PRODUCT MONOGRAPH

DIPROSONE®

Betamethasone Dipropionate Cream, Merck Standard,
0.05% W/W betamethasone (as dipropionate)

Betamethasone Dipropionate Ointment, Merck Standard,
0.05% W/W betamethasone (as dipropionate)

Betamethasone Dipropionate Lotion, USP,
0.05% W/W betamethasone (as dipropionate)

Topical Corticosteroid

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PHARMACOLOGICAL CLASSIFICATION

Topical corticosteroid

CLINICAL PHARMACOLOGY

Many clinical studies have established the efficacy and relative safety of DIPROSONE® (betamethasone dipropionate) in a variety of steroid responsive dermatological conditions.

In the course of clinical investigations, special emphasis was placed on the more troublesome conditions such as psoriasis and/or atopic dermatitis.

INDICATIONS AND CLINICAL USES

DIPROSONE® (betamethasone dipropionate) cream and/or ointment provides anti-inflammatory, antipruritic and anti-allergic activity in the topical management of corticosteroid-responsive dermatoses. Such disorder include: psoriasis, contact dermatitis (dermatitis venenata), atopic dermatitis (infantile eczema, allergic dermatitis), neurodermatitis (lichen simplex chronicus, lichen planus, eczema, eczematous dermatitis), intertrigo, dyshidroses (pompholyx), seborrheic dermatitis, exfoliative dermatitis, solar dermatitis, stasis dermatitis, anogenital and senile pruritus. The lotion is

formulated to spread easily without adherence to hairy areas to facilitate treatment of dermatoses, such as psoriasis, and seborrheic dermatitis of the scalp.

CONTRAINDICATIONS

Topical steroid are contraindicated in:

1. Untreated bacterial, tubercular and fungal infections involving the skin, and in certain viral diseases such as herpes simplex, chicken pox, and vaccinia.

2. Hypersensitivity to any of the components.

WARNINGS

Pregnancy and lactation: Since safety of topical corticosteroid use in pregnant women has not been established, drugs of this class 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 in large amounts or for prolonged periods of time in pregnant patients.

Since it is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in breast milk, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics: Any of the side effects that have been reported following systemic use of corticosteroids, including adrenal suppression, may also occur with topical corticosteroids, especially in infants and children.

Systemic absorption of topical corticosteroids will be increased if extensive body surface areas are treated or if the occlusive technique is used. Suitable precautions should be taken under these conditions or when long-term use is anticipated, particularly in infants and children. Pediatric patients may demonstrate greater susceptibility than mature patients to topical corticosteroid-induced HPA axis suppression and to exogenous corticosteroid effects because of greater absorption due to a larger skin surface area to body weight ratio. Use of topical corticosteroids in children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with growth and development of children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include a bulging fontanelle, headaches and bilateral papilledema.

The lotion contains isopropyl alcohol, and may cause stinging upon application to abraded or sun-burned skin. Do not use in or near the eyes.

DIPROSONE® is not for ophthalmic use.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

PRECAUTIONS

Topical corticosteroids should be used with caution on lesions close to the eye.

Although hypersensitivity reactions have been rare with topically applied steroids, the drug should be discontinued and appropriate therapy initiated if there are signs of sensitivity or irritation.

In cases of bacterial or fungal infections of the skin, appropriate antimicrobial agents should be used as primary therapy. If it is considered necessary, DIPROSONE® may be used as an adjunct to control inflammation, erythema, and itching.

If a symptomatic response is not noted within a few days to a week, the local applications of DIPROSONE® should be discontinued until the infection is brought under control.

Significant systemic absorption may occur when steroids are applied over large areas of

the body, especially under occlusive dressings. To minimize this possibility, when long term therapy is anticipated, interrupt treatment periodically or treat one area of the body at a time.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Occlusive dressings should not be applied if there is an elevation of body temperature.

ADVERSE REACTIONS

The following local adverse skin reactions have been reported rarely with the use of topical steroids: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis. The following may occur more frequently with occlusive dressing: maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

Systemic adverse reactions, such as vision blurred, have also been reported with the use of topical corticosteroids.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Excessive or prolonged use of topical corticosteroids can suppress pituitary-adrenal function, resulting in secondary adrenal insufficiency, and produce manifestations of hypercorticism, including Cushing's disease.

Treatment: Appropriate symptomatic treatment is indicated. Acute hypercorticoid symptoms are usually reversible. Treat electrolyte imbalance, if necessary. In case of chronic toxicity, slow withdrawal of corticosteroids is advised.

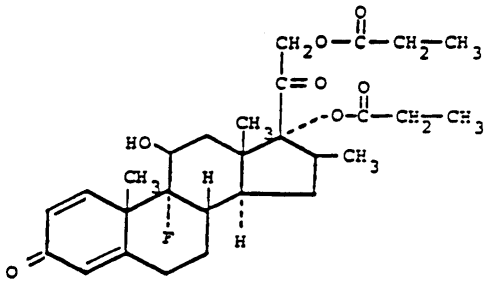
DOSAGE AND ADMINISTRATION

A thin film of DIPROSONE® should be applied to completely cover the affected area. The preparation should be massaged gently and thoroughly into the skin. The usual frequency of application is twice daily. For some patients adequate maintenance therapy may be achieved with less frequent application.

PHARMACEUTICAL INFORMATION

Drug substance:

Betamethasone dipropionate



Molecular Formula: $C_{28}H_{37}FO_7$

Molecular Weight: 504.59

Chemical Name:

Pregna-1, 4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis (1-oxopropoxy)-, (11β,16β)

or

9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Description:

White to cream-coloured powder, free from foreign matter with melting point $\pm 3^0$, between 170^0 and 179^0 with decomposition.

