

PRODUCT MONOGRAPH

 **DIPROLENE®**

Glycol OINTMENT/CREAM
(betamethasone dipropionate 0.05% W/W)

Topical Corticosteroid

Merck Canada Inc.
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PRODUCT MONOGRAPH

NAME OF DRUG

DIPROLENE® Glycol Ointment/Cream

Betamethasone Dipropionate 0.05% W/W

PHARMACOLOGICAL CLASSIFICATION

Topical corticosteroid

ACTIONS

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

CONTRAINDICATIONS

DIPROLENE® Glycol 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® Glycol 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® Glycol 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® Glycol, 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.

DIPROLENE® cream has been shown to suppress the hypothalamic-pituitary adrenal (HPA) axis with repeated application of 7 g/day.

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® Glycol: 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

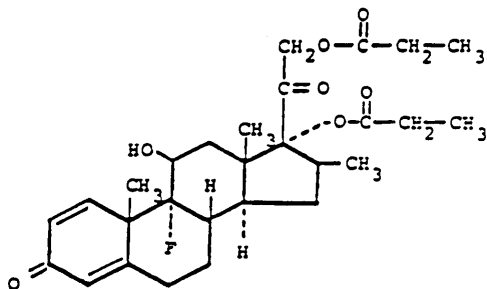
Cream and Ointment: A thin film of DIPROLENE® Glycol Ointment/Cream should be applied to cover completely the affected area once daily, in the morning. DIPROLENE® Glycol may also be applied twice daily, in the morning and at night or as directed by the physician. Treatment should be discontinued when 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® Glycol should not be used under occlusive dressing.

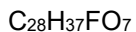
PHARMACEUTICAL INFORMATION

Drug substance:

Betamethasone-17,21-dipropionate (USP):



Molecular Formula:



Molecular Weight:

504.59

Chemical Name:

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

or

9-Fluoro-11 β ,17,21-trihydroxy-16 β -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 $\pm 3^\circ$, between 170 °C and 179 °C with decomposition.

Storage:

Store between 15° and 30°C.

Availability:

DIPROLENE® Glycol Ointment/Cream 0.05% W/W

is packaged in aluminum tubes of 50 g.

Composition:

DIPROLENE® Glycol Ointment:

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

DIPROLENE® Glycol Cream:

Each gram of cream contains 0.5 mg betamethasone (as dipropionate Merck Standard, micronized). Non-medicinal ingredients: carbomer 940, propylene glycol, sodium hydroxide, titanium dioxide and purified water.

CLINICAL STUDIES

McKenzie-Stoughton vasoconstrictor test:

DIPROLENE® Glycol ointment/cream:

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® Glycol 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

	No. of Test Panels	Elapsed Time After Topical Application	
		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® Glycol 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® Glycol Ointment, its vehicle and white petrolatum. DIPROLENE® Glycol Cream was studied in 12 patients - one patient exhibited slight erythema at the irradiation and non-irradiation sites. DIPROLENE® Glycol Cream and its vehicle were not considered phototoxic under the conditions of the current, standard test procedure and should prove to be nonphototoxic when used as intended.

Photo-allergenicity study:

In a photo-allergenicity study, 25 subjects had zero (negative) induction phase evaluations for DIPROLENE® Glycol Ointment, its vehicle and white petrolatum. In a 27 subject DIPROLENE® Glycol Cream study, no photoallergic reactions were elicited using standard predictive methodology, and DIPROLENE® Glycol Cream should prove to have a low potential as a photoallergenic agent when used as intended.

Contact irritation and sensitization studies:

In a contact irritation and sensitization study of 198 subjects, four subjects had worse scores for DIPROLENE® Glycol 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 Draize patch testing of DIPROLENE® Glycol Cream with 201 volunteers in a series of 10 alternate-day applications, each of 24 hours' duration, followed by a challenge two weeks later, no visible skin changes signifying reactions to injury were observed in 5.5%. Blanching of the skin occurred occasionally in some subjects.

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

Efficacy and safety:

The safety and effectiveness of DIPROLENE® Glycol Ointment 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® Glycol Ointment 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.

DIPROLENE® Glycol ointment:

Psoriasis:

DIPROLENE® Glycol Ointment 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® Glycol-treated patient; three fluocinonide-treated patients reported mild or moderate local reactions.

