PRODUCT MONOGRAPH

MYLAN-CLOBETASOL OINTMENT

(Clobetasol 17-propionate Ointment 0.05% w/w)

Topical Corticosteroid

Mylan Pharmaceuticals ULC
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THERAPEUTIC CLASSIFICATION

Topical Corticosteroid

ACTIONS AND CLINICAL PHARMACOLOGY

MYLAN-CLOBETASOL (clobetasol 17-propionate) Ointment 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 17-propionate, 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 17-propionate, 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 17- propionate 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 17-propionate and its metabolites, are also excreted in the bile.

INDICATIONS AND CLINICAL USE

MYLAN-CLOBETASOL (clobetasol 17-propionate)Ointment is indicated for short-term topical treatment of recalcitrant corticosteroid-responsive dermatoses, including severe cases of psoriasis and eczematous dermatitis. This product is not recommended for use in children under 12 years of age.

CONTRAINDICATIONS

MYLAN-CLOBETASOL (clobetasol 17-propionate) Ointment is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation. The drug is also contraindicated in infected skin lesions if no anti-infective agent is used simultaneously; fungal and viral infections of the skin, including herpes simplex, vaccinia and varicella; pregnancy and lactation. Topical corticosteroids are also contraindicated in tuberculous lesions of the skin.

WARNINGS

Use in Pregnancy: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Clobetasol 17-propionate is absorbed percutaneously and when administered subcutaneously to animals it is a significant teratogen at very low doses.

Nursing Mothers: Systemically administered corticosteroids are secreted into breast milk and could suppress

growth, interfere with endogenous corticosteroid production, or cause untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Caution should be exercised when MYLAN-CLOBETASOL (clobetasol 17-propionate) Ointment is prescribed for a nursing woman.

General:

When used over extensive areas, or for prolonged periods, or under occlusions, sufficient absorption may take place to give rise to systemic effects. Because of the potential of potent corticosteroids to suppress the hypothalamic-pituitary adrenal (HPA) axis, it is advisable, therefore, to use MYLAN-CLOBETASOL Ointment for brief periods only, and to discontinue its use as soon as the lesions have cleared up. Do not use more than 50 grams of MYLAN-CLOBETASOL Ointment per week. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

MYLAN-CLOBETASOL Ointment is for dermatological use only and should not be used in the eye.

PRECAUTIONS

General

Topical corticosteroids should be used with caution on lesions of the face, groin, and axillae; as these areas are more prone to atrophic changes than other areas of the body. Frequent observations of the patient is important if these areas are to be treated. Posterior Subcapsular cataracts have been reported following systemic use of corticosteroids.

If signs of hypersensitivity or irritation develop, the drug should be discontinued and appropriate therapy initiated.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If it is considered necessary, the topical corticosteroid may be used as an adjunct to control inflammation, erythema and itching.

If a favourable response does not occur within a few days to a week, the local application of corticosteroid should be discontinued until the infection has been adequately controlled.

Clobetasol 17-propionate has been shown to suppress the HPA axis at doses as low as 1 g per day. Systemic absorption of topical corticosteroids has resulted in reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Significant systemic absorption may occur when steroids are applied over large areas of the body, prolonged use and the addition of occlusive dressings. Therefore, patients receiving a large dose of potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

MYLAN-CLOBETASOL (clobetasol 17-propionate) Ointment should be used with caution in patients with stasis dermatitis and other skin diseases associated with impaired circulation.

Since the degree of absorption of MYLAN-CLOBETASOL Ointment when applied under occlusive dressing has not been determined, its use in this fashion is not recommended.

Use in children

Pediatric patients may absorb proportionally large amounts of topical steroids because of a large skin surface area-to-body weight ratio. This results in a greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients. Because the safety and effectiveness of MYLAN-CLOBETASOL Ointment has not been established in children, its use in children is not recommended.

