CLOBEX ®

(clobetasol propionate) Lotion, 0.05%

POM only

Pharmacological Classification: Topical Corticosteroid

Therapeutic Classification: Topical Treatment of Corticosteroid-Responsive Dermatoses

ACTIONS AND CLINICAL PHARMACOLOGY

Clobex (clobetasol propionate) is a highly potent topical corticosteroid. Clobex Lotion (clobetasol propionate lotion, 0.05%) contains clobetasol propionate, a synthetic fluorinated corticosteroid for topical dermatological use. Corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Clobetasol, an analogue of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. Studies performed with clobetasol propionate lotion, 0.05% indicate that it is in the very high range of potency as compared with other topical corticosteroids.

Mechanism of Action

Like other topical corticosteroids, Clobex Lotion has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2**.**

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and occlusion. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and other disease processes in the skin may increase percutaneous absorption.
There is no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Due to the fact that circulating levels are usually below the level of detection, the use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary. They are metabolized primarily in the liver and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Clobex Lotion is in the high range of potency as compared with other topical corticosteroids in vasoconstrictor studies.

INDICATIONS AND CLINICAL USE

Clobex Lotion (clobetasol propionate lotion, 0.05%) is a highly potent corticosteroid with the

potential to suppress the HPA axis.

Clobex Lotion is indicated for the treatment of moderate to severe corticosteroid-responsive dermatoses where an anti-inflammatory or anti-pruritic activity is required for the topical management of these conditions.

Treatment should be limited to 2 consecutive weeks, not to exceed 50 grams (50 mL or 1.75 fl. oz.) per week, and be applied to no more than 10% of the body surface area. Use should be restricted to those 18 years or older.

In the treatment of moderate to severe plaque-type psoriasis that has not sufficiently improved after the initial 2 weeks, Clobex Lotion can be used for up to 2 additional weeks. Any additional benefits of extending treatment should be weighed against the risk of HPA axis suppression. Patients should be instructed to use Clobex Lotion for the minimum amount of time necessary.

Use in patients younger than 18 years of age in not recommended due to numerically high rates of HPA axis suppression.

CONTRAINDICATIONS

Use of Clobex Lotion (clobetasol propionate lotion, 0.05%) is contraindicated in:

- patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation
- Skin areas affected by bacterial and mycobacterial, viral, fungal, parasitic infections or ulcerous wounds.
- Children under 2 years of age
- Application to the eyes and eyelids (risk of glaucoma, risk of cataract)

Treatment with topical corticosteroids is not indicated in patients with untreated tubercular, bacterial and fungal infections involving the skin, and in certain viral diseases such as herpes simplex, chickenpox, and vaccinia.

WARNINGS

Use in those under 18 years of age is not recommended.
In the treatment of moderate to severe plaque-type psoriasis, Clobex Lotion (clobetasol propionate lotion, 0.05%) applied to no more than 10% of the body surface area can be used up to 4 consecutive weeks (when dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression).

<u>Visual disturbance</u>

Visual disturbance may be reported 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) which have been reported after use of systemic and topical corticosteroids.

Patients should be instructed to use Clobex Lotion for the minimum amount of time necessary

to achieve the desired results (see PRECAUTIONS

PRECAUTIONS

General Hypersensitivity to corticosteroids can be observed.

Clobetasol propionate is contraindicated in patients who are hypersensitive to other corticosteroids.

Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency, manifestations of Cushing's syndrome, hyperglycemia, and glycosuria in some patients.

Treatment of large surface areas, long-term continuous therapy with corticosteroids, use of occlusive dressings can enhance absorption and lead to a higher risk of systemic effects.

. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression (see laboratory tests below). If adrenal 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. Abrupt discontinuation can lead to acute adrenal insufficiency, especially in children. Such systemic effects resolve when treatment is stopped. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Clobex Lotion is a highly potent potency topical corticosteroid that has been shown in two adult studies to suppress the HPA axis at the lowest doses tested.

