PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrCLOBEX® SHAMPOO

clobetasol propionate shampoo

solution, 0.05% w/w, topical

Topical Corticosteroid

GALDERMA CANADA INC. 55 Commerce Valley Drive W., 4th Floor Thornhill, ON L3T 7V9	Date of Initial Authorization: July 26, 2004 Date of Revision: May 12, 2022

Submission Control Number: 259690

RECENT MAJOR LABEL CHANGES

1 Indications	05/2022
1 Indications, 1.1 Pediatrics	05/2022
1 Indications, 1.2 Geriatrics	05/2022
4 Dosage and Administration, 4.1 Dosing Consideration	05/2022
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	05/2022
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 a maximum of four consecutive weeks.

1.1 Pediatrics

Use in patients under 18 years of age is not recommended. CLOBEX SHAMPOO is contraindicated in children under 2 years of age. See **7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics**.

1.2 Geriatrics

Limited data are available in patients aged 65 years and over. Dosing selection should be made with caution in geriatric patients. See **7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics**.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.
- On 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.
- In the treatment of rosacea, acne vulgaris, perioral dermatitis or perianal and genital pruritus.
- 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).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment duration should not exceed 4 consecutive weeks.
- CLOBEX SHAMPOO (clobetasol propionate shampoo, 0.05%) should not be used with occlusive dressings unless directed by a physician.

4.2 Recommended Dose and Dosage Adjustment

CLOBEX SHAMPOO 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.

CLOBEX SHAMPOO is a super-high potent topical corticosteroid formulation. Patients should be instructed to use CLOBEX SHAMPOO for the minimum time period necessary to achieve the desired results. Treatment should be limited to 4 consecutive weeks. If treatment with a local corticosteroid is clinically justified beyond 4 weeks, switching to a less potent corticosteroid preparation should be considered.

The maximum amount of CLOBEX SHAMPOO to be used per week is 50 g (50 mL or 1.75 fl.oz.) because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

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.

Pediatrics: Use in patients between 2 and 18 years of age is not recommended and is contraindicated in children below 2 years of age (see **1.1 Pediatrics**).

4.4 Administration

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.

4.5 Missed Dose

In the event of a missed dose, CLOBEX SHAMPOO should be applied 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.

5 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 **7 WARNINGS AND PRECAUTIONS**).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Topical	Shampoo, 0.05% w/w	Alcohol (10%), citric acid monohydrate, coco-betaine, polyquaternium-10, purified water, sodium citrate dihydrate and sodium laureth sulfate.

CLOBEX SHAMPOO (clobetasol propionate shampoo, 0.05%) is supplied in 120 mL bottles.

7 WARNINGS AND PRECAUTIONS

General

CLOBEX SHAMPOO (clobetasol propionate shampoo, 0.05%) 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.

Clobetasol propionate belongs to the most potent class of topical corticosteroids (Class I) and prolonged use may result in serious undesirable effects (see **8.5 Post-Market Adverse Reactions**). Treatment should not exceed 4 consecutive weeks (see **4 DOSAGE AND ADMINISTRATION**).

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

Endocrine and Metabolism

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 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 **14 CLINICAL TRIALS**). Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see Product Monograph for those products.

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.

Cases of systemic immunosuppression and serious infections have been reported with long-term use of clobetasol propionate beyond the maximum recommended doses (see **8.5 Post-Market Adverse Reactions**). Combining clobetasol propionate with other medicines known to weaken the immune system increases the risk of systemic immunosuppression and serious infections.

Monitoring and 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

Musculoskeletal

Cases of osteonecrosis have been reported with long-term use of clobetasol propionate beyond the maximum recommended doses (see **8.5 Post-Market Adverse Reactions**).

Ophthalmologic

Prolonged corticosteroid use may produce posterior subcapsular cataracts (especially in children), increased intraocular pressure and glaucoma with possible damage to the optic nerves, or rare diseases such as central serous chorioretinopathy (CSCR). It may also enhance secondary ocular infections due to fungi or viruses.