Availability:

DIPROSONE® cream, 0.05% W/W is packaged in 50 g tubes.

DIPROSONE® ointment, 0.05% W/W is packaged in 50 g tubes.

DIPROSONE® lotion, 0.05% W/W is packaged in 75 mL plastic squeeze bottles.

Storage:

Store between 15^0C and 30^0C.

Composition:

DIPROSONE® cream:

Each gram of DIPROSONE® cream contains 0.5 mg betamethasone (as dipropionate) in a water miscible base. Nonmedicinal ingredients: cetostearyl alcohol, chlorocresol, liquid paraffin, macrogol cetostearyl ether, phosphoric acid, sodium dihydrogen phosphate dihydrate, sodium hydroxide, water and white soft paraffin.

DIPROSONE® ointment:

Each gram of DIPROSONE® ointment contains 0.5 mg betamethasone (as dipropionate) in a lanolin free base. Nonmedicinal ingredients: liquid paraffin, white soft paraffin.

DIPROSONE® lotion:

Each gram of DIPROSONE® lotion contains 0.5 mg betamethasone (as dipropionate). Nonmedicinal ingredients: carbomer 934P, isopropyl alcohol, sodium hydroxide to adjust pH and water.

CLINICAL STUDIES

The McKenzie-Stoughton[1] vasoconstrictor test was conducted to compare betamethasone dipropionate to a number of other leading fluorinated topical corticosteroids. In this test betamethasone dipropionate was demonstrated to be significantly more active ($p<0.05$) than fluocinolone acetonide, fluocortolone caproate plus fluocortolone, flumethasone pivalate, and betamethasone valerate. While the direct applicability of this vasoconstrictor test to clinical situations has not been conclusively demonstrated, the results showed betamethasone dipropionate to be active in a concentration of 0.000016%, the lowest concentration tested which showed activity.

Early in the clinical pharmacological investigation, a human tolerance and effectiveness study[2] was carried out on four hospitalized psoriasis patients. Each was treated with 15 grams of cream b.i.d. for 10 days. No changes attributable to the treatment were noted in vital signs, weight, blood chemistry, CBC or urinalysis. Three of the four showed decreases in the urinary 17-KS and 17-OHCS levels, however, none showed any significant decrease in serum cortisol levels. There was no evidence of any loss of adrenal responsiveness after the period of treatment.

Clinical trials have shown that betamethasone dipropionate 0.05% is significantly more effective in the treatment of atopic dermatitis than either the vehicle or fluocinolone acetonide cream 0.025%. The same results were obtained in similar comparative trials involving psoriasis.

There was little significant difference when comparative trials were carried out between betamethasone dipropionate 0.05% and fluocinolone acetonide 0.025% in contact dermatitis; both were found effective.

Limited comparative trials with fluocinolone acetonide 0.05% in steroid responsive dermatosis did not show any significant differences between the two.

A study was carried out with the lotion to determine the potential for contact sensitization, assessed by means of the modified Draize test. No cases of sensitization were reported to have the capability of producing photodermatitis.

TOXICOLOGY

Acute (betamethasone dipropionate) single administration

Form	Mouse	Rat	Rabbit	Guinea pig
Oral (or.)	>15,000	>15,000	C	C
Oral (oint.)	>2,000	>1,000	C	>2,000
Oral* (lot.)	>5.0	>5.0	C	C
Dermal (Cr.)	C	>3,330	>3,330	C
Dermal*(lot.)	C	>3.3	>3.3	C
I.M. (inj.)	74	>100	2.5-5.5	C

*Deaths attributable to isopropyl alcohol in the lotion.

Subacute

A four-week oral toxicity study in dogs with betamethasone dipropionate did not cause any toxic effects. Changes in some hematological, biochemical and physiological systems as well as changes seen in some organs were reversible and were considered to be caused by the pharmacological action of the corticosteroid. Subacute dermal toxicity studies were carried out in mice, rats and rabbits. Up to one gram of cream per rat per day for six days per week for eight weeks showed the cream to be well tolerated and no lesions attributable to the betamethasone dipropionate cream were found. Results were similar with the ointment formulation.

Dermal toxicity studies of the lotion showed that there were no adverse skin changes in rats or guinea pigs. In rats created for 15 days there was minimal systemic activity (reduced thymus and adrenal weights). Guinea pigs treated dermally with up to 2 ml/kg of the lotion for 15 treatment days showed no evidence of dermal irritation or of percutaneous absorption of the corticosteroid.

In other chronic intramuscular toxicity studies in rats, it was shown that betamethasone dipropionate administered in doses of 0.1, 0.5 and 1 mg/kg once a week for 13 weeks was well tolerated.

Carcinogenicity

Chronic one-year intramuscular toxicity studies in rats showed no indication of carcinogenic activity of betamethasone dipropionate; dosage ranged from 0.5 mg/kg to 3.5 mg/kg.

Reproduction and teratology

Standard reproduction and teratology studies carried out in rabbits showed that betamethasone dipropionate caused the teratogenic effects typical of many other corticosteroids.

Other effects

The effect of the lotion on the ECG of rats was studied and no alterations occurred. As well as effect of the lotion on the blood pressure of rats and cats was studied and no significant immediate or delayed changes in the blood pressure of rats or cats or the respiratory values of cats were seen.

BIBLIOGRAPHY

1. McKenzie, A.W. and Stoughton, R.B.: Method for comparing percutaneous absorption of steroids. Arch. of Dermatology, 86, 608-610, 1962.

2. Abele, Donald C.: Human tolerance and effectiveness, study of betamethasone dipropionate cream 0.05%, 1972. (Clinical Research Files, Schering Corporation Limited).