Topical corticosteroids are known to potentially induce:

- post treatment rebound, relapses upon discontinuation of treatment
- development of tolerance (tachyphylaxis)
- development of local toxicity such as skin atrophy, telangiectasia of the skin
- immunosuppression and opportunistic infections (including isolated cases of systemic infections), in case of prolonged use of potent topical corticosteroids in rare instances
- cataracts, when applied to eyes or eyelids

In total, 8 of 10 evaluable patients with moderate to severe plaque psoriasis experienced adrenal suppression following 4 weeks of Clobex Lotion treatment (treatment beyond 4 weeks is not recommended in moderate to severe plaque psoriasis). In follow-up testing, 1 of 2 subjects remained suppressed after 8 days.

Furthermore, 5 of 9 evaluable patients with moderate to severe atopic dermatitis experienced adrenal suppression following two weeks of Clobex Lotion treatment (treatment beyond 2 consecutive weeks is not recommended in moderate to severe atopic dermatitis). Of the 3 subjects that had follow-up testing, 1 subject failed to recover adrenal function 7 days post treatment. The proportion of subjects suppressed may be underestimated because the adrenal glands were stimulated weekly with cosyntropin in these studies.

The potential increase in systemic exposure does not correlate with any proven benefit, but may lead to an increased potential for hypothalamic-pituitary-adrenal (HPA) suppression. Patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression. Patients should be advised to use Clobex Lotion for the minimum amount of time necessary to achieve the desired results.

Clobex Lotion should not be used on lesions close to the eye because of the risk of increased intraocular pressure, glaucoma, and cataracts. Clobex Lotion should not be used under occlusion or on limbs with impaired circulation. Clobetasol propionate must not be applied on

intertriginous areas (axillae and genitoanal regions) and on other erosive skin surfaces as this could increase the risk of topical adverse events such as atrophic changes, telangiectasia or cortico-induced dermatitis. If Clobetasol propionate does enter the eye, the affected eye should be rinsed with copious amounts of water.

If irritation develops, Clobex Lotion should be discontinued and appropriate therapy instituted. Cases of osteonecrosis, serious infections (including necrotizing fasciitis), and systemic immunosuppression (sometimes resulting in reversible Kaposi’ s sarcoma lesions) have been reported with long-term use of clobetasol propionate beyond the recommended doses (see Dose and Administration). In some cases, patients used other potent oral/topical corticosteroids or immunosuppressors concomitantly (e.g. methotrexate, mycophenolate mofetil). If treatment with local corticosteroids is clinically justified beyond 4 weeks, a less potent corticosteroid preparation should be considered.

In the presence of fungal infections, an appropriate antifungal treatment should be instituted and Clobex Lotion should be discontinued until the fungal infection is cured. In the presence of a bacterial infection, an appropriate antibacterial agent should be instituted. If a favorable response does not occur promptly, Clobex Lotion should be discontinued until the bacterial infection is adequately controlled.

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

- ACTH stimulation test
- AM plasma cortisol test
- Urinary free cortisol test

Pregnancy
There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobex Lotion should be used during pregnancy only if its benefit justifies the potential risk to the fetus.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Clobex Lotion is administered to a nursing woman. Clobetasol propionate should not be prescribed to nursing women unless clearly indicated.

Pediatric Use
Safety and effectiveness of Clobex Lotion in pediatric patients have not been established and its use in pediatric patients under 18 years of age is not recommended.

Because of a higher ratio of skin surface area to body mass, pediatric patients may absorb a higher percentage of topically applied corticosteroids and therefore may be at a greater risk than adults of HPA axis suppression and Cushing's syndrome. They are therefore also at greater risk of glucocorticosteroid insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

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

The HPA axis suppression potential of Clobex Lotion has been studied in adolescents (12 to 17 years of age) with moderate to severe atopic dermatitis covering a minimum of 20% of the

total body surface area. In total, 14 patients were evaluated for HPA axis function and for safety. Patients were treated twice daily for 2 weeks with Clobex Lotion. After 2 weeks of therapy, 9 out of 14 subjects had suppression of their HPA axis and two weeks after stopping therapy 1 out of 4 continued to have suppression of the HPA axis. None of the patients who developed HPA axis suppression had concomitant clinical signs of adrenal suppression and none of them were discontinued from the study for reasons related to the safety or tolerability of Clobex Lotion. Therefore, use in patients between 2 and 18 years of age is not recommended and is contraindicated in children below 2 years of age.

