

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

17-781/S-015

17-781/S-022

APPROVED DRAFT LABELING

XXXXXXXXXX
PRODUCT
INFORMATION

DIPROSONE®

brand of betamethasone

dipropionate

Lotion, USP 0.05% w/w

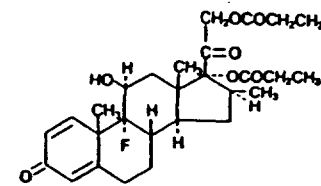
(potency expressed as betamethasone)

For Dermatologic Use Only-

Not for Ophthalmic Use

DESCRIPTION DIPROSONE Lotion 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 C₂₈H₃₇FO₇, 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 Lotion 0.05% w/w contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in a lotion base of isopropyl alcohol, USP (39.25%) and purified water, USP; slightly thickened with carbomer 974P; the pH is adjusted to approximately 4.7 with sodium hydroxide.

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.

Twenty-five pediatric patients ages 6 to 12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Lotion was applied twice daily for 2 to 3 weeks over a mean body surface area of 45% (range 35% to 72%). In 11 of 15 (73%) evaluable patients, adrenal suppression was indicated by either a ≤ 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. Studies performed with DIPROSONE Lotion indicate that it is in the medium range of potency as compared with other topical corticosteroids.

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

CONTRAINDICATIONS DIPROSONE Lotion is contraindicated 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 15 evaluable patients, of the 11 subjects who showed evidence of suppression, 6 subjects were tested 2 weeks after discontinuation of DIPROSONE Lotion, 0.05%, and 4 of the 6 (67%) had complete 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 Lotion 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 Use of DIPROSONE Lotion, 0.05% in pediatric patients 12 years of age and younger is not recommended. (See **CLINICAL PHARMACOLOGY** and **ADVERSE REACTIONS** Sections.) In an open-label study, 11 of 15 (73%) evaluable pediatric patients (aged 6 years-12 years old) using DIPROSONE Lotion for treatment of atopic dermatitis for 2-3 weeks demonstrated adrenal suppression. (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.

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 Lotion 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 Lotion during a pediatric study include: paresthesia (burning), erythema, erythematous rash, and dry skin. These adverse reactions each occurred in a different patient; 4% of the 25 patient population, respectively. An adverse reaction reported to be possibly or probably related to treatment in 2 different patients, 8%, of the 25 patients is puritis.

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 few drops of DIPROSONE Lotion to the affected area and massage lightly until it disappears. Apply twice daily, in the morning and at night. For the most effective and economical use, apply nozzle very close to affected area and gently squeeze bottle.

DIPROSONE Lotion is not to be used with occlusive dressings.

HOW SUPPLIED DIPROSONE Lotion 0.05% w/w is available in 20-mL (18.7-g) (NDC 0085-0028-04) and 60-mL (56.2-g) (NDC 0085-0028-06) plastic squeeze bottles; boxes of one. **Protect from light. Store in carton until contents are used.**

Store DIPROSONE Lotion 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 Lotion
Label for 20-mL Tube
21047821

US Df

Read the accompanying directions carefully.
Keep out of reach of children.
Do not use if the cap is missing or the tube is damaged.
Do not use if the expiration date has expired.
Do not use if the lotion is discolored or contains particles.
Do not use if the tube is swollen or leaking.
Do not use if the tube is damaged.
Do not use if the tube is leaking.
Do not use if the tube is damaged.
Do not use if the tube is leaking.

SCHERING

20 mL (0.7 fl. oz.) of Diprosone Lotion USP 0.05% w/v

For Administration only. For further information, see the accompanying literature.

