PRODUCT MONOGRAPH

HALOG*

(halcinonide)

Cream, 0.1%, Ointment, 0.1%,

Topical Steroid

Bristol-Myers Squibb Canada
2365 Côte-de-Liesse
Montreal, Canada.

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THERAPEUTIC CLASSIFICATION

Topical Steroid

ACTION AND CLINICAL PHARMACOLOGY

HALOG formulations afford relief of itching and burning associated with inflammatory skin lesions, by virtue of the substantial anti-inflammatory, anti-pruritic, and vasoconstrictor actions of halcinonide. Significant or complete therapeutic responses are obtained in patients with acute or chronic corticosteroid-responsive dermatoses.

INDICATIONS

HALOG is indicated for topical application for relief of acute or chronic corticosteroid-responsive dermatoses, including: atopic dermatitis, contact dermatitis, neurodermatitis (lichen simplex chronicus), eczematous dermatitis and psoriasis.

Applied under occlusive dressings, HALOG Cream or Ointment is useful in the management of recalcitrant cases of psoriasis and neurodermatitis (lichen simplex chronicus).

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in untreated tuberculous, fungal and most viral lesions of the skin (including herpes simplex, vaccinia and varicella). HALOG formulations are not to be used in patients with a history of hypersensitivity to any of their components.

HALOG formulations are not intended for ophthalmic use, nor should they be applied in the external auditory canal of patients with perforated eardrums.

WARNINGS

Pregnancy

The safety of topical corticosteroid preparations during pregnancy and lactation has not been established. The potential benefit of HALOG formulations, if used during pregnancy and lactation, should be weighed against possible hazard to the fetus or the nursing infant.

Adrenal suppression and other 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. A patient who has been on prolonged therapy, especially occlusive therapy, may develop symptoms of steroid withdrawal when the medication is stopped.

PRECAUTIONS

In cases of bacterial infections of the skin, appropriate antibacterial agents should be used as primary therapy. If it is considered necessary, HALOG 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 application of corticosteroid should be discontinued until the infection is brought under control.

If local irritation or sensitization develops, HALOG should be discontinued and appropriate therapy instituted.

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

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

Prolonged use of topical costicosteroid 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 topical corticosteroids.

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

Occlusive Dressing Technique

The use of occlusive dressings increases the percutaneous absorption of corticosteroids; their extensive use increases the possibility of systemic effects. For patients with extensive lesions it may be preferable to use a sequential approach, treating one portion of the body at a time with such dressings. The patient should be kept under close observation if treated with the occlusive technique over a considerable period of time.

Thermal homeostasis may be impaired if large areas of the body are occluded. Use of occlusive dressings should be discontinued if elevation of the body temperature occurs.

Plastic films, commonly used as occlusive dressings, are often flammable and patients should be warned when using such materials. Extreme caution should be employed when such films are used on children so that possibility of suffocation is avoided.

Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive, and a substitute material may be necessary.

If infection develops, discontinue the use of the occlusive dressings and institute appropriate antimicrobial therapy.

ADVERSE REACTIONS

HALOG is well tolerated. Significant local irritation is uncommon. Similar to other topically applied corticosteroid preparations, it may cause a transient burning sensation in some patients. The use of corticosteroids under occlusive dressings is known to produce miliaria, folliculitis, maceration of the skin, pyoderma, or localized cutaneous atrophy. When corticosteroid preparations are used extensively in intertriginous areas or under occlusive dressings, striae occasionally may develop. Other adverse skin reactions reported with the use of topical steroids are erythema, dryness, itching, hypertrichosis, and change in skin pigmentation.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Percutaneous absorption of corticosteroids can occur especially under occlusive conditions. When large amounts of corticosteroid are absorbed, toxic effects may include mild reversible suppression of adrenal function, ecchymoses of the skin, peptic ulceration, hypertension, aggravation of infection, hirsutism, acne, edema and muscle weakness, due to protein depletion. Animal studies with halcinonide suggest that overdosage in females may result in swollen mammary glands or lactation. No specific antidote is available: treatment should be chiefly symptomatic and corticosteroid administration should be discontinued.

DOSAGE AND ADMINISTRATION

Usual adult dosage range: Apply to the affected area 2 to 3 times daily. Rub in gently.

