PRODUCT MONOGRAPH

PrClobex® Shampoo

Clobetasol Propionate Solution
0.05% w/w

Topical Corticosteroid

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ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action:
Clobex® (clobetasol propionate) is a super-high potency topical corticosteroid. Like other topical corticosteroids, Clobex® Shampoo (clobetasol propionate shampoo, 0.05%) has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the 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 the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin while inflammation and/or other disease processes in the skin may increase percutaneous absorption.

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 well 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, including clobetasol propionate and its metabolites, are also excreted in the bile.

INDICATIONS AND CLINICAL USE

Clobex Shampoo (clobetasol propionate shampoo, 0.05%) is a super-high potent topical corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of moderate to severe forms of scalp psoriasis in subjects 18 years of age and older.

Treatment should be limited to 4 consecutive weeks because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. The total dose should not exceed 50 g (50 mL or 1.75 fl oz.) per week (see dosage and administration).

Patients should be instructed to use Clobex Shampoo for the minimum time period necessary to achieve the desired results (see WARNINGS AND **PRECAUTIONS**).

Use in patients under 18 years of age is not recommended. Must not be used in Children under 2 years of age.

There were insufficient numbers of non-Caucasian patients in the studies evaluating the safety and efficacy of Clobex Shampoo to determine whether they responded differently than Caucasian patients with regards to efficacy and safety.

CONTRAINDICATIONS

Clobex Shampoo (clobetasol propionate shampoo, 0.05%) is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

Clobex Shampoo is contraindicated in skin areas affected by bacterial or mycobacterial infections (including tuberculosis of the skin), fungal infections, syphilitic skin infections, chicken pox, eruptions following vaccinations, viral diseases of the skin in general, parasitic infections and ulcerous wounds.

This preparation is also contraindicated in the treatment of rosacea, acne vulgaris, perioral dermatitis or perianal and genital pruritis.

Must not be used in Children under 2 years of age

Must not be applied to the eyes and eyelids (risk of glaucoma, risk of cataract).

WARNINGS AND PRECAUTIONS

Clobex Shampoo should not be used under occlusive dressing, over extensive areas, or on the face, axillae and scrotum, as sufficient absorption may occur giving rise to adrenal suppression and other systemic effects.

General:

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary- adrenal (HPA) axis 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.

The effect of Clobex Shampoo (clobetasol propionate, 0.05%) on HPA axis suppression was evaluated in one study in adolescents 12 to 17 years of age. In this study, 5 of 12 evaluable subjects developed suppression of their HPA axis following 4 weeks of treatment with Clobex Shampoo applied once daily.

Conditions which increase 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 applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol 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 topical corticosteroids. (See **CLINICAL STUDIES**) Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Topical corticosteroids are known to potentially induce telangiectasia. If irritation develops, Clobex Shampoo (clobetasol propionate shampoo, 0.05%) should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation, as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of Clobex Shampoo should be discontinued until the infection has been adequately controlled.

Although Clobex Shampoo is intended for the topical treatment of moderate to severe scalp psoriasis, it should be noted that certain areas of the body, such as the face, groin, and axillae, are more prone to atrophic changes than other areas of the body following treatment with corticosteroids. Clobex Shampoo 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. Avoid any contact of the drug product with the facial skin, eyes and lips. In case of contact, rinse thoroughly with water all parts of the body that came in contact with the shampoo.

Suitable precautions should be taken when using topical corticosteroids in patients with stasis dermatitis and other skin diseases with impaired circulation.

Immune:
Corticosteroids have immunosuppressive properties. Topical corticosteroids may decrease resistance to infection, increase the risk of opportunistic infection and also mask some signs of infection. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Use in Geriatrics:

Clinical studies of Clobetasol Propionate Shampoo, 0.05%, did not include sufficient numbers of patients aged 65 years 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.

Use in Pediatrics:

Safety and effectiveness of Clobex Shampoo have been established in patients 18 years and older. Insufficient data have been obtained in patients under the age of 18 years. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal 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.

Use in patients between 2 and 18 years of age is not recommended and is contraindicated in children below 2 years of age.

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 an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Use in Pregnant Women:

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. A teratogenicity study of clobetasol propionate in rats using the dermal

route resulted in dose related material toxicity and fetal effects from 0.05 to 0.5 mg/kg/day. These doses are approximately 0.1 to 1.0 times, respectively, the maximum human topical dose of clobetasol propionate from Clobex Shampoo. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification, and other skeletal abnormalities. Clobetasol propionate administered to rats subcutaneously at a dose of 0.1 mg/kg from day 17 of gestation to day 21 postpartum was associated with prolongation of gestation, decreased number of offspring, increased perinatal mortality of offspring, delayed eye opening and delayed hair appearance in surviving offspring. Some increase in offspring perinatal mortality was also observed at a dose of 0.05 mg/kg. Doses of 0.05 and 0.1 mg/kg are approximately 0.1 and 0.2 fold the maximum human topical dose of clobetasol propionate from Clobex Shampoo.