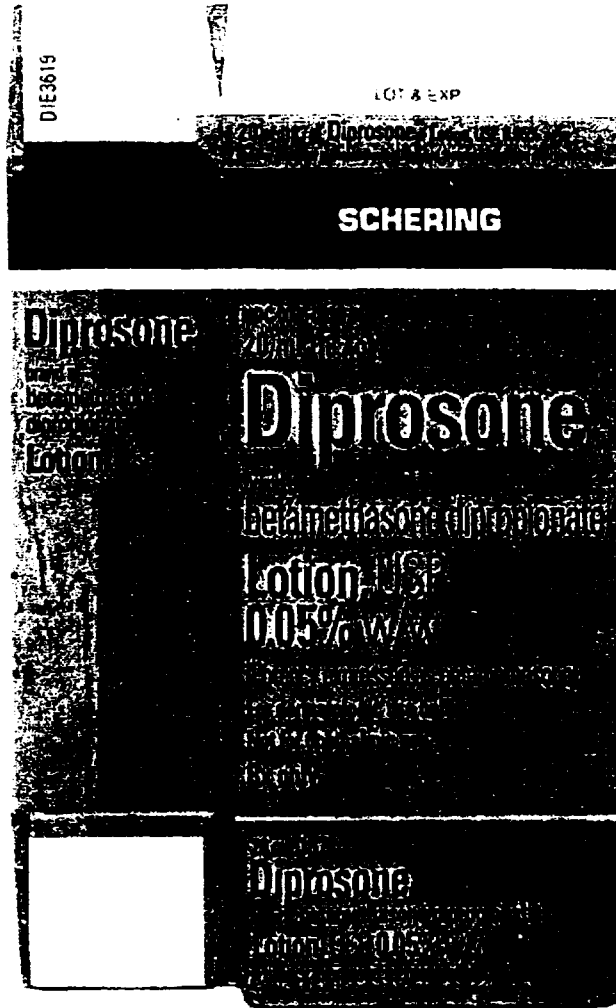
Rx only

Read the accompanying directions carefully.
Keep out of reach of children.
Do not use if the cap is missing or the tube is damaged.
Do not use if the expiration date has expired.
Do not use if the lotion is discolored or contains particles.
Do not use if the tube is swollen or leaking.
Do not use if the tube is damaged.
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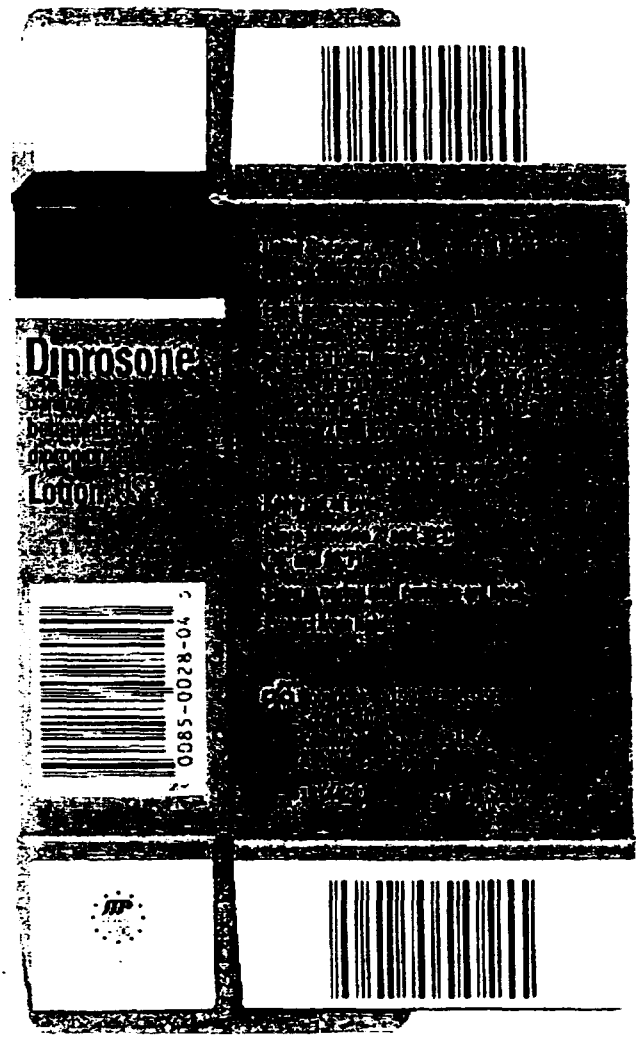
SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Lotion
Carton for 20-mL Tube
18144247



SCHERING-PLOUGH RESEARCH INSTITUTE

Diprosone Lotion
Carton for 20-mL Tube
18144247



Diprosone Lotion
Label for 60-mL Tube

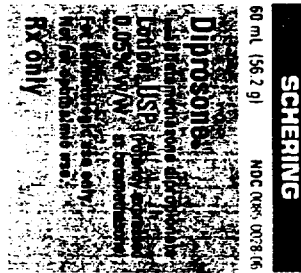
18249820

LOT
EXP

Keep out of eyes.
Store between 2° and 30°C
(36° and 86°F). Protect from light.
Store in carton until contents are used.
Read accompanying directions carefully.

18249820 Rev. 5/99

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Usual Dosage: Apply a few drops of lotion to the affected skin areas twice daily.