Occlusive Dressing Technique

Gently rub a small amount of the HALOG Cream or Ointment into the lesion until the cream or ointment disappears. Then re-apply the cream or ointment, leaving a thin coating on the lesion and cover with a pliable nonporous film. The frequency of changing dressings is best determined on an individual basis. It may be convenient to apply the cream or ointment under such dressings in the evening and remove the dressings in the morning (i.e., 12-hour occlusion). Utilizing the latter regimen, additional HALOG Cream or Ointment should be applied, without occlusion, during the day. Re-application of the preparation is essential at each dressing change.

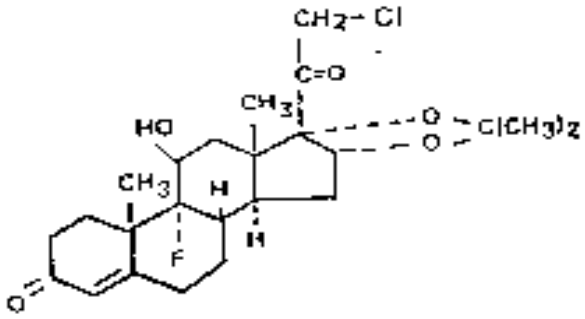
DOSAGE FORMS

HALOG Cream (halcinonide, 0.1%) is supplied in tubes of 15, 30 and 60 g.

HALOG Ointment (halcinonide, 0.1%) is supplied in tubes of 30, and 60 g.

PHARMACEUTICAL INFORMATION

Structural Formula:



Molecular Formula: $C_{24}H_{32}O_5FCl$

Molecular Weight: 454.97

Chemical Name: 9 -Fluoro-2l-chloro-ll,16,17 -trihydroxypregn-4-ene-3,20-dione cyclic 16,17-acetal with acetone.

Description: Halcinonide is a white to off-white fine crystalline powder with a melting point of about 265˚C.

Solubility: It is soluble in acetone and chloroform, slightly soluble in ethanol, ethyl ether, and benzene (upon warming), very slightly soluble in propylene glycol (upon warming) and insoluble in water and hexane. HALOG (halcinonide), a potent synthetic corticosteroid, is available in the following topical formulations:

HALOG Cream, 0.1%:

Halcinonide, 0.1%, in glyceryl monostearate N.F., cetyl alcohol, synthetic spermaceti, isopropyl palmitate, polysorbate 60, propylene glycol, and purified water. Each g contains: halcinonide 0.1%. Nonmedicinal ingredients: cetyl alcohol, dimethicone, glyceryl monostearate, isopropyl palmitate, polysorbate, propylene glycol, titanium dioxide and water.

HALOG Ointment, 0.1%:

Halcinonide, 0.1%, in Plastibase (Squibb-Plasticized Hydrocarbon Gel) with polyethylene glycol 400, polyethylene glycol 6000 distearate, polysorbate 65, polyethylene glycol 300, polyethylene glycol 1540 and butylated hydroxytoluene. Each g contains: halcinonide 0.1%. Nonmedicinal ingredients: butylated hydroxytoluene, mineral oil, polyethylene, polyethylene glycol and polyethylene glycol distearate..

Storage

Store at room temperature. Avoid freezing. Avoid storage at temperatures exceeding 30˚C.

PHARMACOLOGY

Studies with halcinonide in standard anti-inflammatory tests have shown it to possess activity similar to, or better than, that of triamcinolone acetonide.

In the Reversed Passive Arthus reaction in rabbits a dose of 400 mg of the 1% cream produced a 70% reduction in edema when applied topically. Approximately 60% inhibition was produced by doses of 400 µg, intradermally, or 5.0 mg/kg, intramuscularly, of the unformulated halcinonide.

In guinea-pigs, subcutaneous administration of doses of 6.2 to 100 mg/kg of halcinonide or triamcinolone acetonide, suspended in sesame oil, produced comparable results in the inhibition of the erythema and in duration of the delayed hypersensitivity skin reaction.

The ID_{50}'s for the Inhibition of edema in the Carrageenin-induced Paw Edema test in rats were 1.1, 3.1 and 1.3 mg/kg for oral, subcutaneous or intramuscular administration, respectively.

When tested against Adjuvant-induced Arthritis in rats, halcinonide and triamcinolone acetonide exhibited comparable activities in preventing or curing both locally and systemically induced inflammation.

Halcinonide was not as active as triamcinolone acetonide in decreasing the formation of exudate at the knee-joint of rabbits in the test for inhibition of synovitis.

Percutaneous absorption of halcinonide has been demonstrated in dogs (intact skin 0.4% to 5% of a 1 g dose of HALOG Cream, abraded skin 4% to 10%) and in rabbits (intact skin 6% to 16%; abraded skin 14% to 23%). In rabbits the formation of a depot of halcinonide in the skin after 24 hours. The half-life for excretion in urine and feces was 1.8 days.

