New Zealand Datasheet

1 PRODUCT NAME
CLOBEX® Shampoo

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Clobetasol propionate 0.05% w/w

3 PHARMACEUTICAL FORM
CLOBEX Shampoo contains 0.05% w/w clobetasol propionate. CLOBEX Shampoo is a viscous, translucent, colourless to pale yellow liquid shampoo with an alcoholic odour. One millilitre of CLOBEX Shampoo contains 500 micrograms of clobetasol propionate.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Topical treatment of moderate to severe scalp psoriasis.

4.2 Dosage and method of administration
CLOBEX Shampoo should be applied to the dry (not wet) scalp once daily taking care to cover and massage the lesions well. Using the measuring cup included, measure out 7.5 mL which is sufficient to cover all the scalp and is the maximum daily dosage. CLOBEX Shampoo should be then left in place without covering for 15 minutes before rinsing. As with any topical medication, patients should wash their hands carefully after application. After 15 minutes, the product must be rinsed with water and / or hair can be washed by using an additional amount of regular shampoo if needed to facilitate washing. In order to avoid interaction with hair colour dying product, such as hair colour changes, CLOBEX Shampoo should be thoroughly rinsed. Then, hair can be dried as usual.

Avoid contact with the eyes. If the shampoo accidentally comes in contact with the eyes, rinse out the eyes with water immediately.

The treatment duration should be limited to a maximum of 4 weeks. The total dosage should not exceed 50mL per week. As soon as clinical results are observed, applications should be spaced out or replaced, if needed, by an alternative treatment. If no improvement is seen within four weeks, reassessment of the diagnosis may be necessary.

Chronic over dosage may occur in the case of continuous use of large quantities for long periods of time.

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

4.3 Contraindications
Hypersensitivity to any of the ingredients in the preparation.

Skin areas affected by bacterial and mycobacterial, viral (varicella, herpes simplex, herpes zoster), fungal or parasitic infections and specific skin diseases (skin tuberculosis, skin diseases caused by lues) or to ulcerous wounds.

CLOBEX Shampoo must not be applied to the eye and eyelids (risk of glaucoma, risk of cataract).

Do not use on children under 2 years of age.

4.4 Special warnings and precautions for use

Topical corticosteroids should be used with caution for a number of reasons including post treatment rebound relapses, development of tolerance (tachyphylaxis) and development of local or systemic toxicity such as skin atrophy, infection (including isolated cases of systemic infections), telangiectasia of the skin or hypothalamic-pituitary-adrenal (HPA) axis suppression. There is a risk of HPA suppression with prolonged use and also with the use of large volumes. CLOBEX Shampoo should not be used for more than 4 consecutive weeks; nor should a dose greater than 7.5 mLs daily be used. In rare instances, treatment of psoriasis with corticosteroids (or its withdrawal) is thought to have provoked generalised pustular psoriasis in case of intensive and prolonged topical use. In very rare cases, hypersensitivity to corticosteroids can be observed. Clobetasol propionate is not recommended in patients who are hypersensitive to other corticosteroids.

In general, treatment of large surface areas, long-term continuous therapy with corticosteroids, use of occlusive dressings can enhance absorption and lead to a higher risk of systemic effects. In such cases, medical supervision should be increased and patients may be evaluated periodically for evidence of HPA axis suppression. Patients applying doses of CLOBEX Shampoo in excess of 50mL per week should be carefully monitored. Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Such systemic effects disappear when treatment is stopped. However, abrupt discontinuation can lead to acute adrenal insufficiency, especially in children.

CLOBEX Shampoo is only intended for the treatment of scalp psoriasis and should not be used to treat other skin areas. In particular, CLOBEX Shampoo must not be applied on the face, 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.

CLOBEX shampoo is not recommended in patients with acne vulgaris, rosacea or perioral dermatitis.

If CLOBEX Shampoo enters the eye; it should be rinsed thoroughly with copious amounts of water.

Patients should be instructed to use Clobetasol propionate for the minimum amount of time necessary to achieve the desired results.

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

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use in the Elderly
No specific studies have been performed.