There have been no adequate and well-controlled studies in pregnant women. Clobex Shampoo should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactating Women:

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 human milk. Because many drugs are excreted in human milk, caution should be exercised when Clobex Shampoo is administered to a nursing woman. Clobetasol propionate should not be prescribed to breastfeeding women unless clearly indicated.

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 Shampoo on fertility have not been performed.

Laboratory Tests:

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

- ACTH stimulation test
- A.M. plasma cortisol test
- Urinary free cortisol test

Information to Provide to the Patient:

Patients using topical corticosteroids 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 period. Patients should not use more than 50 g (50 mL or 1.75 fl. oz.) per week of clobetasol propionate shampoo 0.05%. It is for external use only. 2.

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

3. This medication should not be used for any disorder other than that for which it was prescribed.
4. The scalp area should not be covered while the medication is on the scalp (e.g., shower cap, bathing cap) so as to be occlusive unless directed by the physician.
5. Patients should report to their physician any signs of local adverse reactions.
6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, contact the physician.
7. Patients should wash their hands after applying the medication.
8. Do not apply to the eyes and eyelids.
9. Patients should inform their physician(s) that they are using Clobex Shampoo if surgery is contemplated.

For additional information, see **INFORMATION FOR THE CONSUMER**.

ADVERSE REACTIONS

Adverse Reactions Overview

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions include: irritation, dryness, itching, burning, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, skin atrophy, atrophy of subcutaneous tissues, telangiectasia, hypertrichosis, change in pigmentation, opportunistic infection, hypersensitivity, glaucoma, striae, and miliaria. If applied to the face, acne, rosacea or perioral dermatitis can occur. When occlusive dressings are used, pustules, miliaria, 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.

Rebound effect may occur upon treatment discontinuation.

Clinical Trial Adverse Reactions

A total of 214 (23.8%) of the 900 subjects in the safety population reported at least one AE during the nine Phase II and III studies. Out of the total 558 subjects exposed to Clobex Shampoo, 129 (23.1%) experienced at least one adverse event. These AEs were mainly dermatological (49 subjects, 8.8%), leading to discontinuation in 6 subjects and were considered to be related to the drug for 40 subjects. Of the 6 discontinued subjects, 5 had dermatological events and 2 had non-dermatological events (one

subject had one dermatological and one non-dermatological events).

See Table 1 below for a summary of adverse events in the safety population of 558 patients for Clobex Shampoo and 127 patients in the Vehicle Shampoo group.

Table 1: Summary of Adverse Events by Body System and Detail of Events with Frequency of 1% or more in Clobex Shampoo Group

Body System Costart Term*	Clobex Shampoo (N=558)	Vehicle Shampoo (N=127)
Total Number of AE(s)	166	69
Total Number of Subjects with AE(s)^	129 (23.1%)	40 (31.5%)
SKIN AND APPENDAGES	**49 (8.8%)**	**28 (22.0%)**
DISCOMFORT SKIN	26 (4.7%)	16 (12.6%)
BODY AS A WHOLE	**33 (5.9%)**	**12 (9.4%)**
HEADACHE	10 (1.8%)	1 (0.8%)
INJURY/ ACCIDENT	8 (1.4%)	3 (2.4%)
FLU SYNDROME	6 (1.1%)	3 (2.4%)
RESPIRATORY SYSTEM	**20 (3.6%)**	**6 (4.7%)**
PHARYNGITIS	12 (2.2%)	4 (3.1%)
DIGESTIVE SYSTEM	(2.9%)	4 (3.1%)
TOOTH DISEASE	6 (1.1%)	0 (0.0%)
GASTROENTERITIS	6 (1.1%)	0 (0.0%)
UROGENITAL SYSTEM	**9 (1.6%)**	**1 (0.8%)**
HEMIC AND LYMPHATIC SYSTEM	**4 (0.7%)**	**0 (0.0%)**
METABOLIC AND NUTRITIONAL DISORDER	**4 (0.7%)**	**1 (0.8%)**
NERVOUS SYSTEM	**4 (0.7%)**	**2 (1.6%)**
CARDIOVASCULAR SYSTEM	**3 (0.5%)**	**0 (0.0%)**
MUSCULOSKELETAL SYSTEM	**3 (0.5%)**	**1 (0.8%)**
SPECIAL SENSES	**2 (0.4%)**	**1 (0.8%)**

*: A subject was counted once per COSTART term even if more than one occurrence of the event was experienced within the COSTART term.

