

XXXXXXXXXX
PRODUCT
INFORMATION

DIPROSONE®

brand of betamethasone

dipropionate

Ointment, USP 0.05%

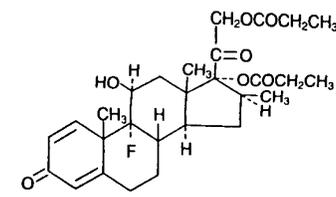
(potency expressed as betamethasone)

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-11 β ,17,21-trihydroxy-16 β -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 ≤ 5 mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤ 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/m² 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/m² 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.

Nursing Mothers It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

Pediatric Use DIPROSONE Ointment is not recommended in pediatric patients 12 years of age and younger. (See **CLINICAL PHARMACOLOGY** and **ADVERSE REACTIONS** Sections.)

In an open label study, 15 of 53 (28%) evaluable pediatric patients (aged 6 months – 12 years old) using DIPROSONE Ointment for treatment of atopic dermatitis demonstrated HPA axis suppression. The proportion of patients with adrenal suppression in this study was progressively greater, the younger the age group. (See **CLINICAL PHARMACOLOGY - Pharmacokinetics**.) Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. The study described above supports this premise as adrenal suppression in 9-12 year olds, 6-8 year olds, 2-5 year olds, and 3 months – 1 year old was 17%, 27%, 29%, and 36%, respectively.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

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 occurred 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

YYYYYYYYYY

Copyright © 1974, 1991, 1999, 2001

Schering Corporation. All rights reserved.

DIVISION OF DERMATOLOGIC AND DENTAL DRUGS
NDA 17-691

1

AUGUST 2, 2001

Diprosone Ointment
Label for 15-g Tube

22124013

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.

Copyright © 1991, 1998,
Schering Corporation,
Kenilworth, NJ 07033
USA. All rights reserved.
22124013 Rev. 5/98 1547



SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Ointment
Carton for 15-g Tube

13284059

DIE1031



REXAM

17



SCHERING-PLOUGH RESEARCH INSTITUTE

DIVISION OF DERMATOLOGIC AND DENTAL DRUGS
NDA 17-691

2

AUGUST 2, 2001

Diprosone Ointment
Carton for 15-g Tube

13284059



15g Diprosone[®] brand of
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.

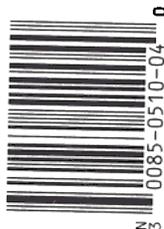
Each gram contains:
0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil, USP and white petrolatum, USP.

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

Read accompanying directions carefully.

Copyright © 1986, 1991,
Schering Corporation,
Kenilworth, NJ 07033 USA.
All rights reserved.

6505-01-034-3651



13284059

Rev. 5/99



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.

 Copyright © 1991, 1999,
Schering Corporation,
Kenilworth, NJ 07033
USA. All rights reserved.

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



SCHERING-PLOUGH RESEARCH INSTITUTE

DIVISION OF DERMATOLOGIC AND DENTAL DRUGS
NDA 17-691

14

AUGUST 2, 2001

Diprosone Ointment
Carton for 45-g Tube

13237654

6505-01-035-6358

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

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

DIE 1012



/ RESEARCH INSTITUTE

DIVISION OF DERMATOLOGIC AND DENTAL DRUGS
NDA 17-691

4

AUGUST 2, 2001

Diprosone Ointment
Carton for 45-g Tube
13237654



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.



 Copyright © 1991,
Schering Corporation,
Kenilworth, NJ 07033 USA.
All rights reserved.

13237654 Rev. 5/99

REXAM

16



TUTE

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jonathan Wilkin
10/3/01 10:05:54 AM