In endocrinological studies halcinonide has been shown to possess the following properties:

- antigranuloma and thymolytic potency in rats comparable to triamcinolone acetonide;
- 20 to 40 times the potency of hydrocortisone in inducing liver glycogen deposition in rats;
- little or no sodium retention and only a slight increase in potassium excretion when tested in male rats;
- progestational activity approximately thirty times greater than progesterone, when administered subcutaneously to rabbits, and approximately 130 times greater when administered intramuscularly;
- slight estrogenic activity in rats, probably as a result of its progestational activity;
- anti-estrogenic and anti-uterotrophic activities in rats;
- anti-androgenic activity in cockerels.

Clinical Pharmacology

In a series of special safety studies halcinonide did not produce any primary irritation nor did it demonstrate any potential for producing contact sensitization (5), phototoxicity (7) or photoallergy (16).

Six patients with extensive dermatoses and five normal subjects were treated for 5 days with 30g daily applied under occlusive dressing to 50% of the body surface. The only systemic effect observed was the anticipated (2) reversible suppression of pituitary-adrenal axisfunction. Two patients did not show adrenal suppression. All patients reverted to normal by the time of the next metyrapone challenge 6 days later.

TOXICOLOGY

HALOG Cream, 0.1%

In acute toxicological studies in mice the intraperitoneal LD_{50} for halcinonide varied between 150 and 220 mg/kg. Oral doses of up to 212.5 mg of halcinonide/kg (i.e. 21.25 g/kg of the 1% cream formulation) were administered without toxic effects.

In subacute dermal toxicity studies in dogs, halcinonide cream, 0.1% (0.5 to 5.0 mg of halcinonide/kg per day) caused no marked changes, except for a decrease in weight of the adrenal glands, a slight increase in liver weight, and slight lactation in five of six females. These findings reflect known systemic effects of corticosteroids and were attributed to percutaneous absorption. Weight gain was observed in some animals.

In similar studies in rabbits, halcinonide, 0.1%, (0.1 to 1.5 mg of halcinonide/kg per day) caused a higher percentage gain in body weight and efficiency of food utilization in all animals, when compared to controls. A slightly elevated cholesterol value, blood sugar, and SGPT were observed in three separate animals. There was a decrease in weight of the adrenal glands in all treated animals.

In subacute intramuscular studies in monkeys, bulk halcinonide (0.05 to 0.5 mg/kg per day) caused the following expected findings: a decrease in weight as well as a depletion of sudanophilic material of the adrenal glands; endometrial progestational effects, with the degree of response being within the range normally observed during a menstrual cycle; and a slightly decreased serum glucose in two monkeys in each of the high- and Intermediate-dose groups.

Stage II teratology studies were done in mice, rabbits, and rats with topically applied halcinonide cream, 0.1%, (0.15 to 1.5 mg of halcinonide/kg per day). Typically of corticosteroids, halcinonide induced cleft palate in the offspring of mice and rabbits. Halcinonide did not induce any teratologic effects in the offspring of rats; maximal doses were embryotoxic in rats and rabbits.

HALOG Ointment 0.1%

In acute toxicological studies the estimated intraperitoneal LD_{50} for halcinonide ointment, 0.1%, was 8,000 mg of sample/kg (equivalent to 8 mg of halcinonide/kg). Mice that died in 2 to 5 days were ataxic or prostrate on the first post-dose day. Most animals given the 8,000 mg/kg dose and a few given the 4,000 mg/kg dose had weight losses by the second post-dose day, but all surviving mice were gaining weight by the end of the test period.

In dermal irritation studies in rats, approximately 250 mg of halcinonide ointment was applied once daily for five consecutive days to abraded application sites on each side of the back of four female rats. Examination of the sites showed no signs of irritation.

IRRITATION STUDIES

HALOG Cream 0.1%

HALOG Cream, 0.1%, failed to produce any signs of irritation when instilled into the eyes of rabbits or applied topically to the abraded skin of rats. Bulk halcinonide or triamcinolone acetonide, suspended in agar, when injected into the vastus lateralis muscles of rabbits,

produced mild irritation.

HALOG Ointment. 0.1%,

There was negligible irritation of the eyes and no photophobia or corneal lesions were observed after application of approximately 80 mg of the ointment, 0.1%, once daily for three consecutive days into the conjunctival sacs of four normal New Zealand white rabbits.

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