DIPROLENE®

Brand of augmented betamethasone dipropionate lotion*

Lotion 0.05% (potency expressed as betamethasone)

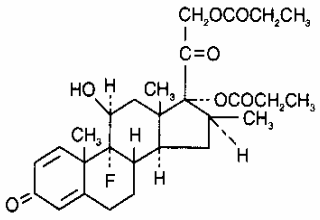
* Vehicle augments the penetration of the steroid.

For Dermatologic Use Only

Not for Ophthalmic Use

DESCRIPTION DIPROLENE® (augmented betamethasone dipropionate lotion) Lotion contains betamethasone dipropionate, USP, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has a high degree of corticosteroid activity and a slight degree of 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:



It is a white to creamy-white, odorless powder insoluble in water; freely soluble in acetone and in chloroform; sparingly soluble in alcohol.

Each gram of DIPROLENE Lotion 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in an augmented lotion base of purified water; isopropyl alcohol (30%); hydroxypropylcellulose; propylene glycol; sodium phosphate; phosphoric acid and sodium hydroxide used to adjust the pH.

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** section).

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

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

Studies performed with DIPROLENE Lotion indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE DIPROLENE Lotion is a super-high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older. The total dose should not exceed 50 mL per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

CONTRAINDICATIONS DIPROLENE Lotion is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS Systemic absorption of topical corticosteroids has produced reversible 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 corticosteroids, 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** section.)

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. Patients should not be treated with amounts of DIPROLENE Lotion greater than 50 mL per week because of the potential for the drug to suppress HPA axis. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time and only small areas should be treated at any one time due to the increased risk of HPA axis suppression.

DIPROLENE Lotion was applied once daily at 7 mL per day for 21 days to diseased scalp and body skin in patients with scalp psoriasis to study its effects on the HPA axis. In 2 out of 11 patients, the drug lowered plasma cortisol levels below normal limits. HPA axis suppression in these patients was transient and returned to normal within a week. In one of these patients, plasma cortisol levels returned to normal while treatment continued.

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.

DIPROLENE Lotion should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin or in the axillae.

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

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.

2. This medication should not be used 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, so as to be occlusive (See DOSAGE AND ADMINISTRATION section). .
4. Patients should report to their physician any signs of local adverse reactions.
5. Patients should be advised not to use DIPROLENE Lotion in the treatment of diaper dermatitis. DIPROLENE Lotion should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing (See **DOSAGE AND ADMINISTRATION**).
6. This medication should not be used on the face, underarms, or groin areas unless directed by the physician.
7. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
8. Other corticosteroid-containing products should not be used with Diprolene Lotion.

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

ACTH stimulation test

Urinary free cortisol 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. Studies in rabbits, mice and rats using intramuscular doses up to 1, 33 and, 2, mg/kg, respectively, resulted in dose related increases in fetal resorptions in rabbits and mice.

Pregnancy: Teratogenic effects: Pregnancy category C. 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 in laboratory animals. 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 0.2 times the human topical dose of DIPROLENE Lotion in mg/m^2 of body surface area, assuming 100% absorption and the use in a 60 kg person of 7 g per day. The abnormalities observed included umbilical hernias, cephalocele and cleft palate. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. DIPROLENE Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Pediatric Use: Use of DIPROLENE Lotion, 0.05%, in pediatric patients 12 years of age and younger is not recommended. (See **CLINICAL PHARMACOLOGY and ADVERSE REACTIONS** sections.)

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 children receiving topical corticosteroids. Manifestations of adrenal suppression in children 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. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS The local adverse reactions which were reported with DIPROLENE Lotion during controlled clinical trials were as follows: erythema, folliculitis, pruritus and vesiculation each occurring in less than 1 % of patients.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae and miliaria.

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

DOSAGE AND ADMINISTRATION Apply a few drops of DIPROLENE Lotion to the affected skin once or twice daily and massage lightly until the lotion disappears.

DIPROLENE Lotion is a super-high potency topical corticosteroid. **Treatment with DIPROLENE Lotion should be limited to two weeks, and amounts greater than 50 mL per week should not be used.**

As with other highly active corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

DIPROLENE Lotion should not be used with occlusive dressings. DIPROLENE Lotion should not be applied to the diaper area if the patient requires diapers or plastic pants as these garments may constitute occlusive dressing.

HOW SUPPLIED DIPROLENE Lotion 0.05% is supplied in 30 mL (29g) (NDC 0085-0962-01), and 60 mL (58g) (NDC 0085-0962-02), plastic squeeze bottles; boxes of one.

Store between 2° and 25°C (36°and 77°F).

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