Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Clobetasol propionate

Proprietary Product Name: Clobex

Sponsor: Galderma Australia Pty Ltd

May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	6 February 2013
Active ingredient:	Clobetasol propionate
Product Name:	Clobex
Sponsor's Name and Address:	Galderma Australia Pty Ltd 13B Narabang Way Belrose NSW 2085
Dose form:	Shampoo
Strength:	500 µg/g
Container(s):	Bottle
Pack size:	4, 8 or 16 doses of 7.5 mL (30, 60 and 125 mL bottles)
Approved Therapeutic use:	*Topical treatment of moderate to severe scalp psoriasis in adults.*
Route of administration:	Topical
Dosage:	3.75 mg (7.5 mL) once daily
ARTG Number:	188346

Product background

This AusPAR describes the application by Galderma Australia Pty Ltd to register a new chemical entity, clobetasol proprionate (0.05%; 500 µg/g; Clobex), originally as both a spray or shampoo formulation for the topical treatment of moderate to severe plaque-type or scalp psoriasis, respectively. The application to register Clobex topical spray solution was withdrawn by the sponsor on the 23 of October 2012. Thus, this document will not refer to the spray submission.

Clobetasol propionate (CP) bears structural similarity to other betamethasone-type corticosteroids including betamethasone, dexamethasone and fluocortolone. Clobetasol propionate (CP) was previously registered on the Australian Register for Therapeutic Goods (ARTG) as Dermovate. This range has been delisted from the ARTG so, as advised by the TGA, in this proposed application,clobetasol-17-propionate will be classified as a new chemical entity (NCE). It has been marketed overseas (USA and Europe) for over 20-30 years and has been widely available for topical administration at a concentration of 0.05% in several dosage forms (including ointment, cream, solution and gel) for use in inflammatory diseases.

The sponsor requested the following indications:

Topical treatment of moderate to severe scalp psoriasis in adults.

with the following dosing regimen: (Abridged)

> *"Clobex Shampoo: Should be applied directly on dry scalp once daily taking care to well cover and massage the lesions. An amount equivalent to approximately one and a half teaspoons (approximately 7.5 mL) per application is sufficient to cover all the scalp. Clobex shampoo should be then kept in place without covering for 15minutes before rinsing....*
>
> *Treatment duration should be limited to a maximum of 4 weeks. As soon as clinical results are observed, applications should be spaced out or replaced, if needed, by an alternative treatment. .*
>
> *Repeated courses of Clobex Shampoo may be used to control exacerbations provided the patient is Under regular supervision".*

Regulatory status

The following table summarises the international regulatory status for this product.

Table 1. Summary of the international regulatory status of Clobex shampoo

Country*	Local Product Name	Registration Date	Indication
Canada	Clobex Shampoo	29 July 2004	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.
New Zealand	Clobex Shampoo	6 September 2007	Topical treatment of moderate to severe scalp psoriasis.
Sweden	Clobex 500 mikrogram/ g schampo	16 February 2007	Topical treatment of moderate to severe scalp psoriasis.
Switzerland	Clobex Shampoo	13 September 2007	Psoriasis and recalcitrant eczemas of the scalp in adults from 18 years of age. Maintenance treatment for prevention of recurrence.
United Kingdom	Etrivex 500 micrograms /g shampoo	26 February 2007	Topical treatment of moderate to severe scalp psoriasis.
USA	Clobex (clobetasolp ropionate) Shampoo, 0.05%	5 February 2004	Clobex Shampoo is a super-high potent topical corticosteroid formulation indicated for the treatment of moderate to severe forms of scalp psoriasis in patients 18 years of age and older.

*The registration of this product in Europe covers 19 countries.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

List of abbreviations

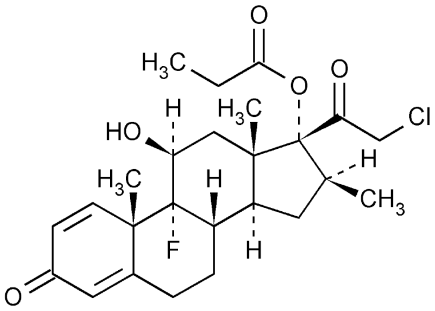
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BP	blood pressure
BSA	body surface area
CC	Cyclocort Cream
CPS	clobetasol propionate spray
CPSH	clobetasol propionate shampoo
DAE	discontinuation due to AE
DLQI	Dermatology Life Quality Index
HPA	hypothalamic pituitary axis
IGA	Investigator Global Severity Assessment
IOP	intraocular pressure
ITT	intention to treat
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MED	Minimal erythema dose
min	minute
NSAID	non-steroidal anti-inflammatory drug
ODS	overall disease severity
POQL-12	Koo Menter Psoriasis Index 12-Item Psoriasis Quality of Life Questionnaire
PUVA	psoralen plus ultraviolet light
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ classification
TDSS	total disease severity score
TEEC	Temovate E® emollient cream
TPS	target plaque severity
95% CI	95% confidence interval

II. Quality findings

Drug substance (active ingredient)

Clobetasol propionate is 21-chloro-9-fluoro-*11β*-hydroxy-*16β*-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate and its chemical structure is shown in Figure 1.

