PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

℞ DIPROLENE®

betamethasone dipropionate ointment, Organon Standard

0.05% W/W

Topical Corticosteroid

Organon Canada Inc.
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Date of Initial Approval
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April 13, 2021

Control: 249779

PRODUCT MONOGRAPH

NAME OF DRUG

DIPROLENE®

betamethasone dipropionate ointment 0.05% W/W

PHARMACOLOGICAL CLASSIFICATION

Topical corticosteroid

ACTIONS

DIPROLENE® provides anti-inflammatory, antipruritic and vasoconstrictive effects. The propylene glycol components of the vehicle increase penetration and enhance the local effectiveness of betamethasone dipropionate.

INDICATIONS AND CLINICAL USES

DIPROLENE® is indicated for the relief of the inflammatory manifestations of resistant or severe psoriasis and corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

DIPROLENE® is contraindicated in viral diseases including vaccinia, varicella, herpes simplex, and fungal infections; also, tuberculosis of the skin. DIPROLENE® products are contraindicated in those patients with a history of sensitivity reactions to betamethasone dipropionate, other corticosteroids or to any of the components of DIPROLENE® products.

WARNINGS

Do not use in or near the eyes since DIPROLENE® is not formulated for ophthalmic use. This product should not be used under occlusive dressing.

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

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.

Pediatric use: This product is not recommended for use in children under 12 years of age.

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.

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. Manifestation of intracranial hypertension include a bulging fontanelle, headache and bilateral papilledema.

DIPROLENE® 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

Suitable precautions should be taken in using topical glucocorticoids in patients with stasis dermatitis and other skin diseases with impaired circulation; hypersensitive subjects and in patients with glaucoma.

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

If irritation, sensitization, excessive dryness develop with the use of DIPROLENE®, treatment should be discontinued.

During the use of topical corticosteroids, infections may occur. If an overt infection is present, appropriate anti-microbial treatment is indicated.

If symptomatic response is not noted within a few days to a week, the local application of corticosteroids should be discontinued and the patient re-evaluated.

Prolonged use of corticosteroid preparations may produce striae or atrophy of the skin or subcutaneous tissues. If this occurs, treatment should be discontinued.

At 14 grams per day for nine days, DIPROLENE® was shown to depress plasma cortisol levels following repeated applications to diseased skin in patients with psoriasis.

Application of corticosteroids over extensive lesions, or failure to follow dosage schedule may result in

significant systemic absorption producing hypercortisolism manifesting itself by adrenal suppression, moon facies, striae and suppression of growth.

Systemic absorption of topical corticosteroids will be increased with the use of more potent corticosteroid formulations, with prolonged usage or if extensive body surface areas are treated. Therefore, patients receiving large doses of potent topical corticosteroids, applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression. If HPA axis suppression occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute with a less potent corticosteroid agent.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of corticosteroid withdrawal may occur, requiring supplemental systemic corticosteroid therapy.

ADVERSE REACTIONS

The following adverse reactions were reported with DIPROLENE®: mild to moderate transient folliculitis, increased erythema, itching, vesiculation, perilesional scaling, telangiectasia, dryness, stinging, burning, skin atrophy, local irritation, urticaria. Rarely reported adverse effects include tingling, prickly skin, tightening or cracking of skin, warm feeling, laminar scaling, follicular rash, hyperesthesia and pruritus. Subnormal plasma cortisol levels were also reported.

The following local adverse skin reactions have been reported with the use of topical steroids: itching, folliculitis, striae, hypertrichosis, change in pigmentation, secondary infection, perioral dermatitis, allergic contact dermatitis, maceration of the skin, acneiform eruptions and miliaria.