Adverse Events Reported at Less Than 1% Frequency

Adverse events with a frequency less than 1% include eye stinging/burning, eye irritation, ocular tight sensation, pruritus, urticaria, pain of skin, oedema, telangiectasia, psoriasis aggravation, alopecia, dry skin, skin atrophy, skin tightness, skin irritation and acne.

Post-Market Adverse Reactions

The following adverse reactions have been reported in the post-marketing setting: adrenal suppression, Cushing syndrome, glaucoma, hypersensitivity, allergic contact dermatitis, erythema and rash.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In case of chronic overdose or misuse, the features of hypercortisolism may appear and in this situation, treatment should be discontinued gradually. However, because of the risk of acute adrenal suppression, this should be done gradually under medical supervision (See WARNINGS AND **PRECAUTIONS**).

If you think you have used too much Clobex Shampoo, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

DOSAGE AND ADMINISTRATION

Clobex Shampoo (clobetasol propionate) should be applied in a thin film to the affected areas of the scalp one application per day. The product should be applied on dry scalp and left in place for 15 minutes before lathering and rinsing.

Move the hair away from the scalp so that one of the affected areas is exposed. Position the bottle over the lesion. Apply a small amount of the shampoo directly onto the lesion, letting the product naturally flow from the bottle (gently squeeze the bottle), avoiding any contact of the product with the facial skin, eyes or lips. In case of contact, rinse thoroughly with water. Spread the product so that the entire lesion is covered with a thin uniform film. Massage gently into the lesion and repeat for additional lesion(s). Wash your hands carefully after applying Clobex Shampoo.

Leave the shampoo in place for 15 minutes. Add water, lather and rinse thoroughly all parts of the scalp and body that came in contact with the shampoo (e.g., hands, face, neck and shoulders). Avoid contact with eyes and lips. Minimize contact to non-affected areas of the body. Although no additional shampoo is necessary to cleanse your hair, you may use a non-medicated shampoo if desired.

Clobex Shampoo is a super-high potent topical corticosteroid formulation. Treatment should be limited to 4 consecutive weeks. The maximum amount of clobetasol propionate shampoo 0.05% to be used per week is 50 g (50 mL or 1.75 fl.oz.).

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, reassessment of diagnosis may be necessary.

Use in patients between 2 and 18 years of age is not recommended and is contraindicated in children below 2 years of age.
Clobex Shampoo should not be used with occlusive dressings unless directed by a physician.

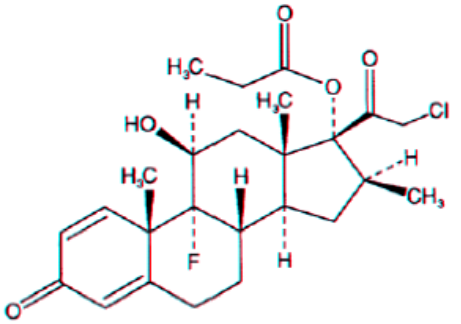
PHARMACEUTICAL INFORMATION

Drug Substance:

Common 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: $C_{25}H_{32}ClFO_5$ (CAS Registry Number 25122-46-7)

Molecular Weight: 466.97 grams/mole

Description: White to practically white crystalline powder.

Solubility: Insoluble in water

Melting Point: Approximately 196EC

Composition:

Clobex Shampoo contains clobetasol propionate, 0.05%, USP, in a shampoo base consisting of alcohol, 10%; citric acid monohydrate; coco-betaine; polyquaternium-10; purified water; sodium citrate dihydrate and sodium laureth sulfate.

Stability and Storage Recommendations:

Keep tightly closed. Store at controlled room temperature 15°C - 30°C.

AVAILABILITY AND DOSAGE FORMS

Clobex Shampoo (clobetasol propionate shampoo, 0.05%) is supplied in 118 mL bottles.

PHARMACOLOGY

Animal Studies:

Although its mechanism of action has not been established, clobetasol propionate is thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. In literature, among others by Schimmer and Parker (2001) it is described 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. The physiological release of arachidonic acid from membrane phospholipids is under control of phospholipase A_2.