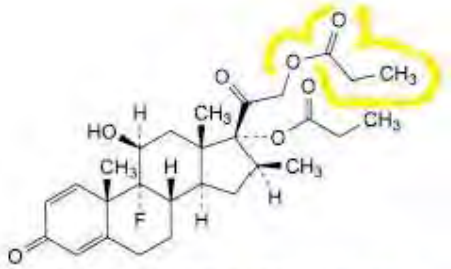
Figure 1. Chemical structure



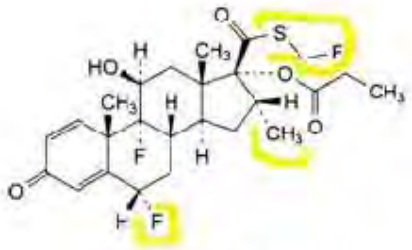
clobetasol propionate

Clobetasol propionate has multiple chiral centres but is used as a single enantiomer. It is structurally related to other steroids (Figure 2).

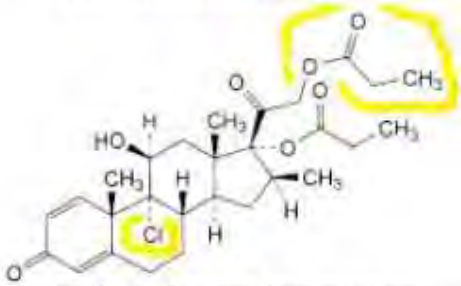
Figure 2. Chemical structure of related steroids



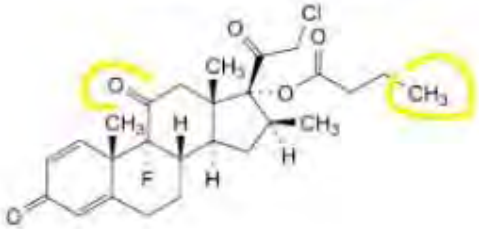
betamethasone dipropionate



fluticasone propionate



beclomethasone dipropionate



clobetasone butyrate

Clobetasol propionate drug substance is the subject of European Pharmacopoeia and United States Pharmacopeia (USP) monographs. Clobetasol propionate is practically insoluble in water; in Clobex it is dissolved in ethanol and other excipients.

Drug product

Clobetasol propionate is not in any product currently registered in Australia. Galderma states that clobetasol propionate was historically registered by Glaxo as Dermovate, but the evaluator was unable to locate any records (it may have been supplied under State

based registration). The reason for removal from the market, if any, is unknown. Thus, registration of Clobex is treated as registration of a new chemical entity.

Related clobetasol propionate products have been supplied overseas and there are British Pharmacopoeia and US Pharmacopeia (USP) monographs for Clobetasol Propionate Cream and Clobetasol Propionate Ointment and a USP monograph for Clobetasol Propionate Topical Solution.

Clobex Shampoo

Clobex Shampoo is a viscous liquid with an alcoholic odour. The shampoo contains 500 µg clobetasol propionate per mL. It is presented in a plastic bottle (4, 8 or 16 doses = 30 mL, 60 mL or 125 mL). The 60 and 120 mL bottles are packed in cartons. It is unclear how usage directions (in the CMI) will be supplied with the 30 mL pack.

The shampoo is used by applying directly to dry scalp once daily "an amount equivalent to approximately one and a half teaspoons (approximately 7.5 mL)", leaving for 15 minutes, then rinsing. The daily dose is thus 3.75 mg clobetasol propionate (in 7.5 mL). There is no dose delivery device, so dosing is likely to be erratic in use.

The shampoo is labelled in terms of the amount per gram, with a percentage also quoted (for the shampoo, density 1.0, so weight/weight (w/w) ≡ weight/volume (w/v)) and with the pack size given as a volume. Neither the labels nor the PI give the *number* of doses in the different packs. The open shelf life proposed is 4 weeks.

Clobex Shampoo has an aqueous-alcoholic formulation in which the drug is dissolved.

The formulation "*was selected due to the pro-penetrating properties of ethanol (96%) in order to enhance the penetration of [clobetasol propionate], and to reduce the application time with currently available therapies*." Two formulations were used during the clinical development. Formulation 662.064 with preservative was used in three Phase II exploratory efficacy and safety studies (Studies 2577, 2578 and 2591). The proposed commercial formulation (662.066), without preservative, was used in the eight main clinical studies.

Although without direct preservatives, the ethanolic formulation shows acceptable preservative efficacy.

Some details of the manufacture and testing of the shampoo have been queried with Galderma. The sponsor was at the time of this report undertaking some more laboratory studies which would be available in December 2012. It was considered appropriate to supply the shampoo until these aspects are finalised. To allow consideration by the Advisory Committee for Prescription Medicines (ACPM), the product will only be approved with an impractically short shelf life. This will need to be extended by a variation application after registration to resolve this issue.

Biopharmaceutics

Clobex Shampoo appears to act locally. The formulation includes penetration enhancers. Determination of systemic bioavailability of topical steroids is expected as part of the evaluation of safety (in combination with cortisol suppression studies etc).

