PRODUCT MONOGRAPH

PrTEVA-CLOBETASOL
Clobetasol 17-propionate

0.05%
Cream, Ointment and Scalp lotion

Topical anti-inflammatory steroid

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CLINICAL PHARMACOLOGY

Actions

TEVA-CLOBETASOL (clobetasol 17-propionate 0.05%) is a highly potent topical corticosteroid. The corticosteroids are a class of compounds comprising steroid hormones that are secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects. Topical corticosteroids such as clobetasol are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions.

Pharmacokinetics:
In man, the extent of percutaneous absorption of topical corticosteroids, including clobetasol, is determined by many factors, including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressing.

As with all topical corticosteroids, clobetasol can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids.

Once absorbed through the skin, topical corticosteroids enter pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids, including clobetasol and its metabolites, are also excreted in the bile.

BIOAVAILABILITY

The relative potency of corticosteroids is usually assayed by the vasoconstriction test which reflects the potency of the steroid molecule, its topical activity, as well as its bioavailability from the particular formulation. In a recent study, the vasoconstrictor response of **TEVA-CLOBETASOL** (clobetasol 17-propionate 0.05%) cream, ointment

and scalp lotion were compared with Dermovate® (clobetasol 17-propionate 0.05%) cream, ointment and scalp lotion, respectively, in 30 healthy volunteers. The mean pharmacokinetic parameters are presented below:

Mean pharmacokinetic parameters of clobetasol 17-propionate

Brand	AUC_{1-24} (Sum of scores. Hr)	R_{max} (Sum of scores)	T_{max} (Hours)	Relative Potency*
TEVA-CLOBETASOL				
Cream	62.4	3.8	2.7	106 - 110%
Ointment	65.9	3.9	1.9	87 - 90%
Scalp Lotion	68.3	4.0	2.1	100 - 102%
Dermovate®				
Cream	58.8	3.5	3.7	--
Ointment	73.0	4.4	1.0	--
Scalp Lotion	66.7	4.0	1.9	--

** Relative potency (***TEVA-CLOBETASOL** */ Dermovate®) for AUC_{1-24} and R_{max}.*

The results demonstrated that each dosage form of **TEVA-CLOBETASOL** was comparable in vasoconstrictor response to that of the corresponding dosage form of Dermovate®.

INDICATIONS AND CLINICAL USE

TEVA-CLOBETASOL (clobetasol 17-propionate 0.05%): **Cream** and **Ointment:** For the topical therapy of recalcitrant corticosteroid-responsive dermatoses, including severe cases of psoriasis (excluding widespread plaque psoriasis) and eczematous dermatitis.

Scalp lotion: Application is indicated for the topical treatment of recalcitrant corticosteroid-responsive dermatoses of the scalp, including recalcitrant cases of psoriasis and seborrheic dermatitis.

CONTRAINDICATIONS

Rosacea, acne vulgaris, perioral dermatitis or perianal and genital pruritus. These preparations are contraindicated also in primarily infected bacterial or fungal skin lesions if no anti-infective agent is used simultaneously, in primary cutaneous viral infections (i.e. herpes simplex, vaccinia and varicella) and in tuberculous skin lesions. Clobetasol should not be used in patients who are hypersensitive to any of the components of the preparation.

WARNINGS

Use with caution on lesions close to the eye. Care is needed to ensure that the preparation does not enter the eye as glaucoma may result. Posterior subcapsular cataracts have been reported following systemic use of corticosteroids.

When used over extensive areas for prolonged periods, it is possible that sufficient absorption may take place to give rise to adrenal suppression. Therefore, it is advisable to use clobetasol for brief periods only and to discontinue its use as soon as the lesion has resolved. No more than 50 g of the cream or ointment or 50 mL of the scalp application should be used per week.

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

PRECAUTIONS

General

Children: Because the safety and effectiveness has not been established in children, its use in this age group is not recommended.

The face, more than other areas of the body, may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematous and severe eczema.

Prolonged use of topical corticosteroids may produced atrophy of the skin and of subcutaneous tissues. If this is noted, the use of the product should be discontinued.

Although hypersensitivity reactions are rare with topically applied steroids, the drug should be discontinued and appropriate therapy initiated if there are signs of hypersensitivity.