Geriatric Use

Clinical studies of Clobex Lotion did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be made with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Carcinogenesis, Mutagenesis, and Reproduction

Long term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate. Clobetasol propionate did not produce any increase in chromosomal aberrations in Chinese hamster ovary cells *in vitro* in the presence or absence of metabolic activation.

Clobetasol propionate was also negative in the micronucleus test in mice after oral administration.

Studies of the effect of Clobex Lotion on fertility have not been performed.

ADVERSE EVENTS

In controlled clinical trials with Clobex Lotion (clobetasol propionate lotion, 0.05%), the following adverse reactions have been reported: burning/stinging, skin dryness, irritation, erythema, folliculitis, pruritus, skin atrophy, and telangiectasia.

The incidence of local adverse reactions reported in the trials with Clobex Lotion was 1% or less, with the exception of telangiectasia (3.2%) and skin atrophy (4.2%). Similar rates of local adverse reactions were reported in the comparator groups (two formulations of clobetasol propionate cream).

Most adverse events were rated as mild to moderate and they are not affected by age, race or gender. No serious drug-related adverse events were reported during any of the clinical trials.

Adverse Events

PHASE II/ III STUDIES - Number of Subjects (%)		
	Clobex Lotion	**Lotion vehicle**
Patients with Psoriasis	188	62
Patients with Atopic Dermatitis	121	33
Total Number of Patients	309	95
Subjects w/Adverse Events	49 (15.9%)	9 (9.5%)
Subject w/ Drug-Related* Adverse Events	13 (4.2%)	5 (5.3%)
Dermatological	13 (4.2%)	4 (4.2%)
Non-dermatological	0	1 (1.1%)
Adverse Events with incidence >1%		
No. of Subjects with Increases in Skin Atrophy Scores (%)		
Psoriasis	7 (3.7)	0
Atopic Dermatitis	6 (4.9)	0
Totals	13 (4.2)	0
No. of Subjects with Increases in Telangiectasia Scores (%)		
Psoriasis	6 (3.2)	0
Atopic Dermatitis	4 (3.3)	0
Totals	10 (3.2)	0

*Possibly, probably, definitely related

In controlled clinical trials with other internationally marketed topical clobetasol propionate formulations (creams), burning/stinging, folliculitis, cracking and Assuring of the skin, numbness of the fingers, tenderness of the elbow, skin atrophy and telangiectasia have been reported. Cushing's syndrome has been reported in infants and adults as a result of prolonged use of other topical clobetasol propionate formulations.

The following additional local adverse reactions have been reported with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, use over a prolonged period of time, use over large surface areas and use of super-high potency corticosteroids, such as clobetasol propionate. These reactions are listed in an approximate decreasing order of occurrence: irritation, dryness, itching, burning, local irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, skin atrophy, atrophy of subcutaneous tissues, telangiectasia, hypertrichosis, change in pigmentation, secondary infection, striae, miliaria, blurred vision. If applied to the face, acne rosacea or perioral dermatitis can occur. When occlusive dressings are used, pustules, milaria, folliculitis and pyoderma may occur. In rare instances, treatment of psoriasis with systemic or very potent topical corticosteroids (or their withdrawal) is thought to have provoked the pustular form of the disease.

Systemic absorption of topical corticosteroids has produced reversible adrenal suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria.

Tabulated list of adverse reactions

The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data including post market experience).

Psoriasis indication

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Uncommon	Hypersensitivity*
Endocrine disorders	Uncommon	Adrenal suppression* Cushing syndrome*
Eye disorders	Not known	Vision, blurred
Skin and subcutaneous tissue disorders	Common	Skin atrophy (3.7%) Telangiectasia (3.2%)_ Allergic Contact Dermatitis* Pigmentation changes*
	Uncommon	Dry skin (0.5%) Pain of skin (0.5%) Psoriasis (aggravation) (0.5%) Skin burning sensation (0.5%) Erythema (0.5%) Pruritis (0.5%) Skin irritation (0.5%)