The nominal topical exposure following 7.5 mL of Shampoo use is 3.75 mg clobetasol propionate per day.

The proposed Clobex Product Information claims *in vitro* studies show "a potentially low systemic exposure after topical application". The PI includes comments on postmarketing experience showing manifestations of Cushing's syndrome following long term use and a

report of adrenal suppression after long-term use in lichen planus (off label[1]). These are consistent with significant absorption under some circumstances. These aspects are addressed in the clinical evaluation.

Systemic bioavailability of clobetasol propionate after Clobex Shampoo dosing was investigated in four studies in patients suffering from scalp psoriasis, undertaken some years ago:

Study 2620	used proposed formulation
Study 18070	used proposed formulation
Study 18075	used proposed formulation
Study 2577	used a formulation with a preservative

Overall 141 subjects were studied, each with only one plasma sample collected at the end of four weeks dosing. The timing of this sample collection relative to the last dosing was not well controlled. Of these samples, only one had a quantifiable plasma level (0.43 ng/mL) and two others had levels between the detection limit (0.1 ng/mL) and the quantification limit (0.2 ng/mL).

However, the method used for plasma analysis was not very sensitive and it is now possible to measure plasma levels in the picogram range.

Galderma argues that pharmacodynamic measurements are more sensitive. These aspects are addressed in the clinical evaluation.

Advisory committee considerations

Consideration by the Pharmaceutical Subcommittee (PSC) of ACPM

The PSC considered the application at its 144th (2012/2) meeting and recommended (Recommendation 2261):

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects. In particular, the Committee supported the issues raised in relation to the analysis, quality assurance and stability of the drug products.
2. The Committee advised that all outstanding issues should be addressed to the satisfaction of the TGA.
3. The PSC agreed that:
   - Shampoo doses were likely to be very variable, in part because of the difficulty in measuring the dose. The Committee advised that this problem could be reduced by the provision of a measuring cup with this presentation.
   - The Consumer Medicine Information (CMI) should be supplied directly with all presentations.
4. The PSC was concerned about the lack of comparative information on systemic exposure between the two presentations.
5. The PSC advised that:
   - The Sponsor should be asked to provide batch analysis data on three consecutive validation batches of the drug substance manufactured at both manufacturing sites.

[1] Sponsor comment: "Off label use of leave-on products."

- Ensure that drug substances from both nominated manufacturing sites are included in future validation and stability trial protocols.

6. The Product Information (PI) and Consumer Medicine Information (CMI). The PI and CMI for both products should be amended to bring clarity to the composition and directions of use of the products.
7. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

It has not been possible to fully resolve all of the pharmaceutical issues; note previous comments regarding shelf life.

The recommendation relating to the Spray is now not relevant.

Quality summary and conclusions

There are some outstanding chemistry and quality control aspects. To allow consideration now by the ACPM, the product should only be approved with an impractically short shelf life. This will need to be extended by a variation application after registration which resolves these issues.

The investigation of systemic exposure following Shampoo doses did not use analytical methods available today which would better quantify blood levels.

III. Nonclinical findings

Introduction

The toxicity profile of CP has been extensively described in published literature of acute, subacute and chronic studies by several routes of administration (including oral, subcutaneous and topical).

Scope and quality of the dossier

The TGA adopted EU "G*uideline on the non-clinical documentation for mixed marketing authorisation applications*"[2] notes that "*a combination of limited nonclinical studies and of literature references from published pharmaco-toxicological information including scientifically accepted monographs and clinical trials, as well as results of postmarketing experience gained by widespread clinical use in man*" constitute a reasonable body of knowledge for products with a long history of clinical use. Accordingly, the sponsor has submitted literature references along with the following nonclinical studies to support the registration of CP shampoo and spray:

- *In vitro* human skin absorption data and *in vivo* absorption data in rats with various CP formulations but not the CP spray or shampoo.
- Repeated dermal safety of CP shampoo in minipigs (≤3months).
- Genotoxicity evaluation of CP *in vitro* in a chromosome aberration assay in Chiniese Hamster Ovary (CHO) cells and *in vivo* in a micronucleus assay in mice.

[2] CPMP/SWP/799/95, April 2006. <http://www.tga.gov.au/pdf/euguide/swp079995en.pdf>

- Carcinogenicity in rats and photocarcinogenicity (40 weeks) in mice evaluated following dermally applied CP lotion.
- Fertility, embryofetal and pre and post-natal development study evaluation in rats with dermally or subcutaneously (SC) administered CP.
- Local tolerance evaluation in rabbits receiving CP shampoo.
- Antigenicity evaluation in guinea pigs receiving CP shampoo.

The dossier also contained additional studies and supporting literature concerning the toxicity of a primary excipient in the spray but these will not be discussed in this AusPAR.

Overall, the pivotal studies performed by the sponsor were Good Laboratory practice (GLP) compliant and generally used adequate animal numbers, treatment regimens and upper dose levels. In contrast, several of the literature references included in the submission provided only summary information and in some cases contained figures and diagrams which were difficult to read, thus precluding a thorough primary evaluation of the submitted information.

