PRODUCT MONOGRAPH

PrCLOBEX™ Lotion

(clobetasol propionate lotion, 0.05%)

Topical Lotion

Topical Corticosteroid

Galderma Canada Inc.
105 Commerce Valley Drive West
Suite 300
Thornhill, Ontario
L3T 7W3

Date of Preparation:
July 26, 2004

Control No.: 085305

PRODUCT MONOGRAPH

CLOBEX™ Lotion

(clobetasol propionate lotion, 0.05%)

Topical Lotion

Pharmacological Classification:

Topical Corticosteroid

Therapeutic Classification:

Topical Treatment of Corticosteroid-Responsive Dermatoses

ACTIONS AND CLINICAL PHARMACOLOGY

Clobex (clobetasol propionate) is a super-high potency 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 are 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 super-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 super-high potency corticosteroid with the potential to suppress the HPA axis.

Clobex Lotion is indicated for the treatment of 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 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.

CONTRAINDICATIONS

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.

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).

Patients should be instructed to use Clobex Lotion for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

PRECAUTIONS

General
Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which increase systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. 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. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. 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 super-high potency topical corticosteroid that has been shown in two adult studies to suppress the HPA axis at the lowest doses tested.

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. Clobex Lotion should not be used on the face, groin or axilla.

If irritation develops, Clobex Lotion should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by a failure to heal rather than noting a clinical exacerbation, as with most products not containing a corticosteroid.

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.

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.

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%)
Subjects 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 fissuring 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 and miliaria. 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.

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. 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)

Clobex Lotion contains a super-high potency 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 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.

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.

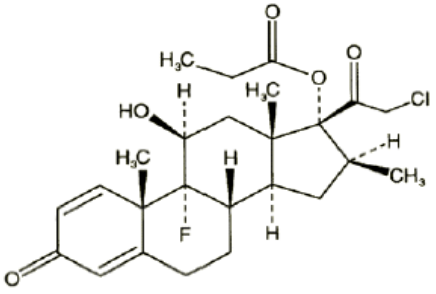
PHARMACEUTICAL INFORMATION

Drug Substance: clobetasol propionate

Proper name: clobetasol propionate

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

Structural Formula:



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

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:
Hydroxypropyl methylcellulose
Propylene glycol
Mineral oil
Polyoxyethylene glycol 300 isostearate
Carbomer 1342
Sodium hydroxide
Purified water.

Stability and Storage Recommendations:
Store at controlled room temperature (15 - 30 °C). Do not freeze.

AVAILABILITY OF DOSAGE FORMS

Clobex Lotion (clobetasol propionate lotion, 0.05%) is supplied in the following sizes:

30 mL HDPE bottles.
60 mL HDPE bottles.
120 mL HDPE bottles.

INFORMATION FOR THE CONSUMER

For External Use Only
Not for Ophthalmic Use

Clobex Lotion
clobetasol propionate lotion, 0.05%

Read this information carefully before you begin treatment with Clobex Lotion. It is important to read this information even if it is not your first time using this product because there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about Clobex Lotion, ask your doctor. Only your doctor can determine if Clobex Lotion is right for you.

What is the most important information I should know about Clobex Lotion?
What is Clobex Lotion?
Your doctor has prescribed Clobex Lotion (clobetasol propionate lotion, 0.05%) for the treatment of redness, scaling, and itching of moderate to severe plaque type psoriasis. Clobex Lotion is also used for a short time to treat the redness and itching of certain rash-like skin diseases that can be treated with topical corticosteroids. Clobex Lotion works because its active ingredient belongs to a group of medicines known as topical corticosteroids. It is very important that you use Clobex Lotion only as directed in order to avoid serious side effects.

Who should not use Clobex Lotion?
Do not use Clobex Lotion if you are allergic to this medicine or to any of its ingredients or any other corticosteroid. The ingredients are listed at the end of this leaflet. Ask your doctor or pharmacist if you need a list of other corticosteroids.

Clobex Lotion is not recommended for use by children under 18 years of age.

Do not use Clobex Lotion if you have bacterial/fungal/viral infections, including chicken pox and eruptions following vaccinations. Clobex Lotion should not be used in the treatment of rosacea, acne vulgaris, inflammation or itching around the mouth, anus, or genitals, unless your doctor has recommended it.

What should I tell my doctor before using Clobex Lotion?
If you answer YES to one or more of the following questions, tell your doctor (or pharmacist) before using this medicine, so you can get advice about what to do. They will advise you if the benefits of using the lotion will be greater than the risks .

