calculations).

The Pregnancy section of the label is similar to the labels of other topical corticosteroids. The teratogenic potential of betamethasone dipropionate has been tested in rabbits and this information has been included in the label for Lotrisone. This information should be included in the label for Diprosone Ointment as shown below.

> 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 0.03 fold the estimated maximum human dose based on a mg/m^2 comparison. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

This information may be included in addition to the pregnancy information proposed by the sponsor.

Conclusion:
The sponsor should include the specific genotoxicity, fertility and teratogenicity information about betamethasone in the label of Diprosone Ointment.

Recommendations:
The text for the Carcinogenesis, Mutagenesis, and Impairment of Fertility section and the Pregnancy section shown below should be used in the label for Diprosone Ointment. This incorporates genotoxicity, fertility and teratogenicity information about betamethasone into the label and makes the label consistent with other Schering betamethasone containing products. This may be done after an overall review of the label involving all disciplines via a Division labeling meeting. (*Note: This information was incorporated into a draft label for this NDA during a labeling meeting on 8/1/01.)*

> **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.
>
> Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), 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.
>
> 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 0.5 and 4 fold the estimated maximum human dose based on a mg/m^2 comparison, respectively.

Pregnancy: Teratogenic effects: Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

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 0.03 fold the estimated maximum human dose based on a mg/m^2 comparison. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:
NDA 17-691
HFD-340
HFD-540
HFD-540/Pharm/Brown
HFD-540/Sup./Jacobs
HFD-540/MO/Cook
HFD-540/Chem/Pappas
HFD-540/PM/Cintron

Concurrence Only:
HFD-540/DD/Wilkin

HFD-540/Sup./Jacobs

Draft date (# of drafts): August 2, 2001 (1st draft)

Appendix 1: Dose multiple calculations.

Maximum human dose:

Total body coverage requires approximately 30 g of product. Twice per day application would result in a daily dose of 60 g.

For betamethasone dipropionate:

$$60\text{ g ointment/day} \times \frac{0.643\text{ mg betamethasone diproprionate}}{1\text{ g ointment}} = 38.58\text{ mg betamethasone dipropionate/day}$$

$$\frac{38.58\text{ mg/day}}{60\text{ kg}} = 0.643\text{ mg /kg/day} \qquad \text{(assumes 60 kg human)}$$

$$0.643\text{ mg/kg/day} \times 37 = 23.8\text{ mg/m}^2\text{/day} \quad (km = 37)$$

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 ($mg/m^2 \div 23.8\ mg/m^2$)
Mouse (*km* = 3)		
33	99	4.16
Rabbit (*km* = 12)		
0.05	0.6	0.03
1.0	12.0	0.50