PRODUCT MONOGRAPH

[Pr]pdp-DESONIDE

(Desonide Cream and Ointment)

0.05% (w/w)

Glucocorticoid

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[Pr]pdp-DESONIDE

(Desonide Cream and Ointment)

0.05% (w/w)

THERAPEUTIC CLASSIFICATION

Glucocorticoid

ACTIONS AND CLINICAL PHARMACOLOGY

pdp-DESONIDE (desonide) 0.05% is an anti-inflammatory and antipruritic corticosteroid designed for topical use in inflammatory dermatoses.

Human dose titration studies were carried out using two different methods, both in a double-blind randomized fashion with fluocinolone acetonide 0.025% as the reference steroid. In the first method, patients with symmetrical bilateral skin lesions were selected. In the second method, ambulatory or hospitalized patients afflicted with stabilized psoriasis were employed. In the former investigation desonide 0.025% cream was found equipotent with fluocinolone acetonide 0.025%. However, using the sign test at a significant level of $\alpha=0.05$, the same concentration of desonide was shown to be superior ($p<0.03$) to fluocinolone acetonide 0.025% on first week objective evaluation. The second investigation yielded similar results.

Human systemic effects studies were carried out with desonide cream 0.02% in parallel with fluocinolone acetonide cream 0.01% on patients with 10%, 30%, 60%, and 90% of the body surface treated and occluded for one week in a double-blind design.

All of the patients had dermatoses responsive to corticosteroid preparations, primarily psoriasis or exfoliative dermatitis, but a rare patient was included who had an eczematous dermatitis. The patients were divided into groups of six according to body surface involvement with random assignment to the steroids under investigation. Testing for suppression of the pituitary-adrenal axis with metapyrone before and just after treatment revealed unequivocal suppression in one patient in

the desonide group with 60% body surface involvement. In the same group another patient exhibited mild adrenal suppression. In contrast, in the fluocinolone acetonide group with 60% body surface involvement, two patients showed unequivocal adrenal suppression. In the 90% body surface group both steroids caused unequivocal adrenal suppression for one patient each.

Blood chemistry (hemoglobin, hematocrit, red and white cell counts with differential, fasting blood sugar), hepatic function tests (alkaline phosphatase, SGOT and SGPT) and renal function tests (BUN and complete urinalysis) were investigated before and after 4 weeks treatment with desonide or fluocinolone acetonide in 204 patients ranging in age from 2 to 84 years. One patient treated with desonide had a slightly elevated post-treatment fasting blood sugar, and three showed slight elevations in their post-treatment SGOT levels. Both laboratory alterations were equally and more frequently observed following treatment with fluocinolone acetonide.

In all probability, these laboratory alterations following either topical steroid are not drug-related but appeared to be intrinsic to the clinical population.

INDICATIONS AND CLINICAL USE

pdp-DESONIDE (desonide) 0.05% topical preparations are intended for use in the management of acute or chronic dermatoses. They have been demonstrated to have anti-inflammatory activity when used topically in:

- Atopic Dermatitis
- Contact Dermatitis (including Poison Ivy and Venenata)
- Psoriasis
- Eczema (including Nummular Eczema)
- Neurodermatitis
- Seborrheic Dermatitis
- Lichen Simplex Chronicus (Lichen Planus)
- Dyshidrosis
- Acute Solar Dermatitis (Sunburn)
- Statis Dermatitis

CONTRAINDICATIONS

As with all topical corticosteroids, pdp-DESONIDE (desonide) should not be used in untreated bacterial, tubercular and fungal infections of the skin or in viral infections with skin lesions, including herpes simplex, vaccinia and varicella. It is also contraindicated in individuals with history of hypersensitivity to its components.

WARNINGS

- The safety of topical corticosteroids during pregnancy or lactation has not been established. The potential benefit of topical corticosteroids, if used during pregnancy or lactation, should be weighed against possible hazard to the fetus or the nursing infant.
- If used under an occlusive dressing, particularly over extensive areas, sufficient absorption may take place to give rise to adrenal suppression and other systematic effects.
- Topical corticosteroids are not for ophthalmic use.

PRECAUTIONS

Although side effects are not ordinarily encountered with topically-applied corticosteroids, as with all drugs, a few patients may react unfavorably under certain conditions. Should sensitivity or idiosyncratic reactions occur, the agent should be discontinued and appropriate steps taken. Topical steroids should not be used extensively on pregnant patients, in large amounts or for prolonged periods of time.

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

Causal factors should be eliminated whenever possible. It is recommended that rotation of the sites of application and intermittent therapy be considered.

Suitable precautions should be taken in using topical corticosteroids in patients with statis dermatitis and other skin diseases with impaired circulation. Prolonged use of corticosteroid-containing products, particularly when applied under occlusive dressings, may produce striae or atrophy of the skin or subcutaneous tissue, in which event treatment with such products should be discontinued. In

case of bacterial infection of the skin, appropriate anti-bacterial agents should be used as primary therapy. If it is considered necessary, the topical corticosteroid 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 corticosteroid should be discontinued until the infection is brought under control.