Pharmacology

Primary pharmacology

Psoriasis is a skin disorder characterised by epidermal hyperplasia, altered epidermal maturation and local accumulation of inflammatory cells. Activated T -lymphocytes and increased levels of lymphokines and other growth factors in active plaques suggest an immune mechanism involved in its pathogenesis.[3,4] Corticosteroids have anti-inflammatory and anti-proliferative properties and as such are widely used in the treatment of psoriasis. They are divided into two categories based on their specific activities; glucocorticoids (that is, prednisone, dexamethasone, clobetasol propionate) which are associated with glucose metabolism and/or anti-inflammatory effects and mineralocorticoids (that is, fludrocortisone) which are associated with sodium retention.

No primary pharmacology studies were conducted with the proposed CP 0.05% w/w shampoo formulation. However, literature references examining anti-inflammatory and anti-proliferative effects of CP *in vitro* and *in vivo* were provided as part of the hybrid submission.

Anti-inflammatory effects

CP demonstrated dose-dependent (10^{-11} to 10^{-8} M) suppression of T cell cytokine secretion (interleukin (IL)-12, and to a lesser extent, IL-6 and tumour necrosis factor (TNF)-α) and inhibition of T cell-mediated inflammation in isolated dendritic cells *in vitro*.

The anti-inflammatory effects of CP were also demonstrated in dermal non-immune and immune inflammation models *in vivo*. CP reduced croton-oil-induced rat ear oedema (50% effective dose (ED_{50})= 0.7 µg/ear), ultraviolet (UV)-induced guinea pig skin dermatitis (ED_{50} = 17.2 µg/flank), and delayed-type hypersensitivity inflammatory reactions induced by oxazolone (1.6 µg/mouse, 4.0 µg/rat) and picryl chloride (Dermovate; 0.05% CP) in mice. CP was generally more potent than hydrocortisone (HC) in these models but less potent than halobetasol propionate (HP).

[3]Barker JNWN. The pathophysiology of psoriasis. The Lancet 338: 227-230, 1991
[4]Gottlieb AB. Immunologic mechanisms in psoriasis. Acad. Dermatol. 18: 1376-1380, 1988

CP (0.3%) was shown to inhibit the recruitment of T-lymphocytes and to prevent T-cell mediated skin inflammation via suppression of chemokine CC27 expression in a mouse model of dermatitis.

Anti-proliferative effects

At high concentrations (10-25 µg/mL), CP reduced the cell proliferation of human fibroblasts, reduced the secretion of acid mucopolysaccharide and reduced collagen synthesis *in vitro*. Topical 0.05% CP application was also shown to stimulate superoxide dismutase activity in the dermis of human skin biopsies *in vitro*. In the epidermis of hairless mice, CP dose-dependently (0.0001-0.1%) inhibited local DNA synthesis after topical application. Topical CP (0.05%) caused epidermal thinning in both parakeratotic mouse tail skin and mouse ear skin models. Similar results were also obtained in the rat cotton-pellet granuloma assay (ED_{30} of 5 µg CP/pellet) and guinea-pig epidermal hyperplasia assay (1% w/w CP). Like the anti-inflammatory studies, CP had inferior anti-proliferative potency to HP but often superior potency to HC and other corticosteroids in many of these studies.

Overall, sufficient information was provided to demonstrate that CP has potent anti-inflammatory and anti-proliferative effects that support its use for the inflammatory, parakeratotic nature of psoriasis.

Secondary pharmacodynamics and safety pharmacology

No secondary or safety pharmacology studies were conducted with the proposed CP 0.05% w/w shampoo formulation. Nevertheless, limited secondary pharmacology studies (summarised in two literature references) with CP demonstrated the expected glucocorticoid effects including liver glycogen deposition, thymus involution, androgenic and anti-estrogenic activities in rodents. CP was generally more potent than betamethasone valerate (BV) and/or hydrocortisone (HC) in these studies. Daily SC doses ranging from approximately 0.2-20 mg/kg (0.6/0.75-75 mg/m^2/day based on body surface area (BSA)) were used, which encompassed and exceeded the anticipated clinical exposure to CP, based on BSA (approximately 2.5 mg/m^2/day for CP shampoo administered as a single daily topical dose to a 50 kg person).

Limited safety pharmacology studies (summarised in two literature references) covering a standard range of physiological systems demonstrated no remarkable effects of CP on smooth muscle *in vitro* or cardiovascular systems *in vivo* at high CP concentrations/doses (100 mg/mL *in vitro;* 7 mg/kg intravenous (IV) in rabbits *in vivo*). Effects on the central nervous system such as decreased alertness, reactivity, analgesia and sleep time prolongation (≥100 mg/kg intraperitoneal (IP) injection in mice; ≥10 mg/kg IV in rabbits) and diuretic effects (≥0.7-50 mg/kg SC in rodents) were observed at high CP doses. No effects were observed in safety pharmacology studies *in vivo* at less than 20 mg/kg CP administered via intraperitoneal (IP), IV and SC routes. Overall, the effects observed in the safety pharmacology studies are not expected clinically as the No Observable Effect Level (NOEL) has one to two orders of magnitude exposure margin (based on BSA) over the clinically anticipated CP exposure following topical CP shampoo administration, even in the absence of dosing route consideration.