Adrenal suppression has also been reported following topical corticosteroid therapy. Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

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 virtually reversible. Treat electrolyte imbalance, if necessary. In case of chronic toxicity, slow withdrawal of corticosteroids is advised.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

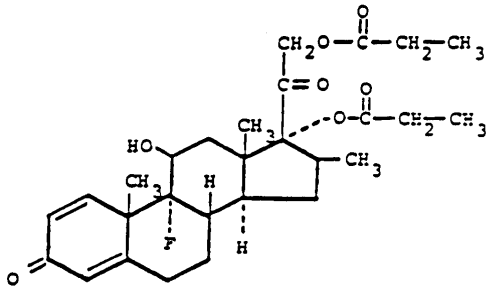
A thin film of DIPROLENE® should be applied to cover completely the affected area once daily, in the morning. DIPROLENE® may also be applied twice daily, in the morning and at night or as directed by the physician. Treatment should be discontinued when the dermatologic disorder is controlled. According to clinical response, duration of therapy may vary from a few days to a longer period of time. However, treatment should not be continued for more than four weeks without patient re-evaluation.

DIPROLENE® should not be used under occlusive dressing.

PHARMACEUTICAL INFORMATION

Drug substance:

Betamethasone-17,21-dipropionate (USP):



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:

Betamethasone dipropionate is a white to cream coloured powder, free from foreign matter with melting point ±3°, between 170 °C and 179 °C with decomposition.

Storage:

Store between 15° and 30°C.

Availability:

DIPROLENE® ointment 0.05% W/W is packaged in aluminum tubes of 50 g.

Composition:

Each gram of DIPROLENE® contains 0.5 mg betamethasone (as dipropionate Organon Standard, micronized). Non-medicinal ingredients: propylene glycol stearate, propylene glycol, white beeswax and white soft paraffin.

CLINICAL STUDIES

Mckenzie-Stoughton vasoconstrictor test:

Betamethasone dipropionate was compared with other fluorinated topical corticosteroids in the McKenzie/Stoughton vasoconstrictor test. In this test, betamethasone dipropionate was significantly more active ($p<0.05$) than fluocinolone acetonide, fluocortolone caproate plus fluocortolone, flumethasone pivalate and betamethasone valerate. The results showed betamethasone dipropionate to be active in a concentration of 0.000016%, the lowest concentration tested which showed activity.

Standardized McKenzie-Stoughton vasoconstrictor potency testing of DIPROLENE® versus betamethasone dipropionate cream or ointment on groups of normal volunteers indicated enhanced clinical potential of the glycol formulation. See Table 1.

Table 1
Comparison of vasoconstrictor potency between betamethasone dipropionate formulations

		Elapsed Time After Topical Application	
	No. of Test Panels	7 Hours	24 Hours
Betamethasone dipropionate glycol ointment, 0.05%	17	1.94[a] (1.44-2.38)[b]	1.09[a] (0.69-1.62)[b]
Betamethasone dipropionate ointment, 0.05%	10	1.37 (1.13-1.81)	0.84 (0.59-1.06)
Betamethasone dipropionate glycol cream, 0.05%	5	1.74 (1.50-2.06)	0.87 (0.75-1.25)
Betamethasone dipropionate cream, 0.05%	16	0.88 (0.56-1.50)	0.61 (0.25-1.31)

[a] Average of pooled scores
[b] Range of averaged pooled scores

Phototoxicity study:

In safety studies, DIPROLENE® ointment vehicle and white petrolatum were used as comparison treatments and each subject received each treatment. In nine subjects tested for phototoxicity, all subjects had negative scores. There was no difference between the phototoxicity potential of DIPROLENE® ointment, its vehicle and white petrolatum.

Photo-allergenicity study:

In a photo-allergenicity study, 25 subjects had zero (negative) induction phase evaluations for DIPROLENE® ointment, its vehicle and white petrolatum.

Contact irritation and sensitization studies:

In a contact irritation and sensitization study of 198 subjects, four subjects had worse scores for DIPROLENE® ointment as compared to two and three subjects for the vehicle and white petroleum, respectively; the final evaluation of sensitization rated all subjects as non-sensitized.

In a cumulative irritation study of 26 subjects treated with DIPROLENE®, one subject has a worse score for DIPROLENE® ointment than its two comparative treatments; three subjects had a worse score for the vehicle as compared to DIPROLENE®.