Dermatopharmacologic investigations were reported by Yawalkar et al. (1991) on clobetasol propionate in comparison with two other topical corticosteroids (halobetasol propionate and hydrocortisone). Several animal models as the croton oil-induced ear edema model in rats and mice, and the ultraviolet-induced dermatitis inhibition test in guinea pigs demonstrated the effects of clobetasol propionate on topical non-immune inflammation. Again, Yawalkar et al. (1991) demonstrated the effects of clobetasol propionate in comparison with halobetasol propionate and hydrocortisone on topical immune inflammation, in oxazolone-induced dermatitis in rats and mice. Bäck and Egelrud (1985) utilised a picryl chloride contact sensitivity model, demonstrating that topical application of clobetasol propionate suppressed completely the hypersensitization reaction resulting in total inhibition of the inflammatory oedema. The inflammation was reduced to a great extent also in the control ear not treated with clobetasol propionate indicating a systemic effect of the product.

The percutaneous absorption of clobetasol propionate in rats after application of clobetasol propionate shampoo 0.05% for 15 or 30 minutes was lower than after application of the commercial Japanese formulation.

If absorbed through the skin, clobetasol propionate will be metabolised by the liver and excreted primarily via bile into the feces.

The fact that clobetasol propionate could induce a six-fold induction of ethoxycoumarin-O- dealkylase activity in skin indicates that there is a potential drug-drug interaction with other topical drugs that could be metabolised by the same enzyme.

Human Studies:

Topically applied clobetasol propionate shampoo 0.05% once daily short-contact therapy poses low systemic exposure. This has been demonstrated an *in vitro* liberation-penetration study and under clinical conditions in four different studies.

The *in vitro* liberation-penetration study evaluated the skin penetration of clobetasol propionate, through washed and unwashed healthy human skin, after topical application of a 10 mg dose of the shampoo formulation (equivalent to 5 µg of clobetasol propionate). After a short contact therapy lasting 15 minutes prior to rinsing only a small percentage (0.1%) of the applied dose of clobetasol propionate penetrated the skin.

This low systemic exposure has been demonstrated under clinical conditions of use in scalp psoriasis subjects by the measuring of clobetasol propionate serum levels in a total of 141 subjects. In four studies which had duration of 4 hours to 4-weeks, blood samples were analyzed by reverse-phase high-performance liquid-chromatography using a method validated between 0.2 and 5 ng/mL with a 0.1 ng/mL limit of detection. Only one subject (0.7%) out of 141 subjects who received clobetasol propionate shampoo and was assayed for plasma clobetasol propionate had a quantifiable clobetasol propionate level (0.426 ng/mL). Two other subjects (1.4%) had levels above the limit of detection (0.1 ng/mL) but below the limit of quantification (0.2 ng/mL).

The pharmacodynamics properties of clobetasol propionate were investigated in a vasoconstrictor study. This was as a single-center, randomized, investigator-blinded, active and vehicle-controlled, intra-individual comparison evaluating the skin blanching capacity of clobetasol propionate versus clobetasol propionate liquid 0.05%, cream 0.05%, and betamethasone dipropionate cream, 0.05% when administered as a 15-minute occlusive patch test on the forearm of 12 healthy subjects. Under the conditions of this study, clobetasol propionate shampoo produced less vasoconstriction than did either clobetasol propionate liquid 0.05% or cream 0.05%, and more vasoconstriction than did betamethasone dipropionate cream, 0.05% allowing its ranking as a "very strong" (class 1) corticosteroid.

A phase I, intra-individual, investigator-blinded, randomized, controlled irritation and sensitization study was conducted. In this study, two clobetasol propionate shampoo vehicle formulations (one with and another without preservative) were assessed to determine their potential to cause irritation and/or sensitization after repeated application three times weekly for three weeks to the skin of healthy subjects, using a standard repeat insult patch testing (RIPT) design (a 3-week induction phase, a 2-week rest period, and a single application challenge phase). In this study, the clobetasol propionate shampoo vehicle showed evidence of mild cumulative irritation potential under occlusion (given that the formulation contains a surfactant) but no evidence of irritation under non-occluded conditions. There was no evidence of sensitization to either of the vehicle shampoos, regardless of the mode of application (occluded or unoccluded).

CLINICAL STUDIES

Two Phase II randomized, investigator-masked safety and preliminary efficacy studies were conducted to evaluate dose-regimens, by assessing scalp conditions (wet or dry) and/or the duration of contact time before rinsing (2.5, 5, 10 and 15 minutes). The results led to the selection that 15 minutes, dry scalp application would be the most effective application regimen.

