DIPROLENE®

**brand of augmented betamethasone dipropionate ointment***

**Ointment 0.05% (potency expressed as betamethasone)**

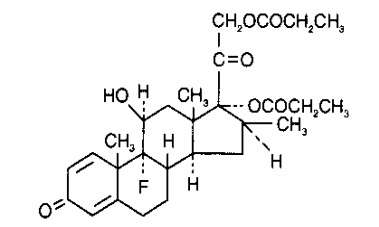
*Vehicle augments the penetration of the steroid.

**For Dermatologic Use Only -**

**Not for Ophthalmic Use**

**DESCRIPTION** DIPROLENE® (augmented betamethasone dipropionate ointment) Ointment 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 Ointment 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a vehicle of propylene glycol, propylene glycol stearate, white wax, and white petrolatum.

**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 Ointment indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

**INDICATIONS AND USAGE** DIPROLENE Ointment 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 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

**CONTRAINDICATIONS** DIPROLENE Ointment is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.
**PRECAUTIONS General:** 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 Ointment greater than 50 g 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 suppression.

At 14 g per day DIPROLENE Ointment was shown to depress the plasma levels of adrenal cortical hormones following repeated application to diseased skin in patients with psoriasis. These effects were reversible upon discontinuation of treatment. At 7 g per day DIPROLENE Ointment was shown to cause minimal inhibition of the HPA axis when applied 2 times daily for 2 to 3 weeks in healthy patients and in patients with psoriasis and eczematous disorders.

With 6 to 7 g of DIPROLENE Ointment applied once daily for 3 weeks, no significant inhibition of the HPA axis was observed in patients with psoriasis and atopic dermatitis, as measured by plasma cortisol and 24-hour urinary 17-hydroxy-corticosteroid levels. 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 Ointment 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.

l. 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, 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 Ointment in the treatment of diaper dermatitis. DIPROLENE Ointment 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 Ointment.

**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 Ointment 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 Ointment 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 Ointment is administered to a nursing woman.

**Pediatric Use:** Use of DIPROLENE Ointment, 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 an 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 Ointment 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.

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 DIPROLENE Ointment can be absorbed in sufficient amounts to produce systemic effects (See **PRECAUTIONS**).

**DOSAGE AND ADMINISTRATION** Apply a thin film of DIPROLENE Ointment to the affected skin once or twice daily. DIPROLENE Ointment is a super-high potency topical corticosteroid. **Treatment with DIPROLENE Ointment should be limited to 50 g per week.**

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

**DIPROLENE Ointment should not be used with occlusive dressings.** Diprolene Ointment 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** Ointment 0.05 % is supplied in 15 g (NDC 0085-0575-02), and 50 g (NDC 0085-0575-05) tubes; boxes of one.

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

Schering Corporation

Kenilworth, NJ 07033 USA



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Stanka Kukich

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