ADVERSE REACTIONS

Clobetasol 17-propionate ointment is generally well tolerated during short-term treatment. The most frequent adverse reactions reported have been local, and have included burning, irritation, itching, skin atrophy, striae, change in pigmentation, secondary infection and hypertrichosis. Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. In rare instances, treatment (or withdrawal of treatment) of psoriasis with corticosteroids may provoke the pustular form of the disease.

SYMPTOMS AND TREATMENT OP OVERDOSE

Topically applied clobetasol 17-propionate can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS). Discontinue therapy when the typical signs of hypercorticism appear.

DOSAGE AND ADMINISTRATION

MYLAN-CLOBETASOL (clobetasol 17-propionate) Ointment is applied thinly to cover the affected area, and gently rubbed into the skin. Frequency of application is 2 to 3 times daily, according to the severity of the condition. The total dose of MYLAN-CLOBETASOL

Ointment applied weekly should not exceed 50 grams. The duration of therapy should be limited to 2 consecutive weeks.

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

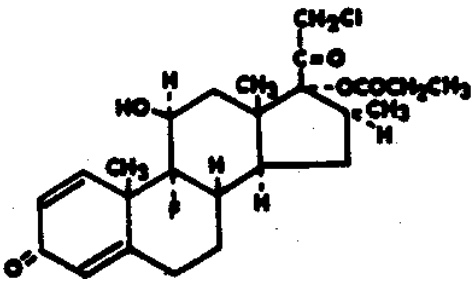
MYLAN-CLOBETASOL Ointment is not to be used under occlusive dressings.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE
Proper Name: Clobetasol 17-propionate

Chemical Name: 21-Chloro-9a-fluoro-118,17a-dihydroxy168-methylpregna-1,4-diene-3,20-dione 17-propionate

Structural Formula:



Molecular Formula: C25H3205C1F

Molecular Weight: 467

Description: Clobetasol 17-propionate is a white-to-cream-coloured crystalline powder. It is insoluble in water, with a melting point of 195.5 to 197°C.

COMPOSITION:

MYLAN-CLOBETASOL OINTMENT contains 0.05% w/w of clobetasol 17-propionate.

STABILITY AND STORAGE RECOMMENDATIONS:

Store between 15°C and 30°C.

AVAILABILITY OF DOSAGE FORMS

MYLAN-CLOBETASOL (clobetasol 17-propionate) Ointment is available in 15 g and 50 g tubes.

INFORMATION FOR THE CONSUMER

This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.

This medication should not be used for any disorder other than that for which it was prescribed.

The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.

Patients should report any signs of local adverse reactions to the physician.

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 carrageenin, clobetasol 17-

propionate was 5 times as potent as betamethasone alcohol, when given subcutaneously. In rats, both steroids 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 antigonadotropic 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 or eczema participated in an international controlled trial, where the efficacy and safety of clobetasol 17-propionate ointment were compared to those of fluocinonide, fluclorolone acetonide and betamethasone 17- valerate. The results showed that clobetasol 17- propionate ointment was effective, especially in psoriasis.

A comparison of the bioavailability of 31 commercially-available topical steroid ointment preparations was made using a modified version of the blanching test. The results demonstrated a high activity in the clobetasol 17-propionate ointment.

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 2to 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 (LD50) 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	Rote	Sex	LD50 (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 intraalveolar 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 gg to 180 gg/kg, results showed growth reduction, increased hemoglobin concentration, leucopenia, 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 gg/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 mg/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 mg/kg; but the drug was teratogenic at 3 and 10 mg/kg. A dose of 3 mg/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:

A comparative skin irritation study was done on New Zealand albino rabbits for MYLAN-CLOBETASOL OINTMENT 0.05% (Mylan) vs a Canadian marketed brand of clobetasol 17-propionate ointment 0.05%. The results show that the Primary Irritation Scores (± S.D.) based on 1, 24 and 48 hours irritancy observations were 0.09 (± 0.09) for MYLAN-CLOBETASOL Ointment and 0.17 (± 0.18) for the Canadian marketed brand of clobetasol 17-propionate ointment 0.05%. The results demonstrate that both formulations have essentially the same non-irritating potential to the skin.

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