Efficacy and safety:

The safety and effectiveness of DIPROLENE® have been studied in patients with corticosteroid-responsive dermatoses including resistant or severe psoriasis and resistant and/or severe atopic dermatitis. Application was twice daily for two weeks. Results of later efficacy studies demonstrated that DIPROLENE® applied once daily for two weeks (approximately 6 g/application) was equivalent to or significantly more effective than topical corticosteroid formulations commonly recognized as Group 1 steroids (highest potency agents) in the treatment of moderate to severe resistant psoriasis and atopic dermatitis.

Psoriasis:

DIPROLENE® applied once a day was an effective treatment for psoriasis and after one and two weeks of treatment was more effective ($p \leq 0.01$) than fluocinonide ointment applied three times a day. No

adverse experiences were reported for any DIPROLENE® treated patient; three fluocinonide-treated patients reported mild or moderate local reactions.

On a twice-daily regimen, DIPROLENE® was more effective than DIPROSONE® ointment and DIPROSONE® cream ($p \leq 0.10$) in a multicenter, randomized, double-blind parallel study group of 283 patients with psoriasis. Ten patients had local adverse experiences, four each in the DIPROLENE® and DIPROSONE® ointment groups, and two in the DIPROSONE® cream group. Most adverse experiences were irritative in nature. One DIPROLENE® treated patient discontinued treatment during the first week because of increased erythema and some vesiculation.

In another study with 41 patients, both DIPROSONE® ointment and DIPROLENE® on a twice-daily regimen were effective in the treatment of psoriasis, however, a significantly higher degree of efficacy was seen for DIPROLENE® ($p \leq 0.01$). There were no adverse experiences reported in either group.

Atopic Dermatitis:

In a multicenter, randomized, double-blind parallel study group of 92 patients, all three preparations administered b.i.d. produced rapid and marked reductions in the disease signs and symptoms of atopic dermatitis (erythema, induration, pruritus, excoriation and lichenification). Complete clearing of disease lesions at the end of treatment was shown in 48% of the DIPROLENE® group, 42% in the DIPROSONE® ointment group and 36% in the DIPROSONE® cream group. One in each treatment group developed folliculitis.

DIPROLENE® once daily was compared with halcinonide t.i.d. in 12 patients with atopic dermatitis of 6-10 years' duration. At the end of three weeks of treatment, disease sign/symptom scores in both groups indicated that the disease had almost disappeared from target lesions; improvement in mean total disease sign score was 87% in the DIPROLENE® group and 77% in the halcinonide group.

TOXICOLOGY

Subacute 21-day Dermal Toxicity of Betamethasone Dipropionate Glycol Ointment in Rabbits

A dermal toxicity study was conducted using male and female New Zealand White rabbits. Betamethasone dipropionate glycol ointment 0.05% or the ointment vehicle was applied daily in two equal portions for 21 consecutive days to intact or abraded skin. Six animals with intact skin and six animals with abraded skin were used for each of the following groups: vehicle control 1 g/kg/day, betamethasone dipropionate glycol ointment low dose 0.5 mg/kg/ day or betamethasone dipropionate glycol ointment high dose 1.0 g/kg/day (one gram betamethasone dipropionate glycol ointment contains the equivalent of 0.5 mg betamethasone alcohol).

The corticosteroid glycol preparation was well tolerated locally. In both intact and abraded animals, treatment did not result in skin edema or interfere with the healing of abrasions. Corticosteroid glycol treatment resulted in a dose-related decrease in hematocrit and hemoglobin values, but, overall, did not significantly affect the total and differential white cell counts, except in the intact animals where a drug-related decrease in lymphocyte counts occurred. In both intact and abraded animals, corticosteroid glycol treatment did not significantly affect urea nitrogen or glutamic pyruvic transaminase values but did slightly increase blood glucose. Lipemia occurred in some animals. These changes represent typical systemic response to corticosteroids. At autopsy, the corticosteroid glycol-treated skin appeared normal. Necropsy findings attributable to corticosteroid glycol treatment were skeletal muscle atrophy, abdominal distention, liver enlargement, liver paleness and/or friability. Based primarily on organ body weight ratios, the liver and kidneys of corticosteroid glycol-treated rabbits generally weighed more than those of controls. Although not statistically significant, thymus weights were reduced in some corticosteroid glycol-treated animals. Histopathologic examination revealed no corticosteroid glycol-related adverse dermal effects; skin abrading induced some inflammatory changes. The systemic changes seen were not unexpected and are typical of those observed after topical corticosteroid administration.