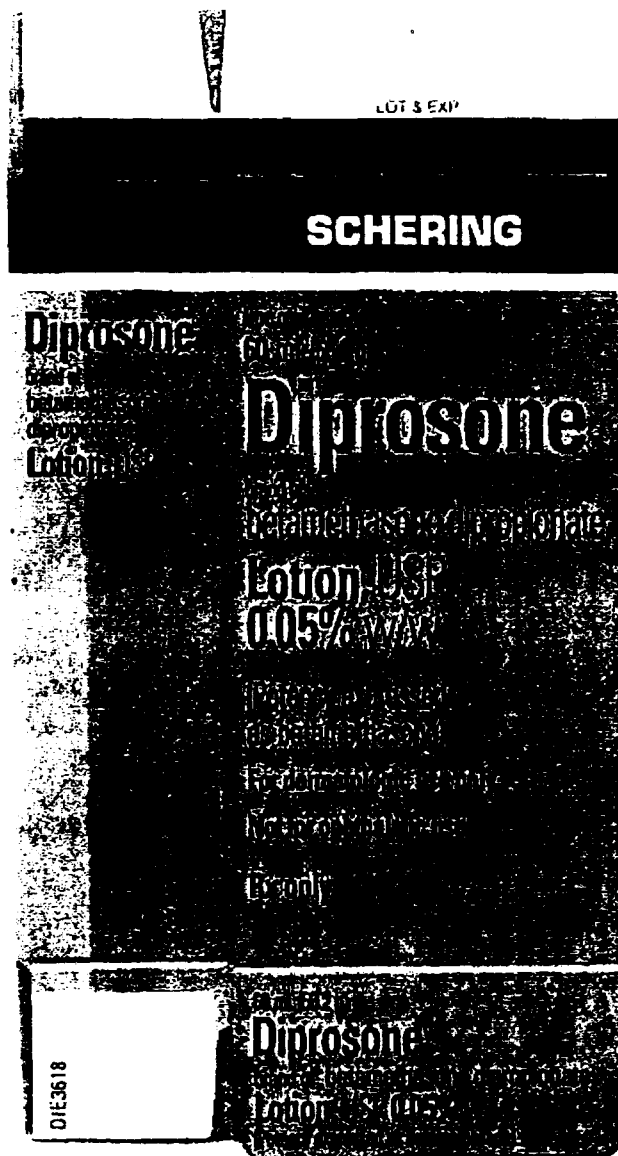
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Diprosone Lotion
Carton for 60-mL Tube

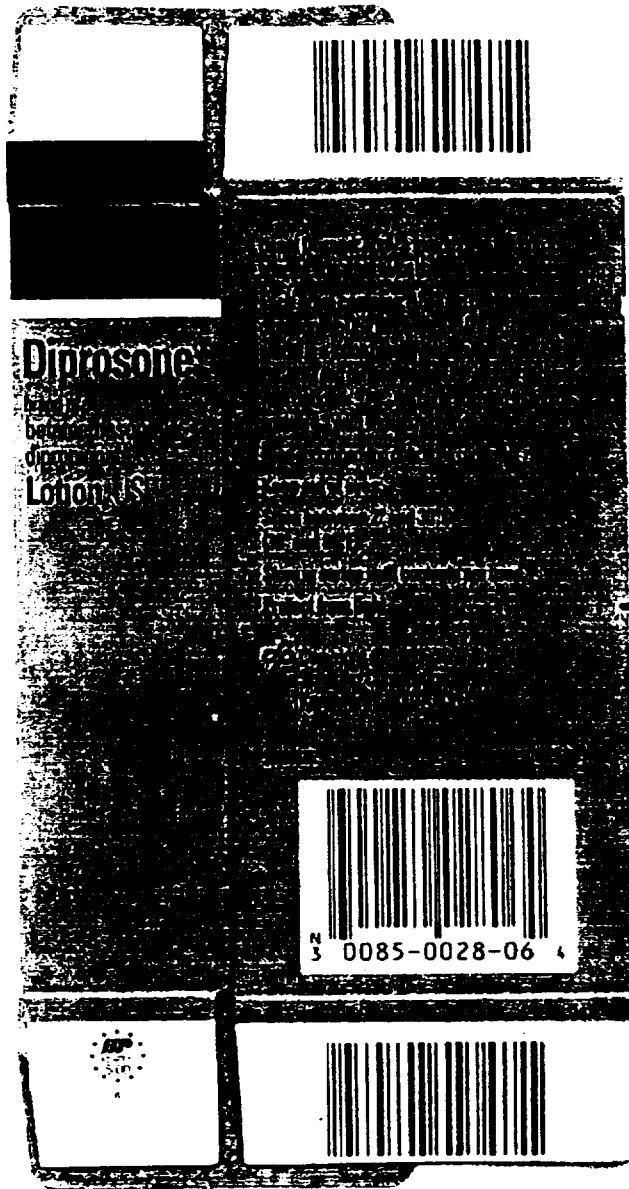
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Diprosone Lotion
Carton for 60-mL Tube

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