Long-term continuous therapy should be avoided where possible as adrenal suppression can occur even without occlusion. Significant systemic absorption may occur when corticosteroids are applied over large areas of the body, especially under occlusive dressings. Because the degree of absorption of clobetasol when applied under occlusive dressing has not been measured, its use in this fashion is not recommended.

Topical steroids may be hazardous in psoriasis for a number of reasons including rebound relapses, development of tolerance, risk of generalized pustular psoriasis and

development of local or systemic toxicity due to impairment barrier function of the skin. If used in psoriasis, careful patient supervision is important.

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and systemic administration of anti-microbial agents.

In cases of bacterial infections 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 application of corticosteroid should be discontinued until the infection is brought under control. Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressings, and the skin should be cleansed before a fresh dressing is applied.

Pregnancy and Lactation: Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development. The relevance of this finding to human beings has not been established. However, the administration of this drug during pregnancy and lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. Drugs of this class should not be used extensively on pregnant patients in large amounts or for prolonged periods of time.

Clobetasol scalp applications should not be used near an open flame.

ADVERSE REACTIONS

As with other topical corticosteroids, prolonged use of large amounts of clobetasol or treatment of extensive areas can result in sufficient systemic absorption to produce the features of hypercorticism.

Provided the weekly dosage is less than 50 g in adults, any suppression of the hypothalamic-pituitary axis (HPA-axis) is likely to be transient with a rapid return to normal values once the short course of steroid therapy has ceased.

Prolonged and extensive treatment with highly active corticosteroid preparations may cause local atrophic changes in the skin such as thinning, striae, and dilatation of the superficial blood vessels, particularly when occlusive dressings are used, or when skin folds are involved. Local burning, irritation, itching, dryness of the skin, telangiectasia, acneform eruptions, change in pigmentation, secondary infection, hypertrichosis and atrophy of skin and s.c. tissue have also been observed following topical corticosteroid therapy. Exacerbation of symptoms may occur.

In rare instances, treatment of psoriasis with corticosteroids (or their withdrawal) is thought to have provoked the pustular form of the disease.

Clobetasol preparations are usually well tolerated, but if signs of hypersensitivity appear, application should be stopped immediately.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdosage is very unlikely to occur. However, in the case of chronic overdosage or misuse, the features of hypercorticism may appear. Treatment should be discontinued in this case.

DOSAGE AND ADMINISTRATION

TEVA-CLOBETASOL Cream and **Ointment:** Apply sparingly to cover the affected area, and gently rub into the skin. Frequency of application is 2 to 3 times daily according to the severity of the condition. The total dose applied should not exceed 50 g weekly. **For short-term external use by adults only.**

Scalp Lotion: Apply once or twice daily to the affected areas of the scalp and rub in gently. The total dose applied should not exceed 50 mL weekly. **For short-term external use by adults only.**

Therapy should be discontinued if no response is noted after a week or as soon as the lesion heals. It is advisable to use **TEVA-CLOBETASOL** (clobetasol) for brief periods only.

PHARMACEUTICAL INFORMATION

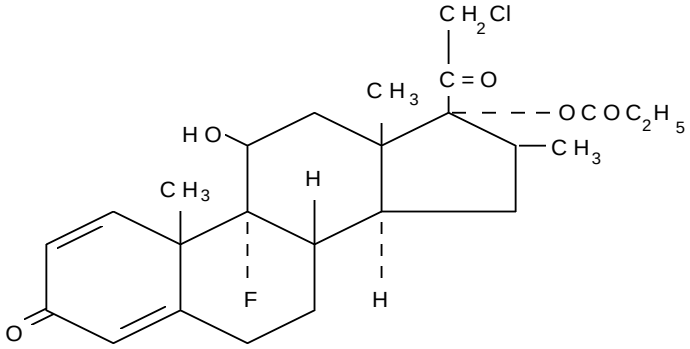
Drug Substance

Proper name: Clobetasol 17-propionate

Chemical name: 21-chloro-9a-fluoro-11b, 17a-dihydroxy-16b-methylpregnan-1,4-diene-3,20-dione, 17-propionate

Molecular formula: $C_{25}H_{32}ClFO_5$

Structure formula



Molecular weight: 467

Physical form: White to cream colored crystalline powder.

Solubility: Soluble in acetone, chloroform and dioxane

Melting point: 195°C

STABILITY AND STORAGE RECOMMENDATIONS

TEVA-CLOBETASOL Cream and **Ointment** should be stored at temperatures between 15° to 30°C.

