PRODUCT MONOGRAPH

PrTOPICORT®
Desoximetasone cream, USP
Desoximetasone gel, USP
Desoximetasone ointment, USP

Cream 0.05% and 0.25%
Gel 0.05%
Ointment 0.25%

Topical Steroid

Bausch Health, Canada Inc.
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ACTIONS

TOPICORT (desoximetasone) Creams, Gel and Ointment are primarily effective because of their anti-inflammatory, anti-pruritic and vaso-constrictive actions.

INDICATIONS

TOPICORT Creams, Gel and Ointment are indicated for the relief of acute or chronic corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in untreated bacterial, tubercular, fungal and most viral lesions of the skin (including herpes simplex, vaccinia and varicella) and in those patients with a history of hypersensitivity to any of the components of the preparation.

TOPICORT Creams, Gel and Ointment are not for ophthalmic use.

WARNINGS

Systemic side-effects may occur with topical corticosteroid preparations, particularly when these preparations are used over large areas or for an extended period of time or with occlusive dressings. A patient who has been on prolonged therapy, especially occlusive therapy, may develop adrenal suppression due to sufficient absorption of the steroid.

The safety of topical corticosteroid preparations during pregnancy and lactation has not been established. The potential benefit should be weighed in these conditions against possible hazard to the fetus or the nursing infant. When indicated, they should not be used extensively, in large amounts or for prolonged periods of time in pregnant patients or nursing mothers.

Visual disturbance may be associated with systemic and topical 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 which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR).

PRECAUTIONS

General

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. [See "Paediatric Use" below].

If local infection exists, suitable concomitant antimicrobial or antifungal therapy should be administered 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 favorable response does not occur promptly, application of the corticosteroid should be discontinued until the infection is adequately controlled.

If local irritation or sensitization develops, TOPICORT Creams, Gel and Ointment should be discontinued, and appropriate therapy instituted.

The use of occlusive dressings increases the percutaneous absorption of corticosteroids; their extensive use increases the possibility of systemic effects and is therefore not advisable. For patients with extensive lesions it may be preferable to use a sequential approach, treating one portion of the body at a time. The patient should be kept under close observation if treated with large amounts of topical corticosteroid or with the occlusive technique over a prolonged period of time.

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

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

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

Prolonged use of topical corticosteroid products may produce atrophy of the skin and of subcutaneous tissues, particularly on flexor surfaces and on the face. If this is noted, discontinue the use of this product.

The product should be used with caution in patients with stasis dermatitis and other skin diseases associated with impaired circulation.

Paediatric Use

Paediatric patients may demonstrate greater susceptibility to topical corticosteroid induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

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

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

TOPICORT Creams, Gel and Ointment are well tolerated; side effects have been rare. Similar to other topical corticosteroid preparations, they may cause burning sensation, dryness, itching, erythema, change in skin pigmentation, folliculitis, pyoderma, striae, telangiectasia and skin atrophy. The following reactions are reported when corticosteroid preparations are used extensively on intertriginous areas or under occlusive dressings: maceration of the skin, secondary infection, striae, miliaria, hypertrichosis and localized skin atrophy.

Adrenal suppression has been shown to occur with prolonged use of large doses of topical corticosteroids, particularly under occlusion due to increased percutaneous absorption.

Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

Hyperglycemia has been reported as a systemic adverse effects of desoximetasone administration.

Eye disorders such as blurred vision and chorioretinopathy have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Toxic effects due to prolonged percutaneous absorption of large amounts of corticosteroids may include: reversible suppression of adrenal function, skin striae, ecchymoses, discoloration or atrophy, acneiform eruptions, hirsutism, infection. Prolonged systemic corticosteroid action may cause hypertension, peptic ulceration, hypokalemia, muscle weakness and wastage and subcapsular cataracts.

Treatment should include symptomatic therapy and discontinuation of corticosteroid administration. In chronically affected patients, a gradual discontinuation may prevent the development of steroid withdrawal symptoms.