If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist.

Skin
Topical corticosteroids are known to potentially induce telangiectasia. If irritation develops, CLOBEX SHAMPOO 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.

7.1 Special Populations

7.1.1 Pregnant Women
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.

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 (see **16 NON-CLINICAL TOXICOLOGY**).

7.1.2 Breast-feeding
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 breast-feeding women unless clearly indicated.

7.1.3 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 below 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.

7.1.4 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2 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 2: 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.

8.3 Less Common Clinical Trial Adverse Reactions

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.

8.5 Post-Market Adverse Reactions

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

Cases of osteonecrosis, Kaposi's sarcoma lesions, and necrotizing fasciitis have been reported with long-term use of clobetasol propionate beyond the maximum recommended doses (see **4 DOSAGE AND ADMINISTRATION** and **7 WARNINGS AND PRECAUTIONS, Immune**).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Clobetasol propionate is a super-high potency topical corticosteroid. Like other topical corticosteroids, clobetasol propionate 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.

10.2 Pharmacodynamics

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).

10.3 Pharmacokinetics

Absorption
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.

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).

Distribution
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.

Metabolism and Elimination
Topical corticosteroids 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.

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

Special Populations and Conditions

- **Ethnic Origin**
  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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

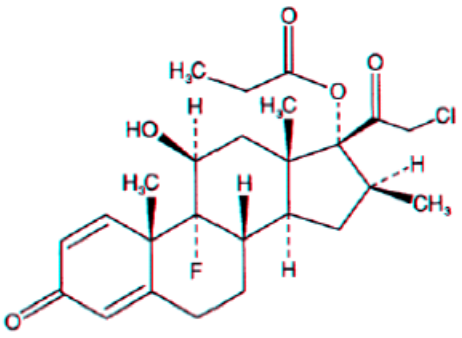
Proper name: clobetasol propionate

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

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

Molecular mass: 466.97 grams/mole

Structural formula:



Physicochemical properties: White to practically white crystalline powder. It is insoluble in water and has a melting point of approximately 196°C

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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-point 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.

14.2 Study Results

The results obtained from both trials demonstrated that CLOBEX SHAMPOO was significantly more effective than its vehicle after 4 weeks of treatment. See Table 3 below.

Table 3: 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 4 and Table 5 below).

Table 4: **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 - 19.6
Post-stimulation Cortisol (µg/dL)	Mean ± SD	29.57 ± 4.659
	Min - Max	24.1 - 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 - 27.7
Post-stimulation Cortisol (µg/dL)	Mean ± SD	39.98 ± 8.191
	Min - Max	10.4 - 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 5: 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%)

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Genotoxicity:
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 metabolic activation. 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 and Developmental Toxicology:
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.

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 subcutaneously 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCLOBEX® SHAMPOO
clobetasol propionate shampoo

Read this carefully before you start using **CLOBEX SHAMPOO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CLOBEX SHAMPOO**.

What is CLOBEX SHAMPOO used for?
CLOBEX SHAMPOO is used in adults with scalp psoriasis to relieve redness, scaling, and itching.

How does CLOBEX SHAMPOO work?
CLOBEX SHAMPOO contains the medicinal ingredient clobetasol propionate. It belongs to a group of medicines called topical corticosteroids or topical steroids. Topical corticosteroids reduce inflammation by decreasing the body's immune response. This can relieve symptoms such as redness and itching. CLOBEX SHAMPOO is not to be used for more than 4 weeks.