AVAILABILITY OF DOSAGE FORMS

TEVA-CLOBETASOL Cream: Each g contains: 0.05% w/w clobetasol 17-propionate in a cream base. **Non-medicinal ingredients in alphabetical order:** ceteareth-20, chlorocresol, citric acid, glyceryl stearate, polyethylene glycol, propylene glycol, purified water, sodium citrate and stearyl alcohol. Tubes of 15 g and 50 g, and jars of 450 g.

TEVA-CLOBETASOL Ointment: Each g contains: 0.05% w/w clobetasol 17-propionate in an ointment base. **Non-medicinal ingredients in alphabetical order:** light mineral oil and petrolatum. Tubes of 15 g and 50 g, and jars of 450 g.

TEVA-CLOBETASOL Scalp Lotion: Each mL contains: 0.05% w/w clobetasol 17-propionate in a hydroalcoholic solution. **Non-medicinal ingredients in alphabetical order:** carbomer, isopropyl alcohol, purified water and triethanolamine. HDPE bottles of 20 mL and 60 mL.

PHARMACOLOGY

Clobetasol 17-propionate has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain.

Animals:

In thymolytic activity, clobetasol 17-propionate exhibited interspecies differences. In mice, the thymolytic activity of clobetasol 17-propionate was 2 to 10 times greater than that of betamethasone alcohol, depending upon route of administration. In rats, the two drugs are equipotent.

A similar species difference was also observed in anti-granuloma activity. When anti-granuloma activity was determined in mice, using cotton wool pellets soaked in carrageenan, clobetasol 17-propionate was 5 times as potent as betamethasone alcohol, when given subcutaneously. In rats, both drugs had approximately equal activity.

Both clobetasol 17-propionate and betamethasone alcohol showed equally weak mineralocorticoid activity in rats.

In female mice, clobetasol 17-propionate showed no androgenic-anabolic activities as determined by preputial gland and growth rate measurements. Clobetasol 17-propionate was equally inactive in male rats, using the seminal vesicle, levator ani and growth rate measurements.

In mice, clobetasol 17-propionate showed antiestrogenic activity, as determined by measuring the uterine weight after estrone and clobetasol 17-propionate administration.

Compared to progesterone, clobetasol 17-propionate showed marked antiestrogenic activity in ovariectomized rats.

In weanling rats, estrogenic activity was about one five-hundredth that of estrone.

In rabbits, progestational activity of clobetasol 17-propionate, administered subcutaneously, was about five times that of betamethasone 17-valerate, while orally, it had only one-half the activity of the latter steroid.

Clobetasol 17-propionate showed no anti-gonadotropic activity in weanling male rats.

Human

The potency of clobetasol 17-propionate was compared with that of fluocinolone acetonide and betamethasone 17-valerate, in volunteers using the vasoconstrictor test.

Clobetasol 17-propionate was found to be 18 times as potent as fluocinolone acetonide, and 6 times as potent as betamethasone 17-valerate.

Eleven-hundred-and-fifty patients with bilateral lesions of psoriasis and eczema participated in an international controlled trial, where the efficacy and safety of clobetasol 17-propionate cream and ointment were compared to those of fluocinonide, fluclorolone acetonide and betamethasone 17-valerate. The results showed that both formulations of the clobetasol 17-propionate were effective, especially in psoriasis.

A comparison of the bioavailability of 30 commercially-available topical steroid preparations was made using a modified version of the blanching test. The results demonstrated a high activity in the clobetasol 17-propionate cream. A similar study was performed comparing 31 ointments. The results were comparable to those obtained with the corresponding creams.

Adrenal suppression is often seen in patients using topical corticosteroids. To study the effect of clobetasol 17-propionate ointment on the above systemic effect, 35 patients with various skin conditions applied clobetasol 17-propionate for 2 to 4 weeks. Thirty patients did not experience any suppression, however of the remaining 5, 2 patients had initially subnormal plasma corticosteroid levels. When 8 g, 40 g and 100 g of ointment per week were applied to 3 patients, adrenocortical suppression was demonstrated during therapy. However, 4 other patients using 100 g of ointment weekly did not experience any decrease in plasma corticosteroid levels.

TOXICOLOGY

ACUTE TOXICITY:

Acute toxicity (LD_{50}) has been determined in several species using oral (PO), subcutaneous (SC) and intraperitoneal (IP) routes of administration. The SC route proved to be the most toxic in both mice and rats.