Pharmacokinetics

All pharmacokinetic data provided came from studies following dermal or SC administration of unlabelled or radiolabelled drug in various formulations.

Pharmacokinetic studies performed with the CP 0.05% w/w shampoo formulation were limited to a skin penetration *in vitro* study and a single dose absorption study *in vivo*. Repeat dose toxicity studies using CP shampoo formulation included toxicokinetic

measurements, however plasma concentrations were often below the limit of quantification for many samples in all species and studies evaluated. Therefore, most of the PK studies were of limited value except to demonstrate minimal systemic exposure.

Studies conducted or commissioned by the applicant were limited to:

- Three Good Laboratory Practice (GLP) compliant *in vitro* human skin penetration studies comparing sponsor CP (lipocream, lotion and/or shampoo (Clobex); 0.05% CP w/w) formulations with commercial Temovate (cream, emollient cream or scalp (0.05% CP w/w)) formulations.
- A GLP compliant *in vivo* rat study comparing the skin absorption of the proposed CP Shampoo (Clobex; 0.05% CP w/w) with a commercial scalp formulation (Dermovate Scalp; 0.05% w/w).

Limited PK information was also provided by a small number of literature references and published reports provided in summary form.

After application to human skin *in vitro* for 16 hours, all CP formulations were primarily recovered in the epidermis, followed by a small amount in the dermis and almost no detectable levels in the liquid receptor. While the CP shampoo had higher absorption levels (19% of the applied dose) than other formulations after the 16 hour exposure period, it is noted that after 15 minutes exposure (proposed application period), the total applied dose recovered in the skin was 0.1% (epidermis only). These results were consistent with other literature data showing limited penetration of CP into the epidermis *in vitro* after 72 hour exposure. Thus, only very limited systemic exposure to CP is expected following topical application as proposed clinically.

Plasma CP concentrations were quantifiable following a single (10 hour) topical application of Dermovate scalp formulation to rats. In contrast, after application of CP shampoo for 15 or 30 minutes most of the samples had CP concentrations below the Lower limit of quantification (LoQ). Nonetheless, plasma levels following application of either substance showed a rapid absorption (time to peak plasma concentration (T_{max})= 0.5-1 hour) profile, with peak plasma concentrations (C_{max}) values of 0.9 and 0.4 ng/mL for CP shampoo after 15 and 30 minutes exposure, respectively and 2.8 ng/mL for Dermovate scalp lotion. After 48 hours, plasma levels were low for both formulations. The area under the plasma concentration time curve between 0 h and 48 h ($AUC_{0\text{-}48h}$) determined for Dermovate scalp formulation (45 ng.h/mL) was around 3 times higher than the maximised $AUC_{0\text{-}48h}$ value (14-15 ng.h/mL) for CP shampoo. Thus, systemic CP absorption in rats after topical application of CP shampoo was lower than that obtained for a commercial CP scalp lotion.

Additional studies in rats demonstrated that occlusion of the treatment site significantly increased CP absorption irrespective of the vehicle or formulation used. Moreover, the CP plasma profile following SC administration displayed a more rapid absorption (T_{max} = 4 hours) and elimination ($t_{1/2}$ = 9 hours) compared to the dermal route (T_{max} = 8 hours; levels remained high at 96 hours).

No protein binding studies were submitted. However, given the low systemic exposure achieved in all toxicology studies, any concentration or species related differences in free CP are likely to be negligible. A single tissue distribution study in rats given radiolabelled CP by the SC route demonstrated high radioactivity levels in the liver, gastrointestinal (GI) tract, kidneys, adrenals, pituitary, thyroid, prostate and fat, which decreased over time in a manner similar to levels in plasma.

The metabolism of CP was not characterised in any nonclinical species; however, the metabolic profile is anticipated to follow that of other systemically administered corticosteroids. Consistent with the expected metabolic profile, CP was primarily excreted in the faeces (4-5 times the urine excretion levels) following SC and dermal administration

to rats. While dermal application of 0.05% CP was found to induce the drug metabolising enzyme CYP1A-mediated ethoxycoumarin-0-dealkylase activity in the skin 5 fold, no pharmacokinetic drug interaction studies were conducted.

Overall, these limited studies suggested minimal systemic exposure to CP following dermal application of CP spray or shampoo when applied as proposed. However, it should be noted that these studies were conducted in normal (intact) rather than psoriatic skin. Skin penetration rates are dependent on many factors including the surface area, to which the product is applied, the anatomical site exposed, the integrity of the skin; whether the vehicle of the formulation is oil or water based and whether the steroid is applied under occlusion. Therefore, it is likely that penetration and absorption rates are underestimated in these studies.