The clinical efficacy of Clobex Shampoo (clobetasol propionate shampoo, 0.05%) has been demonstrated in two pivotal well-controlled clinical trials involving patients of moderate to severe scalp psoriasis. These studies involved 142 (Study A) and 148 (Study B) patients each and were treated with either Clobex Shampoo or with its vehicle shampoo at 15 minutes of exposure, once a day for 4 weeks. The patients also went through 2 weeks of post-treatment follow up. In these two studies, Global Severity Score (GSS) was evaluated for the whole scalp and considered the overall presence and intensity of plaque thickening, scaling and erythema on six pint scales ranging from 0-5. The GSS was dichotomized as success (score of 0 to 1) or failure (score of 2 to 5) to yield a Success Rate which was the primary efficacy variable as measured at Week 4 in the Intent to treat population (ITT). The secondary efficacy variables included the Total Severity Scores (TSS) defined as the sum of the individual scores for erythema, scaling, and plaque thickening with each parameter scored on a 4-point scale from 0 (none) to 3 (severe). Other variables were individual signs and symptoms, scalp surface area of involvement and global assessment improvement. All tests were two-sided and the 0.05 level was used to determine significance.

The results obtained from both trials demonstrated that Clobex Shampoo was significantly more effective than its vehicle after 4 weeks of treatment. See Table 2 below.

Table 2: Summary of Efficacy with Clobex Shampoo versus Vehicle

	Clobex Shampoo n (%)	Clobex Shampoo Vehicle n (%)
STUDY A Total Number of Patients	N = 95	N = 47
Success Rate[1]		
- at Endpoint[2]	40 (42.1%)	1 (2.1%)
- at Week 6 (follow-up)	21 (23.9%)	2 (4.5%)
Subjects with Scalp Psoriasis Parameter		
Clear (None) at Endpoint	17 (17.9%)	3 (6.4%)
Erythema	21 (22.1%)	0 (0%)
Scaling	35 (36.8%)	5 (10.6%)
Plaque Thickening	43 (45.3%)	6 (12.8%)
Pruritus		
STUDY B Total Number of Patients	N = 99	N = 49
Success Rate[1]		
at Endpoint[2]	28 (28.3%)	5 (10.2%)
at Week 6 (follow-up)	18 (19.6%)	6 (13.3%)
Subjects with Scalp Psoriasis Parameter		
Clear (None) at Endpoint	12 (12.1%)	1 (2.0%)
Erythema	15 (15.2%)	2 (4.1%)
Scaling	34 (34.3%)	5 (10.2%)
Plaque Thickening	41 (41.4%)	8 (16.3%)
Pruritus		

[1] The success rate is defined as the proportion of patients with a Global Severity Score of 0 (clear) or (1) minimal on a 0 to 5 point scale

[2] Last observation recorded for a subject during the treatment period, including Baseline if no post-baseline data were available

Three additional Phase III studies were conducted to compare Clobex Shampoo to a representative of every pharmacological class used in the treatment of scalp psoriasis: tars, vitamin D analogues and corticosteroids. These studies were designed to demonstrate non-inferiority of Clobex Shampoo to the chosen comparator. Two of the studies with the tar blend and calcipotriol solution (a vitamin D analogue) demonstrated the superior efficacy of Clobex Shampoo. The other study compared Clobex Shampoo with a clobetasol propionate gel and a vehicle shampoo and showed Clobex Shampoo to be non-inferior to the gel form.

Two studies were conducted and no HPA Axis suppression was observed in adult (18 years and above) psoriatic subjects when Clobex Shampoo was applied once daily for 15 minutes to a dry scalp before lathering and rinsing, over a treatment period of 4 weeks. (See Table 3 and 4 below).

Table 3: Summary of HPA Axis Function in Adolescents Ages 12-17 Years with Scalp Psoriasis

		Clobex Shampoo* N = 13
Baseline (Week 0) Pre-stimulation Cortisol (µg/dL)	Mean ∀ SD	12.57 ∀ 3.778
	Min - Max	7.4 B 19.6
Post-stimulation Cortisol (µg/dL)	Mean ∀ SD	29.57 ∀ 4.659
	Min - Max	24.1 B 39.3
HPA Axis Suppression	N(%)	
End of Treatment (Week 4) Pre-stimulation Cortisol (µg/dL)	Mean ∀ SD	14.38 ∀ 5.586
	Min - Max	7.5 B 27.7
Post-stimulation Cortisol (µg/dL)	Mean ∀ SD	39.98 ∀ 8.191
	Min - Max	10.4 B 42.0
HPA Axis Suppression	N(%)	

*HPA axis suppression defined in the protocol as pre-stimulation cortisol value <7 µg/dL or post-stimulation cortisol value <18 µg/dL

Table 4: Summary of HPA Axis Function in Scalp Psoriasis Patients Aged 18 Years and Older Clobex Shampoo