Reproduction and Teratology

In mice, high doses of up to 32.5 mg/kg caused resorption of conceptuses. In rats, no adverse effects were seen in either dams or offspring at daily intramuscular doses of 1 or 2 mg/kg. In rabbits, betamethasone dipropionate caused teratogenic effects typical of many corticosteroids (0.015 and 0.050 mg/kg).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

℞ DIPROLENE®
betamethasone dipropionate ointment

Read this carefully before you start taking **DIPROLENE®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DIPROLENE®**.

What is DIPROLENE® used for?

DIPROLENE® is used in adults and children over 12 years of age on the skin for the relief of redness, swelling, heat, pain and itching caused by psoriasis and other skin problems.

How does DIPROLENE® work?

DIPROLENE® reduces inflammation and makes the blood vessels constrict to help relieve swelling, redness, heat, pain and itching.

What are the ingredients in DIPROLENE®?

Medicinal ingredient: betamethasone dipropionate
Non-medicinal ingredients: propylene glycol, propylene glycol stearate, white beeswax and white soft paraffin

DIPROLENE® comes in the following dosage forms:

Ointment; 0.05% W/W

Do not use DIPROLENE® if you:

- are allergic to betamethasone dipropionate or any of the other ingredients of **DIPROLENE®**.
- are allergic to a similar medication (corticosteroid).
- have any infections like small pox, chicken pox, cold sores or genital herpes, fungal infections or tuberculosis of the skin.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DIPROLENE®. Talk about any health conditions or problems you may have, including if you:

- already use a similar medication (corticosteroid).
- are pregnant or planning on becoming pregnant. It is not known if **DIPROLENE®** can harm your unborn baby. Your healthcare professional will decide whether giving you **DIPROLENE®** outweighs the potential risk to the unborn baby.
- are breastfeeding or planning to breastfeed. It is not known whether **DIPROLENE®** can pass into your breastmilk. Your healthcare professional will decide whether you should stop breastfeeding or stop using **DIPROLENE®**.
- have any infections.
- have diseases of your skin that are caused by poor blood flow. An example is stasis dermatitis.

- have increased pressure in your eyes (glaucoma).

Other warnings you should know about:

Do not use **DIPROLENE®** in or near your eyes.

Do not use **DIPROLENE®** under an air and water tight (occlusive) dressing.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take DIPROLENE®:

Usual dose: Apply a thin film once a day, in the morning, to cover the affected area. It may also be applied twice daily, in the morning and at night or as directed by your healthcare professional.

Overdose:

If you think you have taken too much **DIPROLENE®**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

What are possible side effects from using DIPROLENE®?

These are not all the possible side effects you may feel when taking **DIPROLENE®**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Itching, dryness, stinging, burning, irritation
- Increased redness
- Blisters
- Thinning of the skin
- Swelling of the hair follicles
- Stretch marks
- Spider veins
- Excessive hair growth
- Change in skin pigmentation
- Secondary infection
- Skin rash around the mouth
- Red, itchy rash caused by allergy to or contact with a substance (allergic contact dermatitis)
- Softening or breaking down of skin due to moisture
- Acne, rosacea

- Heat rash
- Hives
- Blurred vision

Using **DIPROLENE®** can affect how your adrenal glands work. This can cause symptoms such as a round appearance of the face (moon face), stretch marks and slowed growth in children. If you develop any of these symptoms contact your healthcare professional.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15˚C and 30˚C.

Keep out of the reach and sight of children.

If you want more information about DIPROLENE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.organon.ca, or by calling 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

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