Use in renal or hepatic impairment
No specific studies have been performed. Patients with severe liver dysfunction and severe diabetes mellitus should be treated with special caution and closely monitored for side effects.

Use in Children
The experience in the paediatric population is limited. CLOBEX shampoo is not recommended for use in children and adolescents below 18 years of age and is contraindicated in children below 2 years of age. Growth retardation may be observed in case of systemic absorption of topical corticosteroids. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are also at greater risk of adrenal insufficiency after withdrawal of treatment, and of Cushing's syndrome while on treatment.

4.5 Interaction with other medicines and other forms of interaction
No interaction studies have been performed.

4.6 Fertility, Pregnancy and lactation
Fertility
When administered subcutaneously to rats, clobetasol propionate reduced the viability of embryos and reduced maternal reproduction capacities.

Animal studies of the effect of CLOBEX Shampoo on fertility have not been conducted. However, clobetasol propionate had no effect on male or female mating performance in rats when administered subcutaneously (SC) at doses up to 50 µg/kg/day. Reductions in both the number of estrous cycles and embryo viability were observed at SC doses from 25-50 µg/kg/day.

Pregnancy
(Category B3)
Animal studies of the effect of CLOBEX Shampoo on embryofoetal development have

not been conducted. However, clobetasol propionate was shown to be teratogenic when administered topically or subcutaneously during organogenesis in mice, rats and rabbits. Foetotoxicity and foetal malformations (including skeletal abnormalities, cleft palate, cranioschisis or umbilical cord hernia) were observed in mice (30 µg/kg/day SC), rats (50 µg/kg/day topical) and rabbits (3 µg/kg/day SC) at doses (on a mg/m2 basis) less than the maximum human topical dose.

There are no adequate or well-controlled studies of clobetasol propionate in pregnant women. Studies in animals have shown reproductive toxicity. The clinical relevance of the effects of clobetasol and other corticosteroids in developmental animal studies is unknown. CLOBEX Shampoo should be avoided during pregnancy, unless clearly necessary.

Breast feeding
Systemically administered corticosteroids pass into breast milk. There are no adequate data on the possible milk transfer of topical clobetasol propionate. However, studies in rats (see below) have shown postnatal pup effects following subcutaneous maternal dosing during weaning. Thus, CLOBEX Shampoo should be avoided in breastfeeding women, unless clearly necessary.

4.7 Effects on ability to drive and use machines
As a topical corticosteroid, CLOBEX Shampoo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
During clinical development, in a total of 558 patients receiving CLOBEX Shampoo, the most commonly reported adverse drug reaction was skin burning sensation with an incidence of 2.8%. Most adverse events were rated as mild to moderate and they were not affected by race or gender. Clinical signs of skin irritation were uncommon (0.2%). No serious drug-related adverse events were reported during any of the clinical trials.

If signs of local intolerance appear, application should be suspended until they disappear. If signs of hypersensitivity appear, application should be stopped immediately. This can be suspected in case of resistance to treatment.

Table 1 below reports the adverse reactions related to treatment by body system and by absolute frequency according to the following classification:
Very common ≥ 10%, Common ≥ 1% to < 10%, Uncommon ≥0.1% to <1%

Table 1:

Body System	**Incidence**	**Adverse reactions**
Skin and subcutaneous tissue disorders	Common	Skin burning sensation
		Folliculitis
	Uncommon	Pain of skin
		Skin discomfort
		Local signs of irritation
		Pruritus
		Acne
		Skin oedema

		Telangiectasia Psoriasis (aggravation) Alopecia Dry skin Urticaria Skin atrophy Skin irritation Skin tightness
Eye disorders	Uncommon	Eye stinging/burning Eye irritation Ocular discomfort
Nervous System disorders	Uncommon	Headache

As a class attribution, prolonged use of topical corticosteroids, treatment of extensive areas or use of large amounts can result in sufficient systemic absorption to produce the features of hypercortisolism (Cushing syndrome) or of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression. Should HPA axis suppression occur, it is likely to be transient with a rapid return to normal values. However, as CLOBEX Shampoo is to be kept in place for only 15 minutes before rinsing, systemic absorption is seldom observed, see Pharmacokinetics, and therefore, the risk of appearance of HPA axis suppression is very low compared to non rinsed potent corticosteroids products. No HPA axis suppression has been observed during clinical trials with CLOBEX Shampoo.