DOSAGE AND ADMINISTRATION

Apply a thin film of TOPICORT Creams, Gel or Ointment to the affected skin areas twice daily. Rub in gently.

DOSAGE FORMS

TOPICORT is supplied:

- as a cream formulation containing desoximetasone USP, 0.25%, Isopropyl Myristate, Wool Alcohols Ointment, Wool Alcohols, Methylparaben, Propylparaben and Water in tubes of 20 g, 60 g and 10 tubes of 2 g sample pack.

- as a cream formulation containing desoximetasone USP, 0.05%, Isopropyl Myristate, Wool Alcohols Ointment, Wool Alcohols, Methylparaben, Propylparaben, Lactic Acid, Edetate Disodium and Water in tubes of 20 g and 60 g.

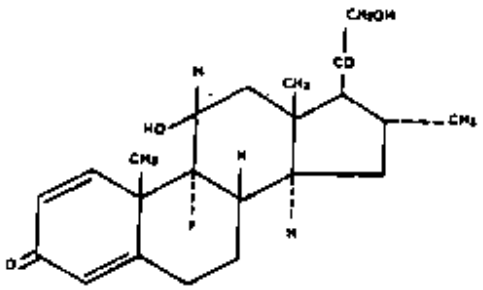
- as a gel formulation containing desoximetasone USP, 0.05%, Isopropyl Myristate, Carbomer Homopolymer Type C, Alcohol, Docusate Sodium, Edetate Disodium, Trolamine and Water in extended-tip tubes of 60 g.

- as an ointment formulation containing desoximetasone USP, 0.25%, Propylene Glycol USP, White Petrolatum USP and Dehymuls® E in tubes of 60 g.
  Dehymuls® E is a proprietary mixture of Sorbitan Sesquioleate, Dicocoyl Pentaerythrityl, Distearyl Citrate, Beeswax, Aluminum Stearates, and Vitamin E (trace amount).

Desoximetasone is a Schedule F prescription drug.

Storage: Store at room temperature, between 15-30 °C.

CHEMISTRY



Molecular Formula: $C_{22}H_{29}FO_4$

Molecular Weight: 376.46 g/mol

Chemical Name: 9α-fluoro,11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Description: White to practically white crystalline powder, with a melting range between 206°C and 218 °C. Insoluble in water; freely soluble in alcohol, in acetone and in chloroform.

PHARMACOLOGY

In experimental studies in laboratory animals desoximetasone was demonstrated to have potent anti-inflammatory activity when compared with other corticosteroids following local or systemic administration.

In the "Granuloma Patch Test" (with croton oil), desoximetasone showed an activity comparable to dexamethasone and approximately ten times weaker than fluocinolone.

Following oral or subcutaneous administration to rats, desoximetasone was five times less potent than dexamethasone in inhibiting granuloma formation (induced by subcutaneously implanted cotton pellets) and in the thymolytic assay system.

A potent anti-inflammatory activity could also be demonstrated comparatively with prednisolone and hydrocortisone following local and topical administration to rats. When administered into the pouch, desoximetasone inhibited granuloma formation twice as effectively as prednisolone and seven times as effectively as hydrocortisone, but was slightly less effective than dexamethasone. When cotton pellets were impregnated with the test drugs prior to implantation, desoximetasone was 3.5 times as potent as prednisolone and six times as potent as hydrocortisone, but four times less potent than dexamethasone.

Additional investigations confirmed the potent glucocorticoid effect following systemic administration. In adrenalectomized fasted rats, the ability of desoximetasone to induce glycogen deposition in the liver was three times less than that of dexamethasone. Following subcutaneous administration, both desoximetasone and dexamethasone showed definite diuretic, natriuretic and kaliuretic effects in rats.

