

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DIPROLENE AF Cream safely and effectively. See full prescribing information for DIPROLENE AF Cream.

DIPROLENE® AF (augmented betamethasone dipropionate) cream, for topical use
Initial U.S. Approval: 1983

RECENT MAJOR CHANGES

Warnings and Precautions

Ophthalmic Adverse Reactions (5.2) 05/2019

INDICATIONS AND USAGE

DIPROLENE AF Cream is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin film to the affected skin areas once or twice daily. (2)
- Discontinue therapy when control is achieved. (2)
- Use no more than 50 g per week. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

- Cream, 0.05% (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this medicine. (4)

WARNINGS AND PRECAUTIONS

- Effects on endocrine system: DIPROLENE AF Cream can cause reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. Risk factor(s) include the use of high-potency topical corticosteroids, use over a large surface area or to areas under occlusion, prolonged use, altered skin barrier, liver failure, and use in pediatric patients. Modify use should HPA axis suppression develop. (5.1, 8.4)
- Ophthalmic Adverse Reactions: DIPROLENE AF Cream may increase the risk of cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist for evaluation. (5.2)

ADVERSE REACTIONS

- The most common adverse reaction reported in 0.4% of adult patients is stinging. (6.1)
- The most common adverse reactions reported in 10% of pediatric patients are signs of skin atrophy, telangiectasia, bruising, shininess. (6.1, 8.4)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Effects on Endocrine System
 - 5.2 Ophthalmic Adverse Reactions
 - 5.3 Allergic Contact Dermatitis
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use

- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DIPROLENE® AF Cream is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years of age or older.

2 DOSAGE AND ADMINISTRATION

Apply a thin film of DIPROLENE AF Cream to the affected skin areas once or twice daily.

Therapy should be discontinued when control is achieved. DIPROLENE AF Cream is a high-potency corticosteroid. Treatment with DIPROLENE AF Cream should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis [see *Warnings and Precautions* (5.1)].

DIPROLENE AF Cream should not be used with occlusive dressings unless directed by a physician.

Avoid contact with eyes. Wash hands after each application.

Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

DIPROLENE AF Cream is for topical use only. It is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Cream, 0.05%. Each gram of DIPROLENE AF Cream, 0.05% contains 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a white cream base.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Endocrine System

DIPROLENE AF Cream can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or after withdrawal of treatment. Factors that predispose to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotrophic hormone (ACTH) stimulation test.

DIPROLENE AF Cream 0.05% was applied once daily at 7 grams per day for 1 week to diseased skin, in adult subjects with psoriasis or atopic dermatitis, to study its effects on the HPA axis. The results suggested that the drug lowered adrenal corticosteroid secretion, although plasma cortisol levels did not go below the lower limit of the normal range.

In an open-label pediatric trial of 60 evaluable subjects (3 months to 12 years of age), 19 subjects showed evidence of HPA axis suppression. Four (4) subjects were tested 2 weeks after discontinuation of DIPROLENE AF Cream 0.05%, and 3 of the 4 (75%) had complete recovery of HPA axis function. The proportion of subjects with adrenal suppression in this trial was progressively greater, the younger the age group.

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Cushing's syndrome and hyperglycemia may also occur with topical corticosteroids. These events are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios [see *Use in Specific Populations* (8.4)].

5.2 Ophthalmic Adverse Reactions

Use of topical corticosteroids, including DIPROLENE AF Cream, may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with

the use of topical corticosteroid products, including DIPROLENE AF Cream [see *Adverse Reactions* (6.2)].

Avoid contact of DIPROLENE AF Cream with eyes. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

5.3 Allergic Contact Dermatitis

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing. If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In controlled clinical trials, involving 242 adult subjects, the adverse reaction associated with the use of DIPROLENE AF Cream reported at a frequency of 0.4% was stinging. It occurred in 1 subject.

In a controlled clinical trial involving 67 pediatric subjects from 3 months to 12 years of age, the adverse reactions associated with the use of DIPROLENE AF Cream occurred in 7 of 67 (10%) subjects. Reported reactions included signs of skin atrophy (telangiectasia, bruising, shininess).

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids may also include: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, hypertrichosis, skin atrophy, striae, and miliaria.

Hypersensitivity reactions, consisting of predominantly skin signs and symptoms, e.g., contact dermatitis, pruritus, bullous dermatitis, and erythematous rash have been reported.

Ophthalmic adverse reactions of cataracts, glaucoma, increased intraocular pressure, and central serous chorioretinopathy have been reported with the use of topical corticosteroids, including topical betamethasone products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on DIPROLENE AF Cream use in pregnant women to identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Observational studies suggest an increased risk of low birthweight infants with the use of greater than 300 grams of potent or very potent topical corticosteroid during a pregnancy. Advise pregnant women that DIPROLENE AF Cream may increase the risk of having a low birthweight infant and to use DIPROLENE AF Cream on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, increased malformations, including umbilical hernias, cephalocele, and cleft palate, were observed after intramuscular administration of betamethasone dipropionate to pregnant rabbits. The available data do not allow the calculation of relevant comparisons between the systemic exposure of betamethasone dipropionate in animal studies to the systemic exposure that would be expected in humans after topical use of DIPROLENE AF Cream (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Betamethasone dipropionate has been shown to cause malformations in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

8.2 Lactation

Risk Summary

There are no data regarding the excretion of betamethasone dipropionate in breast milk, the effects on the breastfed infant, or the effects on milk production after topical application of DIPROLENE AF Cream to women who are breastfeeding.