Prolonged and/or intensive treatment with potent corticosteroid preparations may cause immunosuppression and opportunistic infections and local atrophic changes, such as local skin atrophy, striae, telangiectasia, erythema, purpura, generalised pustular psoriasis and contact dermatitis.

Growth retardation may be observed in children in case of systemic absorption of topical corticosteroids.

When applied to the face, very potent corticosteroids can induce perioral dermatitis, skin atrophy or worsen rosacea. During development of CLOBEX Shampoo, skin atrophy was assessed using ultrasound measurement of skin thickness in a specific clinical trial involving 13 patients. After 4 weeks of treatment with CLOBEX Shampoo, no skin thinning was observed.

There are reports of pigmentation changes, acne, pustular eruptions and hypertrichosis with topical corticosteroids.

Cataract has been reported when corticosteroids where applied to the eyes or eyelids.

Rebound effects may occur upon discontinuation of treatment.

Post-marketing safety experience

Manifestations of Cushing's syndrome have been described in post market reports following long term duration of use of clobetasol propionate. In addition, a report of adrenal suppression has been reported following long-term use in an off label indication (lichen planus).

Glaucoma, hypersensitivity, erythema, rash and allergic contact dermatitis have been

described in post-market reports.

Eye disorders: vision blurred.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose
Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the symptoms of severe adrenal suppression and hypercorticism may appear and in this situation topical steroids should be discontinued gradually. However, because of the risk of acute adrenal suppression this should be done under medical supervision. For information on the management of overdose, contact the Poison Information Centre on 0800 764766.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Corticosteroids, Very Potent (Group IV), ATC code: D07AD01

Like other topical corticosteroids, CLOBEX 0.5 mg/g Shampoo has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of topical corticosteroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A2 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 byphospholipase A2.

Clinical Trials
Five, randomised, controlled Phase III clinical trials were conducted to establish the efficacy and safety of CLOBEX Shampoo. In all studies, treatment with CLOBEX Shampoo was for 4 weeks with a daily application for 15 minutes before rinsing. Two studies were vehicle-controlled and three were comparative against an active control [scalp solution of calcipotriol 50µg/ml (Daivonex); coal tar solution at 1 % w/w (Polytar Liquid); clobetasol propionate 0.05% gel].

The two vehicle-controlled clinical trials involved 290 patients with moderate to severe scalp psoriasis treated with either CLOBEX Shampoo or the corresponding vehicle applied once daily for 15 minutes before lathering rinsing for a period of 4 weeks. Efficacy results are presented in the table below.

Table 2: Efficacy outcomes in vehicle-controlled clinical trials

CLOBEX Shampoo n (%)		CLOBEX Shampoo Vehicle n (%)	
Study A	Study B	Study A	Study B

Total number of Patients	95	99	47	49
Success Rate[1] at endpoint[2]	40 (42.1%)	28 (28.3%)	1 (2.1%)	5 (10.2%)
Subjects with Scalp Psoriasis Parameter Clear (None) at Endpoint				
Erythema[3]	17 (17.9%)	12 (12.1%)	3 (6.4%)	1 (2.0%)
Scaling[3]	21 (22.1%)	15 (15.2%)	0 (0%)	2 (4.1%)
Plaque Thickening[3]	35 (36.8%)	34 (34.3%)	5 (10.6%)	5 (10.2%)

[1] Success rate defined as the proportion of patients with a 0 (clear) or 1 (minimal) on a 0 to 5 point physician's Global Severity Scale for Scalp psoriasis.

[2] At four (4) weeks or last observation recorded for a subject during the treatment period (baseline if no post-baseline data were available).

[3] Patients with 0 (clear) on a 0 to 3 point Scalp psoriasis parameter scale.

In all three studies in which comparison was made, CLOBEX Shampoo has shown a superior efficacy compared to the vehicle.