Following subcutaneous injection of ^{3}H-labelled desoximetasone to rats, the blood maximum concentration was observed one hour after administration. The half-life of the tested compound was 2.3 hours. The drug was rapidly eliminated in the urine and feces, with 95% of the administered radioactivity recovered within 24 hours.

The dermal absorption of ^{3}H-labelled desoximetasone was studied in rats; blood level reached a peak at 24 hours. Urinary and fecal excretion accounted for 5-10% of the applied dose. Urinary excretion was four times greater than fecal excretion with 50% of the former as unchanged drug.

TOXICOLOGY

In acute toxicity studies in mice, rats, rabbits and dogs, the oral LD_{50} (95% confidence limits) were determined as follows:

Mice:	1519 (1144-2016) mg/kg
Rats:	1469 (935-2152) mg/kg
Rabbits:	2546 (1926-3365) mg/kg

Mice and rats tolerated a single dose of 50 mg/kg of desoximetasone in various formulations when given either orally, intraperitoneally or subcutaneously.

In an acute oral toxicity study, all rats survived a dose of 36 g/kg desoximetasone gel. Toxic effects, attributed to the alcohol excipient, were decreased spontaneous activity and respiratory rate, ataxia and diminished or absent corneal, tail pinch, and righting reflexes.

Rabbits tolerated a single dose of about 5 mg/kg of desoximetasone, when topically applied to the intact skin for 24 hours. The oral LD_{50} (with 95% confidence limits) in neonatal rats were 230 (204-260) mg/kg for desoximetasone as compared to 134 (96-188) mg/kg for dexamethasone. Neonatal rats survived a single, intraperitoneal dose of 50 mg/kg of desoximetasone, whereas the same dose of dexamethasone killed 7 of 19 pups.

In subacute and chronic toxicity studies the abnormal findings reflected the known systemic effects of corticosteroids.

Subcutaneous administration of desoximetasone to rats for 14 days was well tolerated at the dose of 25 mcg/kg. Doses of 100 mcg/kg inhibited the body weight gain. Rats given 400 and 1600 mcg/kg showed depression in body weight gain and decrease in weights of the thymus, adrenals and spleen.

In similar studies of 26-week duration, the effects of desoximetasone were compared to those of dexamethasone in rats and dogs. Rats given 50 mcg/kg showed a significant elevation of blood glucose. Systemic effects of corticosteroids were seen with doses of 160 mcg/kg and 500 mcg/kg of desoximetasone, the latter dose was also associated with systemic infection and death in 55% of the males and 5% of the females. Dexamethasone, at the dose of 50 mcg/kg showed similar but much less pronounced effects than desoximetasone at 500 mcg/kg. In dogs, typical and dose-related systemic corticosteroid effects were observed in animals treated with doses of 200 to 800 mcg/kg. Dexamethasone, at the dose of 200 mcg/kg, produced more frequent and more marked steroid effects than those observed with 800 mcg/kg of desoximetasone.

Dermal application of desoximetasone on intact or abraded skin was studied in rats, rabbits and dogs. Large doses of desoximetasone applied to the skin for 3 to 24 weeks produced typical local and systemic corticosteroid effects which were attributed to percutaneous absorption.

Desoximetasone failed to produce any signs of irritation when applied directly to the conjunctival sac of the rabbit eye, except for a slight lacrimation immediately following the application. When applied as an emollient cream, the preparation was very well tolerated. When 100 mg of desoximetasone gel 0.05% was instilled into one eye of six New Zealand white rabbits, the other eye serving as a control, very slight conjunctival redness was observed in one treated eye.

A single dose of 100 mg instilled into the right eye of New Zealand white rabbits male and female, the left used as control, failed to produce any sign of ocular mucosal irritation to 72 hours after application and therefore, desoximetasone 0.25% ointment is not considered an irritant to the eye.

Reproduction and teratology studies were done in mice, rats and rabbits.