Toxicology

Acute toxicity

No acute toxicity studies were performed with the proposed CP 0.05% w/w shampoo formulation. Kuramoto et al. (1975a)[5] showed that the acute oral toxicity of CP was low, with no mortality at up to 3 g/kg orally (PO) in mice and rats. However, mortalities were observed in both species following SC or IP administration with 50% lethal dose (LD_{50}) values of 82-156 mg/kg in mice and 351-414 mg/kg in rats. No IV toxicity studies were reported. However, acute studies conducted using several routes demonstrated adequate CP exposure with mortalities, clinical signs of toxicity and target organ toxicities (thymus, spleen, adrenals, kidney, liver, reproductive organs) in both species.

Repeat-dose toxicity

The local and systemic repeat-dose toxicity of CP was mainly examined in rats (≤6 months) and mini- or micropigs (≤9 months). A 3 month dose-range finding study and 9 month photocarcinogenicity study was performed in mice, but only limited toxicological measurements were undertaken in these studies.

Mice and rats are acceptable standard rodent species used for toxicity testing whilst minipigs were chosen as an appropriate non-rodent species given their similar skin histology to humans.

Sponsor studies conducted with the proposed CP shampoo were performed in minipigs (≤3 months) topically exposed for 15 minutes once daily followed by rinsing, as proposed clinically.

Additional literature or sponsor studies used CP lotion, ointment or cream in mice (≤3 months topical; dose-range finding) and rats (≤3 months topical; ≤6 months SC).

All pivotal studies were GLP compliant (with the exception of the published 6 month SC study in rats) and generally employed adequate animal numbers and appropriate dose ranges (usually up to dose-limiting toxicity). The duration of the toxicity studies (6 months in rats, 9 months in minipigs) was sufficient to support the maximum proposed clinical duration (maximum of 4 weeks; with a possibility of retreatment) for the CP shampoo formulation.

[5] Kuramoto M, Ishimura Y, Morimoto J, Lee S-Y, Okubo T. Study on the toxicity of clobetasol 17-propionate 1 - Acute toxicity by oral, subcutaneous and intraperitoneal applications and subacute and chronic toxicities by subcutaneous successive applications in rats. Shikoku Acta Medica, 31 (6), 377-398, 1975.

Relative exposure

Toxicokinetic measurements were included in all pivotal sponsor repeat dose toxicity studies; however plasma concentrations were often below the limit of quantification. Therefore, animal to human exposure ratios were based on body surface area (BSA; refer below). Systemic exposure estimates based on BSA should be viewed with caution given the large variation in experimental conditions between the individual dermal absorption studies (for example, rotated application sites, different site sizes, different vehicles employed, site occlusion versus non-occlusion, once or twice daily dosing, skin condition, different exposure periods). Furthermore, relative exposure margins derived from any SC studies will be underestimated while those from studies conducted in animal models with intact skin (compared to psoriatic skin) will be overestimated.

Relative CP exposure achieved in rodents (BSA) was generally less than one-tenth that anticipated clinically while that in micro and mini-pigs ranged from about one to eight times the expected maximum clinical exposure. However, the high dose levels chosen for the chronic toxicity studies were appropriate (with the exception of the minipig shampoo studies) as dose-limiting toxicity typical of corticosteroid treatment precluded further dose-escalation.

Table 2. Relative exposure in pivotal dermal repeat-dose toxicity studies in mini- and micro-pigs

Species	Study duration and formulation tested	Dose (µg/kg/day)	BSA (mg/m^2)	Animal: Human Exposure ratio
Minipig (Göttingen)	3 months Shampoo	250	5	2
		500	10	4
		1000	20	8
Human (healthy volunteers)	Shampoo [3.75 mg/day]	75.0	2.48	–

#Full toxicological assessment was not performed in the mouse studies; BSA conversion factors and weight ranges observed were as follows: mini-pigs (20; 7-11 kg) and humans (33; 50 kg).

Toxicological profile

Toxicity studies in rats and mini- or micropigs demonstrated a range of typical systemic corticosteroid immunosuppressive and anti-proliferative effects following repeated topical or SC CP administration. Dermal reactions were often observed at the treatment site in both vehicle and (to a greater extent) CP treated groups. Given the wide range of effects observed, systemic and local No Observable Adverse Effect Levels (NOAELs) were often not obtained (with the exception of the 3 month minipig CP shampoo study, see below). However, the observed effects were expected pharmacological consequences of a potent corticosteroid, were reversible following treatment cessation (4 weeks) and were observed after significantly longer treatment durations than that proposed clinically.

The systemic and dermal toxicity of CP in rats was compared to six other corticosteroid ointments in a 4 week study in rats.[6] Similar toxicological profiles were observed but 0.05% CP was shown to be less toxic than 0.05% fluocinonide and 0.01% dexamethasone and more toxic than 0.12% betamethasone valerate, 0.12% dexamethasone valerate, 0.1% hydrocortisone butyrate and 0.025% beclomethasone dipropionate. The relative toxicity of CP corresponds to its relative pharmacological potency among the common corticosteroids (refer to *Pharmacology*).