Species	Route	Sex	LD_{50} (mg/kg)
Mice	SC	M	81.7
		F	81.7
	IP	M	156.4
		F	117.8
Rats	SC	M	397.3
		F	365.8
	IP	M	413.7
		F	351.3
	PO	M & F	>3,000

After a single subcutaneous injection of 1, 2 or 4 g/kg of clobetasol 17-propionate, the majority of the mice developed hepatic necrosis and atrophy of the thymus gland. Some animals also developed interstitial nephritis.

Rats which received a single subcutaneous injection of 1 g/kg of clobetasol 17-propionate, had fatty liver necrosis and nephrocalcinosis on histological examination. An oral dose of 1 g/kg gave similar results.

No drug-related histological changes were found in guinea pigs receiving a single subcutaneous injection of 60 mg/kg of clobetasol 17-propionate.

In contrast, a single intramuscular injection of 60 mg/kg of clobetasol 17-propionate caused intra-alveolar hemorrhage and thymus involution in 3 out of 4 rabbits. All animals had foamy periportal cells with increased glycogen content. Some of the injection sites showed small foci of muscle necrosis. No deaths occurred.

In cats, a single intramuscular injection of 60 mg/kg of clobetasol 17-propionate caused some cytoplasmic changes in the hearts and livers, with lipid infiltration. The thymus glands were involuted. No deaths occurred.

In dogs, a single intramuscular injection of 15 mg/kg of clobetasol 17-propionate caused increased liver glycogen content, weight loss and melena. One dog had inflammation of the salivary gland. A dose of 60 mg/kg caused a local abscess at the injection site in one dog.

Histologically, there was lipid infiltration in the heart and liver, as well as thymus involution. One dog became moribund at the highest dose.

SUBACUTE TOXICITY:

Rats receiving daily subcutaneous injections of clobetasol 17-propionate for 12 weeks at doses from 1.44 μg to 180 μg/kg showed growth reduction, increased hemoglobin concentration, leukopenia, SGOT elevation, reduction of thymus weight, reduced blood glucose and adrenal atrophy.

In females, decreased uterine weight and bone marrow hypoplasia were observed. Some animals had chronic respiratory disease and interstitial nephritis.

In dogs, daily intramuscular injections of 1.44, 7.2, 36.0 or 180 μg/kg of clobetasol 17-propionate were given for 13 weeks. Reduced hemoglobin, leucopenia, increased serum protein, increased liver and kidney weights, adrenal atrophy and increased alkaline phosphatase were observed. One dog died after forty injections of the highest dose.

REPRODUCTION AND TERATOLOGY:

No maternal mortality was observed in mice treated with subcutaneous injections of clobetasol 17-propionate at doses of 0.03, 0.1, 0.3 or 1.0 mg/kg from day 7 to day 16 of pregnancy.

The number of live fetuses decreased and resorption sites increased at the highest dose. There was a dose-related increase in the incidence of cleft palate, skeletal immaturity and abnormalities, at doses from 0.1 to 1.0 mg/kg.

In rabbits receiving clobetasol 17-propionate at doses of 1, 3 or 10 μg/kg daily by subcutaneous injections, from day 6 to day 18 of pregnancy, decreased weight gain of the mothers was observed at the highest dose. No adverse effects on the fetuses were observed at 1 μg/kg; but the drug was teratogenic at 3 and 10 μg/kg. A dose of 3 μg/kg increased skeletal immaturity and caused cleft palate. The highest dose caused a reduced number of live fetuses and of litter weight, in addition to an increased incidence of cleft palate and skeletal abnormalities.

LOCAL IRRITANCY:

Skin: In the 14-day dermal tests, guinea pigs were treated with clobetasol 17-propionate 0.05% ointment, using a total of approximately 120 mg on one clipped flank, while the other side was treated similarly with the ointment base only. Both treatments caused equal extent of erythema. Similarly, no difference in extent of erythema was observed in rabbits receiving similar treatment with clobetasol 17-propionate ointment or its base.

Eye: Application of clobetasol 17-propionate ointment was non-irritating when applied to the eyes of guinea pigs and rabbits for 14 days.

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MORE INFORMATION

This document plus the full Product Monograph prepared for health professionals can be found by contacting Teva Canada Limited by:

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