Desoximetasone, given subcutaneously at the dose of 1600 mcg/kg to pregnant mice during gestational days 7-15, induced a depression of body weight gain and an expected slight increase in the incidence of cleft palate in the fetuses. By comparison, dexamethasone produced, at the lower dose of 400 mcg/kg, a higher incidence of cleft palate in the fetuses.

Desoximetasone and especially dexamethasone produced an inhibitory effect on the weight gain of adult male and female rats during the premating period. The fertility rates were not affected, however, a higher than normal number of resorptions was observed in rats given 100 mcg/kg of dexamethasone. Lower, dose-dependent birth weights of pups as compared to controls were seen in treated animals, especially in those given dexamethasone.

Administered subcutaneously to pregnant rats during gestational days 8-16, desoximetasone produced, at the doses of 400 and 100 mcg/kg, depression of body weight gain in the dams during the treatment period. A retardation of ossification of the odontoid process and an increased incidence of lumbar ribs were also noted.

Topical application of 0.25% desoximetasone ointment to the intact skin of rats during gestational days 7-16 and of rabbits during gestational days 7-19 produced typical corticosteroid

effects in treated animals. The dams showed decreased weight gain, increased rate of abortion, and *in utero* fetal death. Delivered fetuses exhibited varying degrees of growth retardation and corticosteroid induced malformations which were dose-dependent.

REFERENCES

1. Arroum H., Corticosteroids and blurred vision. Clinical Overview. GPE-BW-2017-00521. 2017; 1-13.

2. Arroum H., R. Van Horn. Corticosteroids and Central Serous Chorioretinopathy. Clinical Overview. GPE-BW-2017-00719. 2017; 1-40.

3. Azulay RD, Lemos M. Therapeutic effect of topic desoxymethasone in dermatology. Revta. Bras. Clin. Terap. 1973; 2:179-182.

4. Carr RD, Tarnowski W. Percutaneous absorption of corticosteroids. Acta Derm.-Venereol. 1968; 48:417.

5. Delzant O. Evaluation sur 114 malades de pratique dermatologique quotidienne d'un corticostéroïde topique original. La Clinique 1969; 64:175-177.

6. Draize JH. Dermal toxicity. In: Appraisal of the safety of chemicals in foods, drugs and cosmetics. Ed. Association of Food and Drug Officials of the U.S. 1969; Austin, Texas.

7. Faria JDD. Desoxymethasone (TOPICORT) new steroid for topical use. Derm. Venez. 1970; 9(102):978-984.

8. Fredriksson T. A double-blind clinical trial of desoxymethasone fatty ointment versus flucinolone acetonide ointment in psoriasis. Curr Ther Res 1979; 25(6):809-813

9. Gervini R, Bernardi CDV. Clinical trial with the topic steroid: desoxymethasone (A41-304). Revta. Bras. Clin. Terap. 1973; 2:187-190.

10. Gill KA, Baxter DL. Plasma cortisol suppression by steroid creams. Arch. Dermat. 1964; 89:734-740.

11. Grupper C. Un progrès en corticothérapie topique: essais cliniques d'une molécule originale. G.M. de France 1968; 27:5341-5344.

12. Heite HJ, Kalkoff KW, Kohler H. Uber die entz・dungshemmende Wirkung verschiedener Steroid-Salben an der menschlichen Haut, gemessen am Pyrexal-Erythem. Arzneimittelforschung 1964; 14:222-226.

13. Imbert R, Maurell G. Essai clinique d'un nouveau corticoïde topique: la désoximétasone. Lyon Médical 1970;l 27:47-51.

14. Kuokkanen K. Comparison of 0.25% desoxymethasone ointment with 0.05% fluocinonide ointment in psoriasis. Curr Med Res Opin 1977; 4(10):703-705

15. Kligman AM. The identification of contact allergens by human assay-III. The

maximization test. J. Invest. Derm. 1966; 47:393.