Systemic effects

Typical systemic effects of CP administration included the following:

- Clinical signs: piloerection, inhibition of hair growth, hair loss, rough hair, emaciation, thin appearance, decreased motor activity, lacrimation, diarrhoea and/or vomitus), weight loss, decreased body weight gain, food consumption and/or water consumption.
- Haematology: decreased leukocyte, decreased lymphocyte and/or increased neutrophil counts were observed in both species and were consistent with immunosuppressive effects.
- Macroscopic findings: small adrenal gland, thymus and spleen (and associated decreases in organ weights), lung congestion and hyperaemia; liver, kidney and lung abscesses/spots.
- Summary of histopathology findings: adrenals (cortical atrophy [zona fasciculate], cortical vacuolation, increased prominence of the zona glomerulosa and/or nodular hyperplasia); thymus (cortex atrophy, lymphocyte depletion and/or involution); spleen (lymphocyte depletion, lymphoid atrophy, congestion, enlargement of red pulp); lymph nodes (mandibular, mediastinal and/or mesenteric; atrophy); liver (focal necrosis, histiocyte/ neutrophil infiltration, pigment and/or enlarged hepatocytes); lung (pneumonia, necrosis, histiocyte, cellular and/or neutrophil infiltration); kidney (hyaline or urinary casts and/or neutrophil infiltration); female mammary gland (decreased prominence or hyperplasia).

Less frequent findings included stomach oedema and necrosis in the 3 month rat study. Additional findings in the chronic minipig study included bone trabecular attenuation, tubular degeneration in the testes which was associated with cellular debris and decreased prominence of sperm in the epididymides, and increased ovarian follicular atresia.

The only study where a NOAEL for systemic effects was established was the 3 month minipig shampoo study. This was at the high dose of 1 mg/kg/day which was associated with an 8 fold safety margin over that anticipated clinically (based on BSA). This suggests that the 0.05% CP shampoo formulation and treatment regimen is associated with a greater safety profile than the 0.05% CP spray.

Dermal effects

Dermal reactions were generally observed in most vehicle and CP-treated groups for both species, but the severity and frequency of findings increased dose-dependently with CP administration. The gross observations included dermal atrophy (thinning and reductions in skin-fold thickness), failure of hair to grow at the application site, flaking, scabbing, dryness, eschar, erythema and/or desquamation. Microscopic findings included dermal thinning, adnexal, epidermal or dermal atrophy, hyperkeratosis, parakeratosis,

[6] Shimo T, Takahara Y, Noguchi Y, Mukawa A, Kato H, Ito Y. Comparative toxicity test of dexamethasone valerate (DV-17) and other steroid ointments in rats. J. Toxicol. Sci. 7, 15-33, 1982

hyperplasia, inflammation, focal crust, basophilic glandular secretion, ground substance basophilia, connective tissue degeneration, decreased collagen and/or increased prominence of adipocytes. No NOAEL was established in the pivotal (3 month minipig shampoo) study for dermal CP effects following chronic administration. However, it should be noted the dermal effects generally resolved following a treatment free period and that the intended clinical treatment duration is not more than 4 weeks.

Genotoxicity

CP was negative in the Ames, fluctuation and gene conversion tests *in vitro* (SBA for Removate, 1985) and showed no evidence of clastogenic potential in sponsor-conducted GLP compliant studies of chromosome aberrations in Chinese Hamster Ovary (CHO) cells *in vitro* and mouse micronucleus test *in vivo*.

Overall, CP did not demonstrate any genotoxic potential *in vitro* or *in vivo*. However, only the GLP compliant sponsor clastogenicity studies were validated for study design and protocol.

Carcinogenicity

No carcinogenicity studies were performed with the proposed CP 0.05% w/w shampoo formulation. However, the carcinogenic and photocarcinogenic potential of dermally applied CP lotion (for 6 hours) was examined in GLP compliant 2 year and 40 week studies in rats and mice, respectively. A single 2 year study in rats is considered acceptable for a product intended for short-term (up to 4 weeks) and/or intermittent use. The dose levels employed (dose-limiting toxicity), exposure period, and group sizes chosen were considered acceptable. However, mice were dosed for 5 instead of 7 days per week and toxicological assessments were limited in these studies. No food consumption, haematology, clinical chemistry, urinalysis, organ weight or histopathological examinations (including assessing tumour type) were performed in mice nor clinical chemistry, urinalysis or organ weight assessments were performed in rats. No toxicokinetic samples were taken in the mouse study, while limited measurements at the high dose only were measured in rats. Thus, animal to human exposure ratios were estimated based on BSA (refer to *Relative Exposure*).

No remarkable evidence of tumourigenesis in rats or mice (in combination with low UV irradiation) was observed following repeated dermal CP administration at doses associated with systemic and dermal toxicity (2-2.5 µg/kg/day) and corresponding to less than the anticipated clinical exposure based on BSA.

Reproductive toxicity

No reproductive toxicity studies were performed with the proposed CP 0.05% w/w shampoo formulation. However, sponsor GLP compliant studies were performed in rats examining the effects of CP on fertility, embryofetal and peri/post-natal development after daily dermal or twice daily SC administration. The dose levels employed (dose-limiting toxicity), routes (dermal; clinical route, SC; associated with greater exposure), exposure period (6 or 12 hours) and group sizes (22-25) chosen were considered acceptable. Consistent with repeat-dose toxicity studies, relative CP exposure achieved in all of the rat studies was low, with exposure achieved calculated to be less than or similar to that anticipated clinically, based on BSA.