		Clobex Shampoo N = 14	HPA Axis Suppression*
Baseline (Week 0)			
Pre-stimulation Cortisol (µg/dL)	Mean ∀ SD	21.30 ∀ 7.352	
	Min - Max	12.9 - 36.1	
Post-stimulation Cortisol (µg/dL)	Mean ∀ SD	33.33 ∀ 9.015	
	Min - Max	25.1 - 50.5	
Post-Pre Cortisol (µg/dL)	Mean ∀ SD	12.03 ∀ 5.036	
	Min - Max	2.4 - 21.1	
HPA Axis Suppression	N(%)		0 (0.0%)
End of Treatment (Week 4)			
Pre-stimulation Cortisol (µg/dL)	Mean ∀ SD	23.53 ∀ 10.648	
	Min - Max	10.6 - 49.6	
Post-stimulation Cortisol (µg/dL)	Mean ∀ SD	33.91 ∀ 10.696	
	Min - Max	23.4 - 63.8	
Post-Pre Cortisol (µg/dL)	Mean ∀ SD	10.38 ∀ 3.608	
	Min - Max	4.2 - 15.8	
HPA Axis Suppression	N(%)		0 (0.0%)

*HPA axis suppression defined in the protocol as pre-stimulation cortisol value <10 µg/dL and the change (post-pre) <8 µg/dL

TOXICOLOGY

Acute Toxicity:
Acute toxicity was determined in mice and rats using subcutaneous, oral, and intraperitoneal routes. The animals received a single dose of different concentrations of clobetasol propionate and were observed for 3 consecutive weeks. The LD_{50} value obtained by the subcutaneous route in mice was 81.7 $mg.kg^{-1}$ for all animals. None of the mice died after oral administration up to 3 $g.kg^{-1}$. The LD_{50} value obtained by the intraperitoneal route in mice was 156 $mg.kg^{-1}$ for males and 118 $mg.kg^{-1}$ for females. The subcutaneous LD_{50} value for male rats was 397 $mg.kg^{-1}$ and 366 $mg.kg^{-1}$ for female rats. None of the rats died after oral administration up to 3 $g.kg^{-1}$. The LD_{50} value by the intraperitoneal route for male rats was 414 $mg.kg^{-1}$ and 351 $mg.kg^{-1}$ for female rats.

Long Term Toxicity:
In a four-week dose-range-finding study, Göttingen minipigs (one animal per sex per group) were treated daily on approximately 10% of their body surface area with clobetasol propionate shampoo 0.05% in volumes ranging from 0.5 - 2 $mL.kg^{-1}$. The placebo group was treated with the vehicle at 2 $mL.kg^{-1}$. The exposure time was 15 minutes for all groups, followed by rinsing. The only remarkable sign in this study was erythema and scab formation without histopathological changes observed in some of the animals receiving the high volume, independent of the presence of clobetasol propionate. Hence, it was concluded that the vehicle is slightly irritating.

In a thirteen-week study with four Göttingen minipigs per sex per group and the rest of the design exactly the same as that of the dose-range-finding study, no treatment-related clinical signs or skin effects were observed.

Published literature shows that long term effect of high doses of clobetasol propionate treatment causes emaciation, piloerection, inhibition of hair growth, body weight loss, lacrimation, diarrhea, atrophy of spleen, mesenteric lymph nodes, thymus and adrenal glands, focal necrosis of liver and mortality.

Carcinogenicity:
No classical two-year animal studies applying animal models using genetically engineered mice have been performed to evaluate the carcinogenic potential of clobetasol propionate. One 18-month study was performed in mice to evaluate the carcinogenic potential of fluticasone propionate (medium-potency corticosteroid) when given topically as a 0.05% ointment. No evidence of carcinogenicity was found in this study. No evidence of pre-neoplastic lesions was noted in a 6-month toxicity study performed with clobetasol propionate by the subcutaneous route in rats.

Mutagenicity:
Two mutagenicity studies were performed: an *in vitro* chromosomal aberration study on Chinese Hamster Ovary cells and a mouse *in vivo* micronucleus study.

In *vitro* chromosomal aberration study, concentrations of clobetasol propionate up to 4670 $\mu g.mL^{-1}$ did not induce an increase in the number of aberrant cells neither in the presence or the absence of S9. The highest concentration tested in the 20-hour incubation experiment was 31.3 $\mu g.mL^{-1}$ due to cytotoxicity. Also under the extended incubation conditions there was no increase in the number of aberrant cells.
In the mouse *in vivo* micronucleus study, there was an increase in the number of micronucleated cells in the mice treated with clobetasol propionate. In the high dose group, the ratio of the polychromatic erythrocytes over the total erythrocytes at the 24-hour sampling tended to be less than in the placebo group. This could indicate that this dose was toxic to the bone marrow.