What are the ingredients in CLOBEX SHAMPOO?
Medicinal ingredient: clobetasol propionate
Non-medicinal ingredients: alcohol, citric acid monohydrate, coco-betaine, polyquaternium-10, purified water, sodium citrate dihydrate and sodium laureth sulfate

CLOBEX SHAMPOO comes in the following dosage form:
Shampoo, 0.05% w/w

Do not use CLOBEX SHAMPOO:
- if you are allergic to clobetasol propionate, any other corticosteroids or any of the other ingredients in CLOBEX SHAMPOO.
- on skin areas affected by bacterial, fungal, viral or parasitic infection or any untreated infection.
- on skin areas affected by a mycobacterial infection (including tuberculosis of the skin) or syphilitic skin infection.
- if you have chicken pox.
- to treat rosacea or acne.
- to treat inflammation or itching around the mouth, anus or genitals.
- to treat ulcerous wounds.
- in children under 2 years of age.
- on or near the eyes and eyelids (risk of glaucoma or cataracts).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use CLOBEX SHAMPOO. Talk about any health conditions or problems you may have, including if you:

- think you have an infection on your scalp. Tell your healthcare professional before you use CLOBEX SHAMPOO, because you may need other medicines to treat the infection.
- have a weak immune response. Tell your healthcare professional if you suspect an infection has occurred as corticosteroids can make infections more likely and may mask their signs.
- are using or have previously used corticosteroids for treatment of skin disorders, allergic reactions, arthritis or asthma. Tell your healthcare professional if you have had an allergic reaction or experienced side effects to these medicines.
- have eye problems, such as glaucoma or cataracts.
- have adrenal gland problems. CLOBEX SHAMPOO can affect how your adrenal glands work.
- have skin problems caused by poor circulation.
- have recently had or are about to have any vaccination.
- use other oral or topical medication containing corticosteroids or medication intended to suppress your immune system (e.g. for autoimmune disease or after an organ transplant). Combining CLOBEX SHAMPOO with these medicines may result in serious infections.
- are less than 18 years of age. Children are at a greater risk of side effects, including adrenal suppression and may experience a decrease in the speed of their growth.
- are pregnant or trying to become pregnant.
- are breastfeeding or planning to breastfeed.

Other warnings you should know about:

- Do not use CLOBEX SHAMPOO for more than 4 weeks.
- **Adrenal Suppression:**
    - Too much CLOBEX SHAMPOO passing through your skin can shut down your adrenal glands (**adrenal suppression**). 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. Using CLOBEX SHAMPOO for longer than 4 weeks, over large areas of skin, on broken skin or on the face, underarms or groin can also increase your chances of developing adrenal suppression.
    - If your adrenal glands shut down, they may not start working right away after you stop using CLOBEX SHAMPOO which will make it hard for your body to respond properly to stress or illness. It can also cause the symptoms of **Cushing's syndrome**. This is due to too much cortisol (a hormone) in your blood. It has also caused high levels of blood sugar (**hyperglycemia**) and high levels of sugar in the urine. Your healthcare professional may do special blood and urine tests to check your adrenal gland function, hormone levels and sugar levels while you are using CLOBEX SHAMPOO.
    - Covering the treated area can increase the amount of medicine absorbed through your skin. This may increase your chance of developing adrenal suppression. You should not cover the treated skin area with a bandage,

shower/bathing cap or other covering unless your healthcare professional tells you to.

- **Immunosuppression:** CLOBEX SHAMPOO can suppress your immune system. This may:
  - hide symptoms of infections
  - reactivate dormant infections
  - cause infections due to lowered body resistance

  Tell your healthcare professional if you suspect an infection has occurred while you are using CLOBEX SHAMPOO.
- **Surgery:** Before you have any surgery, including at the dentist's office, tell your healthcare professional that you are using CLOBEX SHAMPOO.
- **Vision Problems:** If you experience symptoms such as increased eye pressure, blurred vision, or other visual disturbances, tell your healthcare professional. Corticosteroids, like CLOBEX SHAMPOO, can cause eye problems.
- **Allergic Contact Dermatitis:** You may develop contact dermatitis (allergic skin reaction) while using CLOBEX SHAMPOO. Tell your healthcare professional if your skin condition is not healing or gets worse.

Tell your healthcare professional about all the medicines you take and skin products you use, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known interactions with this medication.