- Are you pregnant? Planning on becoming pregnant while using Clobex Lotion? If possible, delay the treatment with Clobex Lotion until after the baby is born.
- Are you breast feeding?
- Do you think you have an infection on your skin?
- Are you going to have surgery?
- Have you used or are you using corticosteroids for treatment of skin disorders, allergic reactions, arthritis or asthma? In particular, tell your physician if you have developed an allergy or intolerance to such medicine.
- Do you have allergies to other substances such as foods, dyes, etc.?
- Are you using any other medicines and skin products, including prescription and over the counter medicines, cosmetics, vitamins, and herbal supplements? Some medicines can cause serious side effects if used when you are using Clobex Lotion.

How should I use Clobex Lotion?
Before applying the product, wash the area to be treated with a mild cleanser, pat dry, and wait several minutes.

Turn the bottle upside down and dispense a small amount of Clobex Lotion onto your finger tips or directly onto the lesion. Gently massage into affected skin areas until the lotion disappears. For one application, you should not exceed an amount equivalent to one teaspoon. DO NOT APPLY MORE THAN THE PRESCRIBED AMOUNT (50 mL or 1.75 fl. oz.) per week maximum. Also, do not apply to more than 10% of the body surface area.

- Use Clobex Lotion exactly as directed by your doctor.
- Apply twice daily, once in the morning and once at night. Use only enough to cover the affected areas.
- Wash your hands after applying Clobex Lotion.
- As with other corticosteroids, treatment should be discontinued when control of your condition has been achieved.
- Clobex Lotion is for external use only.

What should I avoid while using Clobex Lotion?
Do not do the following while using Clobex Lotion:

- Do not apply Clobex Lotion to the face, underarms, or groin and avoid contact with eyes and lips.
- Do not cover the affected areas with any type of dressing, such as gauze or tight fitting clothing.
- Do not get Clobex Lotion in your mouth. If you or a child accidentally swallows Clobex Lotion, call your Poison Control centre or local emergency room right away.
- Do not have any immunizations without your doctor's approval if you are using this medication.
- Do not use Clobex Lotion any longer than 2 weeks (14 days) for rash-like skin diseases and 4 weeks (28 days) for plaque-type psoriasis.

What should I do if I miss an application of Clobex Lotion?
If you forget to apply Clobex Lotion at the scheduled time, use it as soon as you remember, and then go back to your regular schedule. If you remember at or about the time of your next daily application, apply that dose and continue with your normal application schedule. If you miss several doses, tell your doctor.

What are the possible side effects of Clobex Lotion?
Clobex Lotion can pass through your skin. Too much Clobex Lotion passing through your skin can shut down your adrenal glands. This may happen if you use too much Clobex Lotion or if you use it for too long, but it can happen with correct use. If your adrenal glands shut down, they may not start working right away after you stop using Clobex Lotion. Shutting down of the adrenal glands can cause nausea, vomiting, fever, low blood pressure, heart attack and even death because your body cannot adequately respond to stress or illness. Your doctor may do special blood and urine tests to check your adrenal gland function while you are using Clobex Lotion.

The most common side effects with Clobex Lotion include burning or itching at the site of application. Other possible side effects include thinning of the skin and widening of small blood vessels in the skin.

If you go to another doctor for illness, injury or surgery, tell your doctor that you are using Clobex Lotion. Tell your doctor right away if you: get sick or don't feel right; have irritation of the treated skin area that does not go away; have unusual effects that you do not understand; have affected areas that do not seem to be healing after 2-4 weeks of using Clobex Lotion. These are not all the possible side effects of Clobex Lotion. For more information, ask your doctor or pharmacist.

Other Important Information:
- ♦ Keep this and all medicines out of the reach of children.
- ♦ Do not use the lotion after the expiration date shown on bottle.
- ♦ Do not give Clobex Lotion to anyone else, even if they have the same symptoms you have. It may harm them. Your doctor has prescribed this medicine for your use only.
- ♦ Do not use this medication for conditions for which it was not prescribed. Discard any unused dispensed medication.
- ♦ Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.
- ♦ This leaflet summarizes the most important information about Clobex Lotion. If you would like more information, talk with your doctor or pharmacist. They have information about Clobex Lotion that is written for health professionals.

Storage: Store at controlled room temperature (15 - 30 °C). Do not freeze.

Ingredients: Active: clobetasol propionate, 0.05% (w/w). Other ingredients: hydroxypropyl methylcellulose, propylene glycol, mineral oil, polyoxyethylene glycol 300 isostearate, carbomer1342, sodium hydroxide and purified water. This lotion is dispensed from a HDPE (high density polyethylene) bottle.