Clobetasol propionate was non-mutagenic in three different test systems reported in the literature for clobetasol

propionate 0.05% cream and ointment: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Reproductive Toxicity:
Segment I fertility studies in rats following oral administration at doses up to 50 $\mu g.kg^{-1}$ per day revealed an increase in the number of the resorbed embryos and a decrease in the number of living foetuses at the highest dose.

Segment II teratogenicity studies in mice, rats and rabbits showed clobetasol propionate to be teratogenic when administered sub-cutaneously or topically. Abnormalities seen include fetal immaturity and several malformations, cleft palate, cranioschisis and skeletal abnormalities, in combination with maternal toxicity. There are no adequate and well-controlled studies in pregnant women.

A segment III study of peri-natal and post-natal effects was performed on 20 female rats at doses of 0, 25, 50 and 100 μg/kg body weight daily through sub-cutaneous route at day 17 of gestation through day 21 post-partum. At the 50 and 100 $\mu g.kg^{-1}$ doses, increased pup loss, total litter loss, acts of cannibalism and diminished parental care were the major effects observed during the first days post-partum. No effects were observed at the dose of 25 $\mu g.kg^{-1}$. Growth and development of the F1 surviving offspring were unaffected by treatment.

Local Tolerance:
Three studies were performed with clobetasol propionate shampoo 0.05% to evaluate the response following a single dermal and a single ocular application, and to evaluate its potential to induce delayed-type of hypersensitization. Clobetasol propionate shampoo 0.05% when administered undiluted for 15 minutes was found to be a slight irritant to the skin whereas the vehicle is considered to be an irritant. Clobetasol propionate shampoo 0.05% and its vehicle, as a 30%-dilution in water were found to be slightly irritating to the eye. In the third study, there were no skin reactions attributable to sensitization, indicating the absence of the potential of the product to induce delayed-type sensitization.

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INFORMATION FOR THE CONSUMER

For External Use Only
Not for Ophthalmic Use

Clobex® Shampoo
clobetasol propionate shampoo, 0.05%

Read this information carefully before you begin treatment with Clobex® Shampoo. 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® Shampoo, ask your doctor. Only your doctor can determine if Clobex Shampoo is right for you.

What is the most important information I should know about Clobex® Shampoo?

What is Clobex® Shampoo?
Your doctor has prescribed Clobex Shampoo for the relief of the redness, scaling, and itching associated with moderate to severe forms of scalp psoriasis. Clobex Shampoo works because its active ingredient, clobetasol propionate, belongs to a group of medicines known as topical corticosteroids. Clobex Shampoo is used for no more than 4 weeks to treat forms of scalp psoriasis. It is very important that you use Clobex Shampoo only as directed in order to avoid serious side effects.

Who should not use Clobex® Shampoo?
Do not use Clobex Shampoo 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.

Clobex Shampoo must not be used in children under 2 years of age and is not recommended for use by children under 18 years of age.

Do not use Clobex Shampoo in skin areas affected by bacterial or mycobacterial infections (including tuberculosis of the skin), fungal infections, syphilitic skin infections, chicken pox, eruptions following vaccinations, viral diseases of the skin in general, and parasitic infections.

Clobex Shampoo should not be used in the treatment of rosacea, acne vulgaris, ulcerous wounds, inflammation or itching around the mouth, anus, or genitals, unless your doctor has recommended it.

What should I tell my doctor before using Clobex® Shampoo?
If you are pregnant, think you are pregnant, plan to be pregnant, or are nursing an infant tell your doctor before you use Clobex Shampoo. Your doctor will decide with you whether the benefits in using Clobex Shampoo will be greater than the risks. If possible, delay treatment with Clobex Shampoo until after the baby is born.

If you think you have an infection on your scalp, tell your doctor before you use Clobex Shampoo, because you may need other medicines to treat the infection.

Tell your doctor if you are going to have surgery.

Tell your doctor if you have a weak immune response.

Tell your doctor about all the other medicines and skin products you use, including prescription and non-prescription medicines, cosmetics, vitamins, and herbal supplements.

Inform your physician of prior or current use of 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. Also, inform your physician of allergies to other substances such as foods, dyes etc.

How should I use Clobex® Shampoo?

