CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-691/S-019

17-691/S-024

APPROVED DRAFT LABELING

XXXXXXXXX

PRODUCT

INFORMATION

DIPROSONE®

brand of betamethasone

dipropionate

Ointment, USP 0.05%

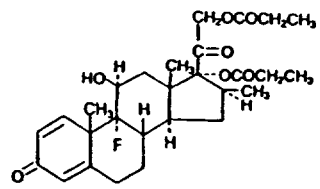
(potency expressed as betamethasone)

For Dermatologic Use Only-

Not for Ophthalmic Use

DESCRIPTION DIPROSONE Ointment contains betamethasone dipropionate, USP, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has high corticosteroid activity and slight mineralocorticoid activity. Betamethasone dipropionate is the 17, 21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of DIPROSONE Ointment 0.05% contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil, USP; and white petrolatum, USP.

CLINICAL PHARMACOLOGY The corticosteroids are a class of compounds comprising steroid hormones, secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See **DOSAGE AND ADMINISTRATION.**)

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See **DOSAGE AND ADMINISTRATION.**)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Eighty pediatric patients ages 6 months to 12 years, with atopic dermatitis, were enrolled in an open-label hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Ointment was applied twice daily for 2 to 3 weeks over a mean body surface area of 58% (range 35% to 99%). In 15 of 53 (28%) evaluable patients, adrenal suppression was indicated by either a pre-stimulated cortisol concentration $\leq$ 5 mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol $\leq$ 18 mcg/dL and an increase of $<$ 7 mcg/dL from the baseline cortisol. Follow-up testing 2 weeks after study

completion available for 2 of the 15 patients demonstrated a normally responsive HPA axis.

Studies performed with DIPROSONE Ointment indicate that it is in the high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE DIPROSONE Ointment is a high-potency corticosteroid indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive-dermatoses in patients 13 years and older.

CONTRAINDICATIONS DIPROSONE Ointment in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in these preparations.

PRECAUTIONS General Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure. (See **DOSAGE AND ADMINISTRATION.**)

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary-free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. In an open-label pediatric study of 53 evaluable patients, of the 15 patients who showed evidence of suppression, 2 patients were tested 2 weeks after discontinuation of DIPROSONE Ointment, and both patients showed recovery of

HPA axis function. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Pediatric patients may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. **(See PRECAUTIONS - Pediatric Use.)**

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for Patients This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

2. Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.

3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive. (See **DOSAGE AND ADMINISTRATION.**)

4. Patients should report any signs of local adverse reactions.

5. Other corticosteroid-containing products should not be used with DIPROSONE Ointment without first talking to your physician.

Laboratory Tests The following tests may be helpful in evaluating HPA axis suppression:

Urinary-free cortisol test

ACTH stimulation test

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

ADVERSE REACTIONS The following local adverse reactions are reported infrequently when DIPROSONE Ointment is used as recommended in the **DOSAGE AND ADMINISTRATION** section. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

Adverse reactions reported to be possibly or probably related to treatment with DIPROSONE Ointment during a pediatric clinical study include signs of skin atrophy (telangiectasia, thinness, shininess, bruising, loss of skin markings). Cutaneous atrophy of the face ocurred in 1/6 (17%) of infants, 2/9 (22%) of 2-5 year olds, and 2/6 (33%) of the 6-8 year olds. Non-facial atrophy occurred in 15%, 8%, and 9% of 2-5 year olds, 6-8 year olds, and 9-12 year olds, respectively. Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

OVERDOSAGE Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS.**)

DOSAGE AND ADMINISTRATION Apply a thin film of DIPROSONE Ointment 0.05% to the affected skin areas once daily. In some cases, a twice-daily dosage may be necessary.

DIPROSONE Ointment is not to be used with occlusive dressings.

HOW SUPPLIED DIPROSONE Ointment 0.05% is supplied in 15-g (NDC 0085-0510-04) and 45-g (NDC 0085-0510-06) tubes; boxes of one.

Store DIPROSONE Ointment between 2° and 30°C (36° and 86°F).

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 5/01

B-XXXXXXXX

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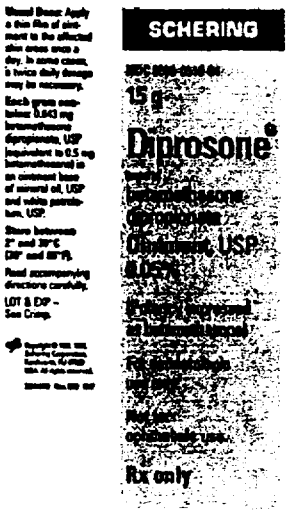
Diprosone Ointment

Label for 15-g Tube

22124013



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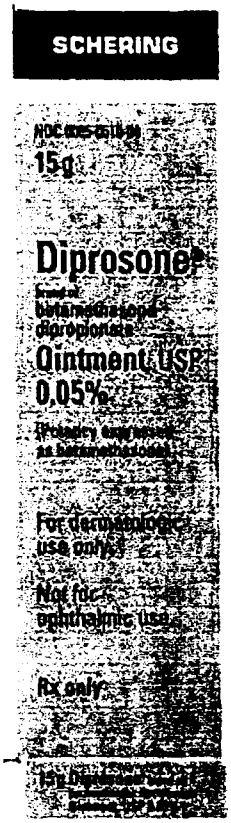
SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Ointment

Carton for 15-g Tube

13284059

DIE1031



REXAM

SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Ointment

Carton for 15-g Tube

13284059

15g DIPROSONE® brand of betamethasone dipropionate USP 0.05%

Usual Dose: Apply a thin film of ointment to the affected skin areas once a day. In some cases, a twice daily dosage may be necessary.

Each gram contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil, USP and white petrolatum, USP.

Store between 2° and 30°C (36° and 86°F).

Read accompanying directions carefully.

6505-01-034-3651

SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Ointment

Label for 45-g Tube

22124714

Usual Dose: Apply a thin film of ointment to the affected skin areas once a day. In some cases, a twice daily dosage may be necessary.

Each gram contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil, USP and white petrolatum, USP.

Store between 2° and 30°C (36° and 86°F).

Read accompanying directions carefully.

LOT & EXP – See Crimp.

22124714 Rev. 5/99 1548

SCHERING

NDC 0085-0510-06

45 g

Diprosone®

brand of

betamethasone dipropionate

Ointment, USP

0.05%

(Potency expressed as betamethasone)

For dermatologic use only.

Not for ophthalmic use.

Rx only

[redacted]

SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Ointment

Carton for 45-g Tube

13237654

SCHERING

6505-01-035-6358

NDC 0085-0510-06

45 g.

Diprosone®

brand of
betamethasone
dipropionate

Ointment, USP
0.05%

(Potency expressed
as betamethasone)

For dermatologic
use only.

Not for
ophthalmic use.

Rx only

DIE 1012

45 g.
Diprosone®
brand of betamethasone dipropionate
Ointment, USP 0.05%

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RESEARCH INSTITUTE

Diprosone Ointment

Carton for 45-g Tube

13237654

45 g
Diprosone®
betamethasone dipropionate
Ointment, USP 0.05%

Usual Dose: Apply a thin film of ointment to the affected skin areas once a day. In some cases, a twice daily dosage may be necessary.

Each gram contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil, USP and white petrolatum, USP.

Store between 2° and 30°C (36° and 86°F).

Read accompanying directions carefully.

13237654 Rev. 5/99

REXAM

SCHERING-

TUTE