The efficacy of CLOBEX Shampoo applied for 15 minutes, once a day was compared over 4 weeks to that of calcipotriol solution 50µg/ml applied twice a day (Daivonex) and to that of a coal tar solution at 1% w/w (Polytar Liquid) applied twice a week. Both trials enrolled subjects with moderate to severe scalp psoriasis. After 4 weeks of treatment (Day 28) CLOBEX Shampoo was shown to be superior to Daivonex solution (table 3) and Polytar Liquid (table 4) on the two co-primary endpoints: Total Sum Score (TSS) and Global Severity Scale (GSS).

Table 3. Efficacy outcomes in trial versus Calcipotriol solution

	CLOBEX Shampoo	Calcipotriol solution 50µg/ml	p
Total number of Patients (ITT)	76	75	
TSS Baseline Mean (SD)	4.86 (1.95)	4.95 (1.49)	
TSS Day 28 Mean (SD)	1.76 (1.57)	2.36 (1.64)	$p < 0.05$
GSS Baseline Mean (SD)	3.49 (0.60)	3.51 (0.60)	
GSS Day 28 Mean (SD)	1.55 (1.20)	2.03 (1.31)	$p < 0.05$

Table 4. Efficacy outcomes in trial versus Polytar Liquid

	CLOBEX Shampoo	Polytar Liquid	p
Total number of Patients (ITT)	121	41	

TSS Baseline Mean (SD)	6.1 (1.4)	6.3 (1.2)	
TSS Day 28 Mean (SD)	3.2 (2.0)	5.2 (1.9)	p =0.0001
GSS Baseline Mean (SD)	3.4 (0.6)	3.5 (0.6)	
GSS Day 28 Mean (SD)	1.9 (1.0)	3.0 (1.0)	p =0.0001

CLOBEX Shampoo (applied daily for 15 minutes and then rinsed) has finally been found non inferior to a clobetasol propionate 0.05% gel applied once a day to the dry scalp without rinsing.

Efficacy and safety of Clobex Shampoo were not investigated beyond 4 weeks of treatment.

5.2 Pharmacokinetic properties

In vitro liberation –penetration studies on human skin showed that only a small percentage (0.1 %) of the applied dose of CLOBEX Shampoo can be found in the epidermis (including the stratum corneum) when applied for 15 minutes and then rinsed. The very low topical absorption of clobetasol propionate from CLOBEX Shampoo when applied according to the recommended clinical use (15 minutes before rinse off) resulted in negligible systemic exposure in animal studies and in clinical trials. Available clinical data revealed that only 1 of 126 subjects had a quantifiable clobetasol propionate plasma concentration (0.43 ng/mL).

The present pharmacokinetic data indicate that systemic effects following clinical treatment with CLOBEX Shampoo are highly unlikely due to the low systemic bioavailability of clobetasol propionate.

5.3 Preclinical safety data

Genotoxicity

Clobetasol propionate did not demonstrate any genotoxic potential in vitro (Ames, fluctuation and gene conversion tests and chromosome aberration assay) or in vivo (mouse micronucleus test).

Carcinogenicity

Long term rodent carcinogenicity studies have not been conducted with CLOBEX Shampoo. However, a clobetasol propionate lotion formulation had no carcinogenic potential when applied topically to rats for 2 years at doses (on a mg/m2 basis) corresponding to less than one thirtieth of the maximum human topical dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate, Coco-betaine, Ethanol, Polyquaternium-10, Purified water, Sodium citrate dehydrate, Sodium laureth sulphate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 25ºC, in the original container. Shelf-life after first opening is 4 weeks.

6.5 Nature and contents of container
The product is packaged in HDPE bottles fitted with polypropylene closure, containing 30 mL, 60 mL and 125 mL of shampoo.

6.6 Special precautions for disposal
Not applicable.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
Sponsor and distributor in New Zealand
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Ph (09) 918 5100
Fax (09) 918 5101

For:
Galderma Australia Pty Ltd
Suite 4, 13B Narabang Way,
Belrose NSW 2085
Australia

9 DATE OF FIRST APPROVAL
6 September 2007

10 DATE OF REVISION OF THE TEXT
12 July 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Inclusion of warning regarding prolonged use
4.4	Warning regarding the consequences of prolonged use included
4.8	Ocular tight sensation changed to ocular discomfort