Clobex Shampoo should be used as instructed by your doctor.
To help you use the medicine correctly, follow these steps:

- Apply Clobex Shampoo on affected areas of the scalp once per day.
- Do not wet your hair at first. Apply the product on dry scalp.
- Move the hair away from the scalp so that one of the affected areas is exposed. Position the bottle over the lesion. Apply a small amount of the shampoo directly onto the lesion, letting the product naturally flow from the bottle (gently squeeze the bottle).
- Use only enough to cover the affected areas of your scalp.
- Spread the product so that the entire lesion is covered with a thin uniform film.
- Massage gently into the lesion and repeat for any additional lesion(s).
- Wash your hands carefully and any other part of your body that came into contact with Clobex Shampoo such as your neck and shoulders.
- Leave the shampoo in place for 15 minutes.
- Add water, lather and rinse thoroughly all parts of the scalp and body that came in contact with the shampoo (e.g., hands, face, neck and shoulders). Although no additional shampoo is necessary to cleanse your hair, you may use a non-medicated shampoo as needed.
- As with other corticosteroids, treatment should be discontinued when control of your condition has been achieved.
- Clobex Shampoo is for use on your scalp only.

What should I avoid while using Clobex® Shampoo?

Do not do the following while using Clobex® Shampoo:

- Do not get Clobex Shampoo on your lips or in or near your eyes or eyelids (risk of glaucoma and cataract). If you do, use a lot of water to rinse the Clobex Shampoo off your face, lips, or out of your eyes. If your eyes keep stinging after rinsing them well with water, contact your doctor right away.
- Do not apply Clobex Shampoo to your face, groin or armpits.
- Do not get Clobex Shampoo in your mouth. If you or a child accidentally swallows Clobex Shampoo, call your Poison Control centre or local emergency room right away.
- Do not use under any dressing, or cover your head with a shower/bathing cap while Clobex Shampoo is on your scalp, unless directed to do so by your doctor.
- Do not use Clobex Shampoo any longer than 4 weeks (28 days) for moderate to severe scalp psoriasis.
- Do not use more than 50 mL (1.75 fluid ounces) of Clobex Shampoo per week.

Do not have any immunizations without your doctor's approval if you are using this medication.

What should I do if I miss an application of Clobex® Shampoo?

If you forget to apply Clobex Shampoo at the scheduled time, use it as soon as you remember. Then go back to your regular schedule. If it is about time for your next dose, apply just that 1 dose, and continue with your regular schedule. Do not make up the missed dose. If you miss several doses, tell your doctor.

What are the possible side effects of Clobex® Shampoo?
Clobex Shampoo contains clobetasol propionate, which can pass through your skin. Too much clobetasol propionate passing through your skin can shut down your adrenal glands. This may happen if you use too much Clobex Shampoo 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 Shampoo. 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. Manifestations of Cushing's syndrome (signs and/or symptoms due to an excess of cortisol, such as obesity of the upper body, puffiness of the face, skin manifestations and hirsutism), hyperglycemia (excessive amount of glucose in the blood), glucosuria (glucose in the urine), infection, can also be produced in some patients by absorption through your skin. Your doctor may do special blood and urine tests to check your adrenal gland function while you are using Clobex Shampoo.

The most common side effects with Clobex Shampoo include skin discomfort, burning or itching at the site of application. Other possible side effects include skin atrophy (thinning of the skin), swelling of the skin, psoriasis aggravation, dry skin, skin tightness, baldness and telangiectasia (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 Shampoo. 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 4 weeks of using Clobex Shampoo. These are not all the possible side effects of Clobex Shampoo. For more information, ask your doctor or pharmacist.

Clobex Shampoo may hide symptoms of infections, may cause inactive infections to become active, and may cause infections by normally inoffensive organisms due to lowered body resistance.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your doctor or pharmacist		
		Only if severe	**In all cases**	
Common	**Burning at the site**	√		
Uncommon	**Nausea**			√
	Vomiting			√
	Fever			√
	Dizziness (adrenal suppression)			√
	Worsening of psoriasis (red, scaly, thick patches of skin)			√
	Irritation at the site	√		

Other Important information:

- Do not use the shampoo after the expiration date shown on bottle.
- Do not give Clobex Shampoo 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 Shampoo. If you would like more information, talk with your doctor or pharmacist. They have information about Clobex Shampoo that is written for health professionals.

Storage: Keep tightly closed. **Keep this and all medicines out of the reach of children.** Store at controlled room temperature 15°C - 30°C.

Ingredients: Active: clobetasol propionate, 0.05% (w/w). Other ingredients in the shampoo base: alcohol, citric acid monohydrate, coco-betaine, polyquaternium-10, purified water, sodium citrate dihydrate, and sodium laureth sulfate. This shampoo is dispensed from a HDPE (high density polyethylene) bottle.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhpmps/ medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

Keep tightly closed. Store at controlled room temperature 15°C - 30°C.

Keep out of the reach and sight of children.

If you want more information about Clobex Shampoo:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (http://www.galderma.ca) or by calling 1-800-467-2081.

This leaflet was prepared by Galderma Canada Inc.

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