PHARMACOLOGY

Pharmacodynamics:

Clobetasol propionate demonstrated marked anti-inflammatory, antiproliferative and vasoconstrictive activity in various animal models including in croton oil-induced ear edema in rats and in mice, and inhibition of UV-induced dermatitis, picryl chloride - induced hypersensitization and epidermal DNA synthesis in hairless mice, as well as inhibition of growth of granulomatous tissue in impregnated cotton pellet test. Clobetasol propionate induced epidermal thinning in mouse tail and mouse ear models, followed by recovery.

Clobetasol propionate was slightly less potent than halobetasol propionate and clearly more potent than hydrocortisone. Clobetasol propionate and halobetasol propionate had a very strong antiproliferative action on hexadecane-induced hyperplasia of the epidermis and showed marked anti-mitotic effect.

Results of two studies in healthy volunteers have shown the vasoconstriction capacity of Clobex Lotion (clobetasol propionate lotion, 0.05%) to be comparable to that of other cream formulations of clobetasol propionate and superior to that of DIPROLENE® (0.05% betamethasone dipropionate) cream, Clobex Lotion vehicle, and untreated controls.

Pharmacokinetics:

An *in-vitro* study was comparing the liberation-penetration of clobetasol propionate from Clobex Lotion showed that the amount of clobetasol propionate recovered in the skin was higher with Clobex Lotion than with the other two formulations of clobetasol propionate cream. Once absorbed through the skin, topical clobetasol propionate is metabolised by the liver and excreted primarily via bile into the feces.

Therapeutic Clinical Trials

The efficacy of Clobex Lotion in psoriasis and atopic dermatitis has been demonstrated in two well-controlled clinical trials. The first study was conducted in patients with moderate to severe plaque-type psoriasis. Patients were treated twice daily for four weeks with either Clobex or vehicle lotion. After 4 weeks of treatment, results demonstrated that the efficacy of Clobex Lotion in treating moderate to severe plaque-type psoriasis was superior to that of the vehicle

Patients with no clinical signs of psoriasis after 4 weeks of treatment [N(%)]

Clinical signs of psoriasis	Clobex Lotion N=82	Vehicle N=29
Scaling	48 (58.5)	2 (6.9)
Erythema	45 (54.9)	0 (0.0)
Plaque Elevation	13 (15.9)	0 (0.0)
Treatment Success*	60 (73.2)	1 (3.4)

*Success rate is the proportion of patients who achieved success at the week 4 endpoint. Success is defined as a score of none, very mild, or mild on the Global Severity scale of psoriasis signs.

The second study was conducted in patients with moderate to severe atopic dermatitis. Patients were treated twice daily for 2 weeks with either Clobex or vehicle lotion. After 2 weeks of treatment, Clobex Lotion was shown to be superior to the vehicle in treating moderate to severe atopic dermatitis.

Patients with no clinical signs of atopic dermatitis after 2 weeks of treatment [N(%)]

Clinical signs and symptoms of atopic dermatitis	Clobetasol Lotion N = 96	Vehicle N = 33
Pruritus	56 (58.3)	5 (15.2)
Excoriation	67 (69.8)	13 (39.4)
Erythema	34 (35.4)	2 (6.1)
Induration/ Papulation	50 (52.1)	5 (15.2)
Lichenification	47 (49.0)	5 (15.2)
Treatment Success*	70 (72.9)	12 (36.4)

* Success rate is the proportion of patients who achieved success at the week 2 endpoint. Success is defined as a score of none, very mild, or mild on the Global Severity scale of atopic dermatitis signs and symptoms

TOXICOLOGY

***Acute Toxicity*:**

Acute toxicity studies showed an oral LD_{50} over 3000 mg/kg in mice and rats.

***Long-Term Toxicity*:**

The effects obtained in the subchronic and chronic studies by the subcutaneous or the percutaneous route in the rat did not indicate any intrinsic toxic effects by clobetasol propionate. They are comparable in nature and extent to those of other highly active corticosteroids. Hence, they are considered as extensions of the pharmacological activity of clobetasol proprionate. The subcutaneous No Adverse Effects Level (NOAEL) is 20 µg/kg. Adverse effects observed in percutaneous studies included thinning of the skin and retardation of hair growth at the application site. Decreased body weight gain, decreased serum corticosterone levels, lymphopenia, involution of the thymus, adrenal gland atrophy and localised hepatic necrosis were also observed in animals treated.