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

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

ADVERSE REACTIONS

Side effects have been rare and consist mainly of local burning irritation and itching. When this occurs, the possibility of sensitization must be kept in mind. Because skin atrophy, striae, hypertrichosis and adrenal suppression have been shown to occur with prolonged and indiscriminate use of topical corticosteroids, particularly under occlusion, due to percutaneous absorption, similar phenomena could conceivably occur with prolonged and excessive use of desonide. Folliculitis, acneform eruptions, dryness of skin, maceration of skin and hypopigmentation have been shown to occur with the use of topical corticosteroids, and could presumably appear with the use of desonide. Allergic contact dermatitis has been reported following the use of products containing methylparaben, which is present in pdp-DESONIDE cream as a preservative. Posterior subcapsular cataracts have been reported following the systematic use of corticosteroids.

Treatment of Accidental Ingestion:

There is no specific antidote, but gastric lavage should be performed.

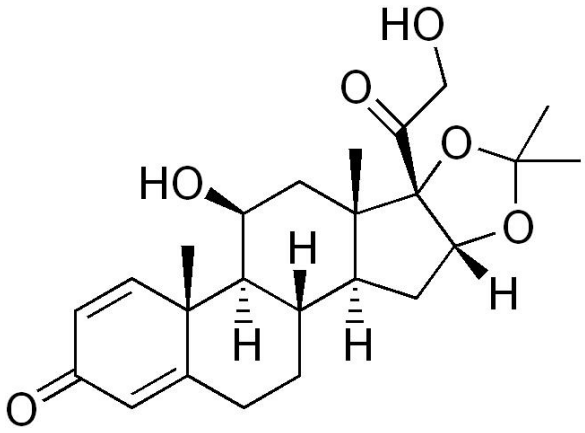
PHARMACEUTICAL INFORMATION

Drug Substance:

Common Name: Desonide

Chemical Name: 11B, 21-Dihydroxy-16a, 17a-isopropylidinedioxy-1, 4-pregnadiene-3, 20-dione.

Structural Formula:



Molecular Formula: $C_{24}H_{32}O_6$

Molecular Weight: 416.52

Description: Desonide is a white to off-white fine powder, it is practically odourless and stable in air.

The vehicle for pdp-DESONIDE Cream is Acid Mantle Creme (Dome), utilizing methylparaben as preservative. The vehicle for pdp-DESONIDE Ointment is White Petrolatum USP, without parabens or other preservatives.

DOSAGE AND ADMINISTRATION

A thin layer of pdp-DESONIDE (desonide) 0.05% Cream or Ointment should be applied to the affected skin thoroughly covering the area. The usual dosage is two to three times daily; however, this may be increased in the treatment of refractory cases.

pdp-DESONIDE Cream contains the following non-medicinal ingredients: aluminum sulfate, calcium acetate, dextrin, glycerin, kolliphor, light mineral oil, methylparaben, purified water, sodium lauryl sulfate, wax, white petrolatum.

pdp-DESONIDE Ointment contains the following non-medicinal ingredient: white petrolatum.

AVAILABILITY OF DOSAGE FORMS

pdp-DESONIDE Cream: Supplied in tubes of 15 grams and 60 grams.
pdp-DESONIDE Ointment: Supplied in tubes of 60 grams.
Store below 30°C. Avoid freezing.

PHARMACOLOGY

Since the introduction of hydrocortisone for the topical treatment of various dermatological disorders, a great many analogs have been synthesized in attempts to increase potency and reduce side effects. Some of the chemical modifications of hydrocortisone which singly or in combination have proven effective in this respect include methylation, halogenation (fluorine), hydroxylation, oxidation (dehydrogenation), esterification and (where the glycol moiety is present) acetonide formation. One or more such structural modifications to the basic hydrocortisone molecule are to be found in each of the several potent topical steroids presently available.

Desonide is a new addition to this important class of therapeutic agents. Being a chemically modified hydrocortisone, its structure is similar in certain respects to other members of the class. Desonide is unique, however, in that it is non-halogenated. Historically, fluorination was one of the first chemical modifications found to dramatically enhance the systemic anti-inflammatory

properties of hydrocortisone and until now this structural feature has persisted in steroids intended for the treatment of dermatological disorders by the topical route of administration.

The anti-inflammatory activity of desonide cream has been assessed using a number of model systems: a summary of the relative potencies obtained in the various assays is found in Table 1. While no single assay system is adequate for predicting relative efficacy, the results indicate that desonide cream is a potent anti-inflammatory steroid, comparable to the fluorinated steroids.