It is possible that topical administration of large amounts of betamethasone dipropionate could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DIPROLENE AF Cream and any potential adverse effects on the breastfed infant from DIPROLENE AF Cream or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use DIPROLENE AF Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply DIPROLENE AF Cream directly to the nipple and areola to avoid direct infant exposure [see *Use in Specific Populations* (8.4)].

8.4 Pediatric Use

Use of DIPROLENE AF Cream in pediatric patients younger than 13 years of age is not recommended due to the potential for HPA axis suppression [see *Warnings and Precautions* (5.1)].

In an open-label HPA axis safety trial in subjects 3 months to 12 years of age with atopic dermatitis, DIPROLENE AF Cream 0.05% was applied twice daily for 2 to 3 weeks over a mean body surface area of 58% (range 35% to 95%). In 19 of 60 (32%) evaluable subjects, adrenal suppression was indicated by either a ≤ 5 mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤ 18 mcg/dL and/or an increase of < 7 mcg/dL from the baseline cortisol. Out of the 19 subjects with HPA axis suppression, 4 subjects were tested 2 weeks after discontinuation of DIPROLENE AF Cream, and 3 of the 4 (75%) had complete recovery of HPA axis function. The proportion of subjects with adrenal suppression in this trial was progressively greater, the younger the age group.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids.

Rare systemic effects such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids.

Local adverse reactions including skin atrophy have also been reported with use of topical corticosteroids in pediatric patients.

Avoid use of DIPROLENE AF Cream in the treatment of diaper dermatitis.

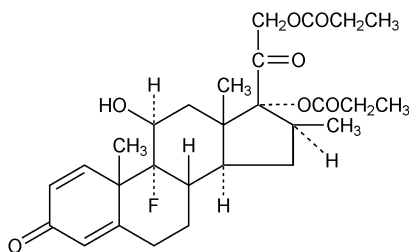
8.5 Geriatric Use

Clinical trials of DIPROLENE AF Cream included 104 subjects who were 65 years of age and over and 8 subjects who were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

DIPROLENE AF (augmented betamethasone dipropionate) Cream 0.05% contains betamethasone dipropionate USP, a synthetic adrenocorticosteroid, for topical use in a cream base. 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-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 DIPROLENE AF Cream 0.05% contains: 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a white cream base of carbomer 940; cetareth-30; chlorocresol; cyclomethicone; glyceryl oleate/propylene glycol; propylene glycol; purified water; sodium hydroxide; sorbitol solution; white petrolatum; and white wax.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of DIPROLENE AF Cream in corticosteroid responsive dermatoses is unknown.

12.2 Pharmacodynamics

Vasoconstrictor Assay

Trials performed with DIPROLENE AF Cream, 0.05% indicate that it is in the high range of potency as demonstrated in vasoconstrictor trials in healthy subjects when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

12.3 Pharmacokinetics

No pharmacokinetics trials have been conducted with DIPROLENE AF Cream 0.05%. 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.

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 (2)*].

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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.

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.

14 CLINICAL STUDIES

The safety and efficacy of DIPROLENE AF Cream for the treatment of corticosteroid-responsive dermatoses have been established in two randomized and active controlled trials in subjects with chronic plaque psoriasis. A total of 81 subjects who received DIPROLENE AF Cream were included in these

trials. These trials evaluated DIPROLENE AF Cream applied once or twice daily for 14 and 21 days, respectively, on bilateral paired psoriatic lesions. DIPROLENE AF Cream was shown to be effective in relieving the signs and symptoms of chronic plaque psoriasis.

16 HOW SUPPLIED/STORAGE AND HANDLING

DIPROLENE AF Cream 0.05% is a white cream supplied in 15-g (NDC 0085-0517-01) and 50-g (NDC 0085-0517-04) tubes.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

- Discontinue therapy when control is achieved, unless directed otherwise by the physician.
- Use no more than 50 grams per week.
- Avoid contact with the eyes.
- Advise patients to report any visual symptoms to their healthcare providers.
- Avoid use of DIPROLENE AF Cream on the face, underarms, or groin areas unless directed by the physician.
- Do not occlude the treatment area with bandage or other covering, unless directed by the physician.
- Note that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.
- Advise a woman to use DIPROLENE AF Cream on the smallest area of skin and for the shortest duration possible while pregnant or breastfeeding. Advise breastfeeding women not to apply DIPROLENE AF Cream directly to the nipple and areola to avoid direct infant exposure.

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