PRODUCT MONOGRAPH

[Pr] pms-CLOBETASOL
(Clobetasol Propionate)

Topical Cream and Ointment (0.05% w/w)

Topical Anti-inflammatory Steroid

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THERAPEUTIC CLASSIFICATION

Topical Anti-inflammatory Steroid

ACTION AND CLINICAL PHARMACOLOGY

Clobetasol propionate is a highly potent fluorinated corticosteroid and has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic to the corticosteroids. Corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex, and their synthetic analogs. They are primarily used for their anti-inflammatory and/or immunosuppressive effects. pms-CLOBETASOL (clobetasol propionate) is effective in the treatment of corticosteroid responsive dermatoses primarily due to its anti-inflammatory, anti-pruritic, and vasoconstrictive actions. Its exact mechanism of action however, has not been fully elucidated.

Pharmacokinetics: As with all topical corticosteroids, clobetasol 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 (see DOSAGE AND ADMINISTRATION). Once absorbed, topical corticosteroids enter pharmacokinetic

pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. They are primarily metabolized in the liver and excreted by the kidneys and in the bile.

Clobetasol propionate cream has been shown to depress the plasma levels of adrenal cortical hormones following repeated nonocclusive application to diseased skin in patients with psoriasis and eczematous dermatitis. These effects have been shown to be transient and reversible upon completion of a two-week course of treatment.

INDICATIONS AND CLINICAL USE

pms-CLOBETASOL (clobetasol propionate) cream and ointment are indicated for the topical therapy of recalcitrant corticosteroid-responsive dermatoses, including severe cases of psoriasis (excluding widespread plaque psoriasis) and eczematous dermatitis.

Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 grams per week, because of the potential for the drug to suppress the HPA axis.
pms-CLOBETASOL is not recommended for use in children under 12 years of age.

CONTRAINDICATIONS

pms-CLOBETASOL (clobetasol propionate) is contraindicated: in patients with infected skin lesions if no anti-infective agent is used simultaneously; in patients with fungal and viral infections of the skin, including herpes simplex, vaccinia and varicella; in patients with tuberculous lesions of the skin; rosacea; acne vulgaris; peri-oral dermatitis; during pregnancy and lactation; in patients who are hypersensitive to clobetasol propionate or to other corticosteroids. Not for ophthalmic use.

WARNINGS

pms-CLOBETASOL (clobetasol propionate) should not be used in the eye. Posterior subcapsular cataracts have been reported following systemic use of corticosteroids. Topical corticosteroids should be used with caution on lesions close to the eye. When used over extensive areas for prolonged periods, it is possible that 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 to use pms-CLOBETASOL 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 pms-CLOBETASOL per week. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

PRECAUTIONS

pms-CLOBETASOL (clobetasol propionate) is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 grams 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.

Conditions that augment systemic absorption include the application of the more potent corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a 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. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. 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.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS: Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. Irritation is possible if clobetasol propionate contacts the eye. If that should occur, immediate flushing of the eye with a large volume of water is recommended. In the presence of dermatologic infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for Patients: Patients using clobetasol propionate cream or ointment should receive the following information and instructions:

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.
4. Patients should report any signs of local adverse reactions to the physician.

Laboratory Tests: The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of pms-CLOBETASOL cream or ointment.

Studies to determine mutagenicity with prednisolone have revealed negative results.

Pregnancy: Teratogenic Effects: The more potent corticosteroids have been shown to be teratogenic in animals after dermal application. Clobetasol propionate has not been tested for teratogenicity by this route; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in the rabbit and mouse. Teratogenic effects were observed in rabbits in doses as low as 3 μg/kg. Clobetasol propionate has greater teratogenic potential than steroids that are less potent. There are no adequate and well-controlled studies of the teratogenic effects of topically applied corticosteroids, including clobetasol, in pregnant women. Therefore, clobetasol and other topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

Pediatric Use: Use of clobetasol propionate cream or ointment in children under 12 years of age is not recommended.