16. Lépine J. Le R-2113: un nouveau corticostéroïde cutané de grand intérêt en thérapeutique dermatologique locale. Médecine Interne 1968; 3:709-712.

17. Maia F, Furtado TA. Clinical trial with the new topic steroid: desoxymethasone (A41-304) 0.25%. Revta. Bras. Clin. Terap. 1973; 2:195-198.

18. Marzulli FN, Maibach HI. Perfume phototoxicity. J. Soc. Cosmet. Chem. 1970; 21:695.

19. McKenzie AW, Stoughton RB. Method for comparing percutaneous absorption of steroids. Arch. Derm. 1962; 86:608.

20. McKenzie AW. Percutaneous absorption of steroids. In: Progress in the biological sciences in relation to dermatology, Volume 2. Ed. Rook A, Champion RH. The University Press 1964; Cambridge:283.

21. Moraes MLT. Clinical trial with the new topical steroid desoxymethasone (A41- 304) in 29 patients with different dermatosis. Revta. Bras. Clin. Terap. 1973; 2:199-202.

22. Nair BKH, Nair CHK. Clinical evaluation of desoximetasone in treatment of dermatoses and psoriasis. Int. J. Derm. 1975; 14(4):277-279.

23. Natarajan M. A comparative clinical trial of desoxymethasone in the treatment of eczematous conditions. The Indian Pract. 1974; 27(11):525-532.

24. Parant M. Remarques sur un nouveau corticostéroïde topique en pratique dermatologique. Rev. Med. Toulouse 1970; 6:371-375.

25. Peryassu D. The use of a new topic steroid - desoxymethasone (A41-304) in treatment of psoriasis. Revta. Bras. Clin. Terap. 1973; 2:191-194.

26. Ramiti N. Clinical test of a new topical steroid A41-304 - desoxymethasone 0.25%. Revta. Bras. Med. 1973 30(6):410-412.

27. Rink K, Ranke M. Cushing syndrome in a baby after 5-month application of a steroid ointment. Paed Prax 1981; 22:551-555

28. Rossetti NM, Mendes JP. Topic use of desoxymethasone (A41-304) in the treatment of different dermatoses. Revta. Bras. Clin. Terap. 1973; 2:183-186.

29. Savin RC, Stoughton RB, Cornell RC, et al. Comparative study of desoximetasone ointment 0.25% versus fluocinonide ointment 0.05% in patients with psoriasis. Clin Ther 1985; 8(1):118-125.

30. Shimao S, et al. A study on the suppression of the adrenocortical function by

percutaneous absorption of a corticosteroid for external use - the case of a 17 -desoxymethasone. Rinsho Hifu 1973; 15(5):303-310.

31. Silva RF, Souza LP. Topical treatment of psoriasis with desoxymethasone (A41- 304). Revta. Bras. Clin. Terap. 1973; 2:557-558.

32. Stoughton RB. Percutaneous absorption. Tox. & Appl. Pharmacol. 1965; 7(Suppl 2):1.

33. Stoughton RB. Vasoconstrictor activity and percutaneous absorption of glucocorticosteroids. Arch. Derm. 1969; 99:753.

34. Takeda Y, Kukita A. Autoradiographic studies on percutaneous absorption and reservoir of 17 -desoxymethasone. The Nishi-nihon J. Der. 1973; 35(5):591-596.

35. Texier ML. Expérimentation clinique d'un nouveau topique corticoïde: la désoximétasone. Bordeaux Médical 1969; 3:687-690.

36. Theron HP. Résultats cliniques du traitement par la désoxymétasone de 47 cas d'affections cutanées périorbitaires. La Clinique 1971; 56(676):195-197.

37. Tkalych O., MD and R. Singh, BDS. Desoximetasone and hyperglycemia. Clinical Overview: GPE-BW-2017-00197. 2017; 1-13.

38. Willis I, Kligman AM. Photocontact allergic reactions. Arch. Derm. 1969; 100:535.