TABLE 1
A Summary of the Relative Potencies of Desonide Assay Systems

	Relative Potency / (95% Confidence Limits)		
Assay	**Hydrocortisone**	**Desonide Cream**	**Prednisolone**
Ocular Inflammation Model[a]	1.0	100[b]	---
Ear Edema Model[c]			
Assay No. 1	---	6.95[d]	1.0
Assay No. 2	---	4.30[d]	1.0
Cotton Pellet Granuloma[e]	1.0	66.2 (29.8-153.1)	---
Liver Glycogen deposition[f]	1.0	38.4 (29.1-51.2)	---
Growth Suppression	1.0	59.8 (23.9-136.1)	---
Thymus Involution	1.0	57.5 (33.1-120.8)	---

[a] Based on the ability of the steroid to reverse (or prevent the full development of) ocular inflammation produced by irradiation with ultraviolet light.
[b] Not determined in parallel with hydrocortisone.
[c] Adapted from a method described by Tonelli, et al.: Endocrinology, 77: 625, 1965.
[d] An approximation, due to lack of parallelism.
[e] Based on the method of Winter and Porter; J. Am. Pharm. Assoc. Sci. Ed., 46: 515, 1957.
[f] According to Pabst et al.; Endocrinology, 41: 55, 1947.

TOXICOLOGY

Acute Toxicity

The LD_{50} in rats was 93 mg/kg subcutaneously (with 95% confidence limits to 65 to 134 mg/kg). This compound is approximately six times more toxic than hydrocortisone and at least 60 times more powerful as an anti-inflammatory agent than hydrocortisone. This separation between toxic and

anti-inflammatory properties could substantially reduce the risk of acute toxicity with desonide. Single oral doses of 33.3 and 10 g/kg of a final formulation to 0.20% of desonide were well tolerated in rats and dogs respectively. In view of the fact that a high anti-inflammatory potency was anticipated in this steroid and that probably small quantities may be clinically required, the preceding results indicate that there is minimum risk of clinical toxicity. Acute cutaneous application of 16 g/kg of a final formulation of 0.20% of desonide produced minimum changes. The cutaneous reaction observed with this dose was scarcely apparent and although two deaths were observed, the acute dermal LD_{50} is considerably greater than 16 g/kg.

Subacute Toxicity

In the study of the subacute effects in rabbits the cutaneous application of 2 g/kg of 0.05, 0.10, or 0.20% daily of the final formulation of desonide cream, the following was observed: one death, minimum dermal response, and evidence of systemic absorption.

The dermal responses during the use of these concentrations were not related to the doses and were maximum during the first week of the study. In view of these observations, it seems that the reactions observed were the results of the abrading procedure used, and that the application of the preparations, rather than producing irritation, slowed the formation of scar tissue, thus delaying the normal reduction of the erythema and edema which occurs after abrading.

The observation of one death and of changes in different organs indicate that the dermal application of the final formulation produces systemic effects; the responses observed were characteristic of the changes produced by the repeated administration of steroids. Considering the anti-inflammatory potency of this compound, the high doses used in the sub-acute toxicity study and the clear relationship between the action on the system and the size of dosage, it is possible to predict a minimum risk of systemic toxicity with the use of compounds containing desonide.

Chronic Toxicity

The chronic dermal toxicity of desonide was investigated in rabbits which received daily doses of 0.2, 0.6, or 2.0 gm/kg of a 0.05% cream formulation of the steroid for three months. Body weight

gains were normal in females but were reduced in males at the mid and high dose levels. Food consumption remained normal in both sexes. No meaningful clinical laboratory alterations were observed. Pathological tissue changes observed at autopsy were largely non-specific. Changes in organ weights and/or ratios were increased liver weight and decreased adrenal, gonad, and spleen weights. No pathologic changes were seen in any tissue on microscopic examination. One high dose level female rabbit died late in the study. These findings suggest that the risk of toxicity following chronic dermal application of the material is quite low.

Teratogenicity

The teratogenicity of topically applied 0.05% desonide cream was investigated in pregnant rats and rabbits which received daily doses of 0.02 gm/kg during appropriate gestational periods. Significant increases in the incidence of several fetal abnormalities (types previously reported to occur following systemic administration of corticosteroids) were seen at the mid and high dose level in rabbits. Stillborn fetuses were noted in the rat, and significant increases in resorption sites were observed in both species. A number of pregnant animals died during dosing, and body weight losses were common. It was concluded that 0.05% desonide cream was teratogenic in rats at topical maternal doses of 0.6 and 2.0 gm/kg daily and in rabbits at a dose of 2.0 gm/kg daily. However, in view of the high degree of maternal weight loss and mortality, it is not clear to what degree the defects observed were desonide related.

Dermal Absorption:

The absorption of desonide from large topical doses of 0.1% cream formulation of the steroid (maintained in contact with the skin for eight hours), ranged from 6.5% of the applied dose in rabbits with intact, unoccluded skin to 14.9% in rabbits with abraded skin under occlusion. Absorption of triamcinolone acetonide from a similar formulation averaged 4.4% of the applied dose in rabbits with intact, unoccluded skin and 9.0% in rabbits with abraded skin under occlusion. Dermal absorption of desonide average 54% greater than that of triamcinolone acetonide. Because desonide is about twice as potent as its fluorinated analog upon topical administration, somewhat less steroid will be absorbed from clinically effective doses of desonide than from equi-effective doses of triamcinolone acetonide.

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