Pediatric 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.

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.

ADVERSE REACTIONS

Clobetasol propionate cream or ointment is generally well tolerated when used for 2 week treatment periods.

The most frequent adverse reactions reported with clobetasol propionate have been local burning and stinging. The following local adverse reactions have been reported infrequently when topical corticosteroids are used as recommended. These reactions are listed in an approximately decreasing order of occurrence: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. 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 is thought to have exacerbated the disease or provoked the pustular form of the disease, so careful patient supervision is recommended.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Discontinue treatment with pms-CLOBETASOL (clobetasol propionate) when the typical signs of hypercorticism appear.

DOSAGE AND ADMINISTRATION

A thin layer of pms-CLOBETASOL (clobetasol propionate) cream or ointment should be applied to cover the affected area, and gently rubbed into the skin.

Frequency of application is two times daily, according to the severity of the condition. The total dose applied weekly should not exceed 50 grams. Treatment should be limited to two 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 clobetasol propionate for brief periods only.

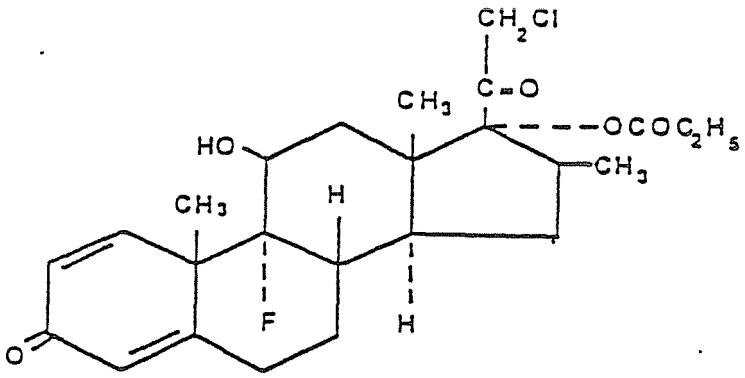
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Clobetasol propionate

Chemical Name: 21-chloro-9-fluoro-ll-hydroxy-16-methyl-17-(I-oxopropoxy)-pregna-I,4-diene-3,20-dione.

Structural Formula:



Molecular Formula: C251-132CIF05 Molecular Weight: 467

Description: Clobetasol propionate is a white to cream-colored crystalline powder insoluble in water.

STABILITY AND STORAGE RECOMMENDATIONS: Store between 15° - 30°C.

AVAILABILITY OF DOSAGE FORMS

pms-CLOBET'ASOL (clobetasol propionate) topical cream and ointment are supplied in tubes of 15 and 50 grams each containing 0.05% w/w clobetasol propionate.

PHARMACOLOGY

Animal:

Thymolytic activity was determined in mice in comparison with betamethasone alcohol. Activity of clobetasol propionate was two to eleven times greater, depending upon the route of administration.

Anti-granuloma activity of clobetasol propionate was determined in mice, using cotton wool pellets soaked in carregeenin. Clobetasol propionate was five times as potent as betamethasone alcohol, when given subcutaneously. In rats, both steroids had approximately equal activity in both tests.

Mineralocorticoid activity was determined in rats and compared with betamethasone alcohol, both steroids showed equally weak activity.

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

Clobetasol propionate showed anti-estrogenic activity in mice as determined by measuring the uterine weight after estrone and clobetasol propionate administration. In ovariectomized rats, it showed marked anti-estrogenic activity when compared with progesterone. Estrogenic activity in weanling rats was about one five hundredth that of estrone.

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

Clobetasol propionate did not demonstrate an antigonadotropic activity in weanling male rats.

Human:

Using the vasoconstrictor test of McKenzie and Atkinson in volunteers, the potency of clobetasol propionate was compared with that of fluocinolone acetonide and betamethasone 17-valerate. The results showed clobetasol propionate to be eighteen times as potent as fluocinolone acetonide, and six times as potent as betamethasone 17-valerate.