Results of local tolerance studies showed that clobetasol propionate lotion did not produce any signs of dermal or eye irritation or delayed-type hypersensitivity in rabbits. These results are consistent with the results obtained in a human study, in which there was no evidence of sensitisation to clobetasol propionate lotion vehicle.

***Carcinogenicity*:**

No animal carcinogenicity studies were conducted.

Results of a 13-week preliminary topical study with clobetasol propionate lotion in hairless mice, with or without simulated sunlight confirmed the strong pharmacological effects of clobetasol propionate (skin atrophy, significant body weight loss, mortality). The severity of the toxic effects observed after 13 weeks of treatment even in the lowest dose group (dose volume of 25 µL administered three times per week) show that similar experimental conditions are not feasible for a photocarcinogenicity study with treatment duration of 40 weeks.

***Mutagenicity*:**

Clobetasol propionate was shown to be not mutagenic in Ames test, gene conversion tests and *E. coli* B WP2 fluctuation test. The long history of clinical practice of clobetasol propionate gives no rise to suspicion for an impact on genetic material.

***Reproduction & Teratology*:**

In a fertility study in the rat by the subcutaneous route, no effects on the reproductive organs or on the mating performance were observed in either sex at doses up to 50 µg/kg/day. The only effect observed in the females at this dosage was an increased number of absorbed embryos and a decreased number of living fetuses.

Clobetasol propionate, like other corticosteroids, induced teratogenicity in laboratory animals when administered systemically but also after dermal application. Topical teratogenicity occurred at relatively low dose levels but at relatively high plasma concentrations. These were due to the occlusion applied to minimize oral uptake.

Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses approximately 0.02 and 0.05 times the human topical dose of clobetasol propionate lotion, 0.05%. Abnormalities were observed including cleft palate, cranioschisis, and other skeletal abnormalities.

A teratogenicity study in rats using the dermal route resulted in dose related maternal and fetal effects from 0.05 to 0.5 mg/kg/day of clobetasol propionate. Abnormalities seen included fetal immaturity and several malformations, in combination with maternal toxicity.

BIBLIOGRAPHY

Carruthers J.A., August P.J., Staughton R.C.D.
Observations on the systemic effect of topical clobetasol propionate (DERMOVATE®). *BMJ*, **2**, 203-204, 1975.

Corticosteroids: Topical[Pr] - General Monograph, Canadian Pharmacists' Association. In. Compendium of Pharmaceutical Specialties (CPS), 2002).

Feldmann R.J., Maibach H.I.
Penetration of ^{14}C hydrocortisone through normal skin. *Arch. Dermat.*, **91**, June, 1965.

Glaxo Wellcome, Inc.
Summary Basis of Approval for TEMOVATE® E (Clobetasol Propionate) Emollient Cream 0.05%, NDA 20-340, 1994.

Gordon M.L.
The role of clobetasol propionate emollient 0.05% in the treatment of patients with dry scaly corticosteroid-responsive dermatoses. *Clinical Therapeutic*; **20**, (1), 26-39, 1998.

Ohman E.M., Rogers S., Meenan F.O., McKenna T.J.
Adrenal suppression following low-dose topical clobetasol propionate. *J R Society of Medicine, 80, 422-424, 1987.*

Olsen E., Cornell R.
Topical clobetasol-17 propionate: Review of its clinical efficacy and safety. *J Am Acad Dermatol,* **15**, 246-255, 1986.

Ponec M., Polano M.K.
Penetration of various corticosteroids through epidermis *in vitro*. *Arch. Dermatol. Res.*, **265**, 101-104, 1979.

The Safety and Efficacy of Clobetasol Propionate Lotion, 0.05% as Compared to its Vehicle and TEMOVATE® E Emollient Cream in the Treatment of Moderate to Severe Plaque-type Psoriasis: A Randomized, Active- and Vehicle-Controlled, Investigator-masked, Parallel Comparison. Data on file, Galderma Canada Inc.

The Safety and Efficacy of Clobetasol Propionate Lotion, 0.05% as Compared to its Vehicle and TEMOVATE® E Emollient Cream in the Treatment of Moderate to Severe Atopic Dermatitis: A Randomized, Active- and Vehicle-Controlled, Investigator-masked, Parallel Comparison. Data on file, Galderma Canada Inc.

An Adrenal Suppression Study of Clobetasol Propionate Lotion, 0.05% as Compared to TEMOVATE® E Emollient Cream, 0.05% and TEMOVATE® Cream, 0.05% in Adolescents with Atopic Dermatitis. Data on file, Galderma Canada Inc.