How to use CLOBEX SHAMPOO:

- Use CLOBEX SHAMPOO only as directed by your healthcare professional in order to avoid serious side effects. Do not use more of it, do not use it more often, or for a longer period of time than your healthcare professional has told you.
- If you see another healthcare professional for any reason while you are using CLOBEX SHAMPOO, be sure to tell them you are using it.
- Do not use CLOBEX SHAMPOO for longer than 4 weeks. If your skin condition has not improved in 4 weeks, talk to your healthcare professional.
- Apply CLOBEX SHAMPOO on affected areas of the scalp once per day.
- Do not wet your hair at first. Apply CLOBEX SHAMPOO on your 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 area 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, and any other part of your body that came into contact with CLOBEX SHAMPOO such as your neck and shoulders, carefully.
- Leave CLOBEX 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, stop using CLOBEX SHAMPOO once your plaques have healed.
- CLOBEX SHAMPOO is for external use on your scalp only.
- Do not apply CLOBEX SHAMPOO to your face, groin or armpits.
- Do not cover the treated skin area with a bandage, shower/bathing cap or other covering unless your healthcare professional tells you to.
- Do not get CLOBEX SHAMPOO on or near your lips. If you get CLOBEX SHAMPOO on your lips, rinse your face with cold water right away. If you accidentally swallow CLOBEX SHAMPOO, call your regional poison control centre immediately.
- Do not use CLOBEX SHAMPOO near your eyes or eyelids (risk of glaucoma and cataract). If you get CLOBEX SHAMPOO in your eye, flush it with cold water right away. If your eyes keep stinging after rinsing them well with water, tell your healthcare professional right away.
- Do not give CLOBEX SHAMPOO to anyone else, even if their symptoms are similar to yours. It may harm them. Your healthcare professional has prescribed this medicine for your use only.

Usual dose:
Adults: CLOBEX SHAMPOO should be applied in a thin film to the affected areas of the scalp once per day.
Do not use more than 50 mL (1.75 fluid ounces) per week.

Overdose:

If you think you, or a person you are caring for, have used too much CLOBEX SHAMPOO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
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 healthcare professional.

What are possible side effects from using CLOBEX SHAMPOO?
These are not all the possible side effects you may have when using CLOBEX SHAMPOO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dry skin, skin discomfort
- burning, itching, irritation
- thinning of the skin
- swelling of the skin
- stretch marks
- change in skin pigmentation
- excessive hair growth
- inflammation and infection of the hair follicles (folliculitis)
- skin tightness
- hair loss
- spider veins
- acne

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Adrenal suppression: dizziness, nausea, vomiting, fever, chest pain, can lead to death			✓
Osteoporosis or Osteonecrosis (thin, fragile bones): bone/joint pain, broken bones, back pain that gets worse when standing or walking			✓
Vision problems (glaucoma or cataracts): failing eyesight, blurred vision, eye pain, increased pressure in your eye		✓	
Infections: raised temperature and feeling unwell			✓
Worsening of psoriasis or Pustular psoriasis: red, scaly, thick patches of skin, clearly defined raised bumps filled with a white, thick fluid			✓
Wounds that are slow to heal		✓	
Immunosuppression: get sick or have infections often, purplish spots on skin or in the mouth and/or throat, swollen lymph nodes			✓
Cushing's syndrome: weight gain in the upper body, puffy face, skin problems, hirsutism (excessive hair growth in females, acne, irregular periods), infections			✓
Hyperglycemia (high levels of sugar in the blood): increased thirst/hunger, frequent urination, dizziness, sweating		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get**
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Allergic contact dermatitis: red rash, itching, dry, scaly skin, oozing and crusting, swelling, tenderness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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 room temperature 15°C - 30°C.
Keep out of 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the Galderma Canada Inc. website https://www.galderma.com/canada or by calling 1-800-467-2081.

This leaflet was prepared by Galderma Canada Inc.

Last revised: May 12, 2022