Clobetasol propionate cream demonstrated to be effective in an international controlled trial conducted on eleven hundred and fifty patients with bilateral lesions of psoriasis or eczema.

The bioavailability of thirty commercial topical steroid preparations were compared using a modified blanching test of Christie and Moore-Robinson. The results showed clobetasol propionate to have high activity.

TOXICOLOGY

Acute Toxicity:

Animal	Route of Administration	LD50
Mice	Oral	> 4 g/kg
Mice	Subcutaneous	> 4 g/kg
Rats	Subcutaneous	> 1 g/kg

After a single subcutaneous injection of 1, 2 or 4 g/kg of clobetasol propionate, most mice developed hepatic necrosis, thymic atrophy and some developed interstitial nephritis.

Rats received a single subcutaneous injection of 1 g/kg of clobetasol propionate. Histological examination showed fatty liver necrosis and nephrocalcinosis. An oral dose of 1 g/kg gave similar results.

In guinea pigs, a single subcutaneous injection of 60 mg/kg of clobetasol propionate caused no drug related histological changes.

No deaths were caused by a single intramuscular injection of 60 mg/kg of clobetasol propionate in rabbits. Three out of four animals showed intraalveolar hemorrhage and thymus involution. All animals had foamy periportal cells with increased glycogen content. Some of the injection sites showed small foci of muscle necrosis.

In cats, a single intramuscular injection of 60 mg/kg of clobetasol propionate caused no death. There were some cytoplasmic changes in the hearts and livers, with lipid infiltration as well as thymus involution.

A single intramuscular injection of 15 mg/kg of clobetasol propionate caused increased liver glycogen content, weight loss and melena in dogs. One dog had salivary gland inflammation. A dose of 60 mg/kg caused a local abscess at the injection site in one dog. Lipid infiltration in the heart and liver, as well as thymus involution was observed. One dog became moribund at the highest dose.

Long-Term Toxicity:

In rats, daily subcutaneous injections of clobetasol propionate were given for twelve weeks at doses ranging from 1.44 μg to 180 μg/kg. Results showed growth reduction, increased hemoglobin concentration, leucopenia, SGOT elevation, reduction of thymus weight, reduced blood glucose and adrenal atrophy. The females had decreased uterine weight and bone marrow hypoplasia. Some animals had chronic respiratory disease and interstitial nephritis.

Daily intramuscular injections of 1.44, 7.2, 36.0 or 180 μg/kg of clobetasol propionate were given for thirteen weeks to dogs. One dog died after forty injections of the highest dose. In others there was reduced hemoglobin, leucopenia, increased serum protein, increased liver and kidney weights, adrenal atrophy and increased alkaline phosphatase.

Reproduction and Teratology:

Subcutaneous injections of 0.03, 0.1, 0.3 or 1.0 mg/kg of clobetasol propionate were administered to mice from day seven to day sixteen of pregnancy. There was no maternal mortality. The number of live fetuses decreased and resorption sites increased at the highest dose. A dose related incidence of abnormal cleft palate, and skeletal immaturity occurred at doses from 0.1 to 1.0 mg/kg.

In rabbits, daily subcutaneous injections of clobetasol propionate at doses of 1, 3 or 10 μg/kg, from day six to day eighteen of pregnancy caused decreased weight gain of the mothers receiving the highest dose. Skeletal maturity and cleft palate were observed at a dose of 3 μg/kg. The highest dose caused a reduced number of live fetuses and of litter weight, as well as an increased incidence of cleft palate and skeletal abnormalities.

Other Studies:

Local skin irritancy studies were conducted in guinea pigs treated with clobetasol propionate ointment for fourteen days, using a total of approximately 120 mg on one clipped flank, while the other side was treated similarly with the ointment base. Both treatments caused equal extent of erythema.

Rabbits similarly treated showed identical results.

Application of clobetasol propionate ointment to the eyes of the same animals caused no irritation.

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