On a twice-daily regimen, DIPROLENE® Glycol 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® Glycol and DIPROSONE® Ointment groups, and two in the DIPROSONE® Cream group. Most adverse experiences were irritative in nature. One DIPROLENE® Glycol 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® Glycol Ointment on a twice-daily regimen were effective in the treatment of psoriasis, however, a significantly higher degree of efficacy was seen for DIPROLENE® Glycol ($p \leq 0.01$). 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® Glycol group, 42% in the DIPROSONE® Ointment group and 36% in the DIPROSONE® Cream group. One in each treatment group developed folliculitis.

DIPROLENE® Glycol 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® Glycol group and 77% in the halcinonide group.

DIPROLENE® Glycol cream:

A randomized, double-blind, multicentered study compared the onset of action, efficacy and local safety of DIPROLENE® Glycol Cream 0.05% (betamethasone dipropionate glycol formulation) and diflucortolone valerate 0.3% (oil/water cream) in outpatients with resistant or severe psoriasis or with "other" resistant or severe corticosteroid responsive dermatoses. The results of this study indicate that DIPROLENE® Glycol Cream 0.05% applied twice a day for two weeks was highly efficacious in treating patients with resistant and severe psoriasis and was more effective than diflucortolone valerate 0.3% applied twice a day for two weeks. Two patients, one in each treatment group, reported transient, moderate adverse reactions. A DIPROLENE® Glycol treated patient noticed some dryness of the skin and perilesional scaling that was probably related to treatment which disappeared after ten days while pruritic papules developed eight days after the start of diflucortolone valerate therapy. Cortisol levels remained within normal limits in both groups.

The efficacy, safety, onset of relief and tolerance of twice a day application of 3.5 g DIPROLENE® Glycol Cream 0.05% (betamethasone dipropionate glycol formulation) and twice a day application of 3.5 g desoxymethasone 0.25% (water in oil emulsion) were compared during two weeks in patients with resistant or severe steroid responsive dermatoses including psoriasis and atopic dermatitis. No statistically significant differences between treatment groups in overall response was observed. Tolerance to both medications was excellent. No local adverse effects occurred. A decrease in plasma cortisol levels was observed in 4/9 DIPROLENE® Glycol, and 3/6 desoxymethasone treated patients. Plasma cortisol levels decreased on one or more occasions in some patients but were normal by no later than the day 21 visit in 8/9 and 5/6 DIPROLENE® Glycol and desoxymethasone treated patients, respectively.

A randomized, double-blind, multicentered study, compared the onset of action, efficacy and local and systemic safety of DIPROLENE® Glycol Cream 0.05% (betamethasone dipropionate glycol 0.05%) and clobetasol propionate in outpatients with resistant or severe psoriasis, or with "other" resistant or severe corticosteroid-responsive dermatoses. This latter patient group included patients with various commonly encountered forms of eczematous disorders such as atopic dermatitis and nummular eczema. Also included in this group were patients with palmoplantar pustulosis, prurigo nodularis, lichen ruber planus and lichen planus. After two weeks of twice daily treatment with clobetasol propionate there was a 77% improvement in the total disease sign/symptom scores of the psoriasis patients and a 79% improvement in patients with "other dermatoses". Improvement in both treatment groups was also rapid in onset. Results of adrenal safety tests indicated that plasma cortisol levels were below the normal range one or more times during the treatment phase in both the DIPROLENE® Glycol and the clobetasol propionate treatment groups. These changes were generally transient as indicated by measurement of plasma cortisol levels at other times during treatment and after treatment had ended. By the conclusion of the study, values were within or above the normal range in 28 of 32 (87%) DIPROLENE® Glycol-treated patients and in 29 of 35 (82%) clobetasol propionate-treated patients. Local adverse reactions were generally mild to moderate with seven reports of severe reactions for the two treatment groups. These severe reactions were limited to the

patients with "other dermatoses". Three patients from the DIPROLENE® Glycol treatment group reported severe burning. Severe irritation, erythema, and burning were reported in the clobetasol propionate group; one patient exhibited both severe erythema and burning. Only mild reactions to either treatment were reported for the psoriatic patients who experienced adverse reactions. Noteworthy, however, one psoriatic patient from the clobetasol propionate group showed signs of skin atrophy.