*post-marketing experience

Atopic dermatitis indication

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Uncommon	Hypersensitivity*
Endocrine disorders	Uncommon	Adrenal suppression* Cushing syndrome*
Eye disorders	Not known	Vision, blurred
Skin and subcutaneous	Common	Skin atrophy (3.7%)

tissue disorders		Telangiectasia (3.2%)_ Allergic Contact Dermatitis* Pigmentation changes*
	Uncommon	Folliculitis (0.8%) Skin irritation (0.8%) Pain of skin (0.5%) Skin burning sensation (0.8%) Atophic dermatitis (aggravation)*

*post-marketing experience

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Topically applied Clobex Lotion (clobetasol propionate lotion, 0.05%) can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.) In case of chronic overdosage or misuse, features of hypercortism may appear and in this situation, treatment should be discontinused gradually. However, because of the risk of acute adrenal suppression, this should be done under medical supervision. Recovery of the HPA axis is usually prompt and complete following discontinuation; however, if symptoms of adrenal insufficiency occur, supplemental oral steroid therapy may be initiated and tapered off gradually.

DOSAGE AND ADMINISTRATION

Clobex Lotion (clobetasol propionate lotion, 0.05%) should be applied to the affected skin areas twice daily and rubbed in gently and completely. (See INDICATIONS AND USAGE) Hands should be washed carefully after application.

Clobex Lotion contains a highly potent topical corticosteroid; therefore, treatment should be limited to:

- 2 consecutive weeks for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses,
- 4 consecutive weeks in the treatment of moderate to severe plaque-type psoriasis.

The total dosage should not exceed 50 grams (50 mL or 1.75 fl. oz.) per week or be used on more than 10% of body surface area because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Therapy should be discontinued when control has been achieved. If no improvement is seen within two weeks, reassessment of diagnosis may be necessary.

The treatment is limited to maximum 2 weeks.

Use is not recommended in patients under 18 years of age since it has not been studied sufficiently and also due to numerically high rates of HPA axis suppression in this age group.

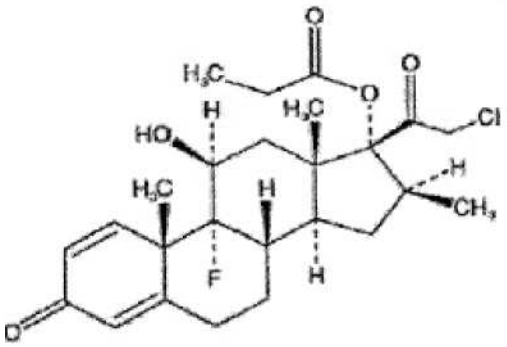
Unless directed by physician, Clobex Lotion should not be used with occlusive dressings.

Clobetasol propionate belongs to the most potent class of topical corticosteroids (class IV/class I) and prolonged use may result in serious undesirable effects (see Warnings and Precautions). If treatment with a local corticosteroid is clinically justified beyond 4 weeks, a less potent corticosteroid preparation should be considered. Repeated but short courses of clobetasol propionate may be used to control exacerbations.

PHARMACEUTICAL INFORMATION

Drug Substance:	clobetasol propionate clobetasol propionate
Proper name:	21-chloro-9-fluoro-l lp, 17-dihydroxy- 16P-methylpregna-1,4diene- 20-dione 17-propionate
Chemical name:	

Structural Formula:



Molecular Formula: C25H32CIFO5

Molecular Weight: 466.98

Physical Form: White to practically white crystalline powder.

Solubility: Insoluble in water. Soluble in acetone, chloroform and dioxane. Sparingly soluble in methanol.

Composition:
Active ingredients
Each g of lotion contains 0.5 mg of clobetasol propionate, USP.

Inactive ingredients:
Hydroxypropylmethyl cellulose
Propylene glycol Mineral oil
Polyoxyethylene glycol 300 isostearate
Carbomer 1342 Sodium hydroxide
Purified water

Stability and Storage Recommendations:
Store at controlled room temperature (20 to 25°C). Do not freeze. Store in original packaging.

AVAILABILITY OF DOSAGE FORMS
Clobex Lotion (clobetasol propionate lotion, 0.05%) is supplied in the following sizes:
59ml (2 fl oz), 118ml (4 fl oz).

Manufacturer By:
DPT Laboratories, Ltd
San Antonio, Texas 78215 USA

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