One investigator-blinded, parallel group study compared the local and systemic tolerance and the efficacy of DIPROLENE® Glycol (betamethasone dipropionate glycol 0.05%) and halcinonide cream 0.1% in outpatients with moderate to severe atopic dermatitis. The study was conducted in three phases: a two-day pretreatment phase during which baseline laboratory values and disease status were established; a 21-day treatment phase during which 6 to 7 g of DIPROLENE® Glycol were applied once a day or approximately 6 g of halcinonide were applied three times a day and safety and efficacy evaluations were performed at regular intervals; and an eight-day post-treatment phase during which follow-up evaluations of safety were performed. The effects of treatment on hypothalamic-pituitary-adrenal (HPA) axis function were assessed by measurement of morning plasma cortisol levels and levels of urinary 17-hydroxycorticosteroids and free cortisol in 24 hour urine collections. Measurements were made during the pretreatment, treatment and post-treatment phases. At the end of treatment, improvement in sign/symptom scored averaged 63% in the DIPROLENE® Glycol treatment group and 60% in the halcinonide treatment group. The mean scores on the physician's overall evaluation of change in disease status indicated marked to moderate improvement in DIPROLENE® Glycol-treated patients and moderate improvement in halcinonide-treated patients. Evaluation of treatment effects on the HPA axis indicated that morning plasma cortisol levels were below the lower limit of the normal range on one or more days during the treatment phase in two of the 12 assessable DIPROLENE® Glycol-treated patients using the medication as directed. Coincidental subnormal levels of plasma cortisol and subnormal levels of urinary components of HPA axis function (free cortisol and 17-hydroxycorticosteroids) were evident in these two patients. By study day 29 (one week after the last application of DIPROLENE® Glycol),

plasma cortisol levels in these two patients returned to pretreatment values and were well within or above the normal limits. One of 15 halcinonide-treated patients had a subnormal level of plasma cortisol after two weeks of treatment. Nine patients (7 of 14 in the DIPROLENE® Glycol treatment group and 2 of 15 in the halcinonide treatment group) reported adverse experiences, mostly local in nature, and those judged related to treatment were mild to moderate in degree. Most reactions were of dry skin.

The efficacy and safety of once a day application (6 to 7 g/day) of DIPROLENE® Glycol Cream 0.05% (betamethasone dipropionate glycol) and twice a day application (approximately 12 g/day) of fluocinonide cream were compared in a five-centre study in patients with moderate to severe psoriasis. In this randomized, single-blind, parallel-group trial, the test substances were applied without the use of occlusive dressings for two weeks. The response to treatment was evaluated in each patient after three, seven and 14 days of treatment. Three disease signs (erythema, induration and scaling) in preselected target areas were rated on a scale ranging from 0 to 3, and a total disease sign score was determined by adding scores for the three signs. Treatment effects were assessed by the change in disease sign score. As an additional assessment of treatment effects, the investigators made a global (subjective) evaluation of overall change in disease status in the target areas and other treated areas. One of the investigators also evaluated the systemic effects of treatment by means of routine hematologic and blood chemistry analyses and urinalyses, and by determinations of morning plasma cortisol levels and levels of urinary free cortisol and 17-hydroxycorticosteroid (17-OHC) in 24-hour urine samples. At the end of the two-week treatment period, mean individual disease sign scores in the DIPROLENE® Glycol treatment group remained significantly lower than those of the fluocinonide group ($p \leq 0.05$) even though fluocinonide was applied twice as frequently as DIPROLENE® Glycol. At this time, improvement in the total disease sign scores was 63% for DIPROLENE® Glycol-treated patients and 54% for fluocinonide-treated patients ($p \leq 0.01$). As indicated by the physician's global evaluation of overall change in disease status, one patient in the DIPROLENE® treatment group and one in the fluocinonide group had complete clearing of disease signs; 70 of 98 (71%) DIPROLENE® Glycol-treated patients as opposed to 55 of 100 (55%)

fluocinonide-treated patients showed marked to moderate improvement after two weeks of treatment. After 14 days of treatment with either DIPROLENE® Glycol Cream or fluocinonide cream, patients showed no apparent trends that were suggestive of effects on HPA axis function, i.e. levels of plasma cortisol and 24-hour urinary free cortisol and 17-OHC were within the normal range limit and/or showed little change from baseline levels. Treatment-related adverse reactions, local in nature, were noted in 7% (7/107) of the patients applying DIPROLENE® Glycol and in 9% (10/107) of the patients applying fluocinonide. All treatment related adverse reactions in the DIPROLENE® Glycol-treated patients were mild to moderate in nature; these reactions included three reports of dryness, two reports each of burning and itching and one report of stinging. One case of mild telangiectasia was also noted at the day 15 follow-up visit. Mild to moderate treatment- related adverse reactions reported in the fluocinonide group included six reports of burning, four reports of stinging and one of itching. One fluocinonide-treated patient also experienced severe burning which was considered to be treatment related.

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. Similar results were obtained with the cream formulation.

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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