While no sponsor studies were conducted in other nonclinical species, published papers were provided which examined reproductive toxicity in mice, rats and rabbits (including embryofetal development) following daily SC CP administration. No placental transfer or milk excretion studies were conducted.

Consistent with rat repeat dose toxicity studies, systemic toxicity (clinical signs, body weight loss, reduced body weight gain and/or reduced food consumption) was evident in all rat reproductive toxicity studies from the lowest dose administered (12.5 µg/kg/day SC or 50 µg/kg/day dermal). No NOAEL was determined.

Fertility and early embryonic development

There was no effect of CP on male or female mating performance in rats given SC doses up to 50 µg/kg/day. However, reproductive effects, including increased seminal vesicle weights in males from 12.5 µg/kg/day and a reduction in oestrus cycles in females from 25 µg/kg/day, were observed. The number of viable embryos was also reduced in females given 50 µg/kg/day SC. The NOAEL for male reproductive performance was not determined, while that of female reproductive performance was 12.5 µg/kg/day. The NOAEL for early embryonic effects was 50 µg/kg/day and 25 µg/kg/day in males and females, respectively. Similar results were obtained in published studies on rats given 6.25-50 µg CP/kg/day SC.[7]

Embryofetal development

A pattern of abnormalities such as cleft palate, skeletal abnormalities and growth retardation was observed in mice, rats and rabbits given dermal or SC CP during organogenesis.

Teratogenicity studies in mice[8] using the SC route resulted in fetotoxicity at the highest dose tested (1000 µg CP/kg/day) and teratogenicity (cleft palate, skeletal abnormalities) at all doses down to 30 µg CP/kg/day (lowest dose examined).

In rats, fetotoxicity (increased resorptions, decreased live young, decreased placental and fetal weights, decreased pup weights and/or decreased anogenital distance) and fetal malformations (including skeletal abnormalities, retinal fold in the eyes, cleft palate or palate irregularity, liver protruding into diaphragm and/or, umbilical cord hernia) were increased in a dose-related manner from 50 µg/kg/day (lowest dose tested) following topical application of CP lotion. While no NOAEL for teratology was established in this study, published embryofetal development studies in rats[9] showed similar results following SC administration of 30-400 µg CP/kg/day, with a teratology NOAEL established at 30 µg/kg/day.

SC studies with CP in rabbits showed no adverse fetal effects at 1 µg/kg/day, cleft palate, cranioschisis and other skeletal abnormalities at doses of 3 to 4 µg/kg/day, and fetotoxicity (decreased live foetuses, fetal body lengths and fetal weights) at 16 µg/kg/day.

These studies are consistent with the known teratogenic potential of corticosteroids inducing foetal immaturity and various skeletal and visceral abnormalities including cleft palate.[10] According to the sponsor, epidemiological studies have shown a slight association between use of systemic corticosteroids during the first trimester and the occurrence of cleft lip with or without cleft palate. Based on the teratogenic effects demonstrated in several animal species at potentially low CP exposure levels, the use of CP is not recommended during pregnancy.

[7] Kuramoto M, Ishimura Y, Ohguro S, Takeda K, Shigemi F, Tanaka M, Ai S, Matsuura H. Research into the effects of Clobetasol 17-propionate on Reproduction - Effects on administration to rats pre-conception and in the early stages of pregnancy Clinical Report, 10 (9): 50-65, 1976b

[8] SBA (Summary Basis of Approval) NDA 19-322 Removate. Review & Evaluation of pharmacology & toxicology data. 1985

[9] Kuramoto M, Ohguro S. Research into the effects of Clobetasol 17-propionate on Reproduction - Effects of administration during fetal organogenesis in rats. Clinical Report, 9(13): 133-157, 1975

[10] Sweetman SC Martindale. The complete drug reference. 34th edition. Corticosteroids. Pharmaceutical press, 2004

Pre and peri/postnatal development

Parturition difficulties (not delivering at all or completing delivery) and a reduced gestation index were observed in rats given 50 µg CP/kg/day SC from early gestation through weaning. Pre- and postnatal pup effects (including increased stillbirths, decreased live young, increased pups with no milk, decreased pup weights and weight gain, decreased pup food consumption, decreased pup survival, and increased numbers of pups with kidney cysts and umbilical hernias) were observed at maternal doses from 25 µg CP/kg/day SC. However, there were no effects on the functional development, mating or fertility of the offspring. The NOAEL for pre and postnatal effects was 12.5 µg CP/kg/day SC (less than the anticipated clinical CP exposure, based on BSA) in this study and 25 µg/kg/day SC in a published peri/postnatal study in rats study using the same route.[11] Based on the pup effects demonstrated postpartum at potentially low CP exposure levels, the use of CP is not recommended during lactation.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[12] for clobetasol propionate. This is considered appropriate given the animal findings and is consistent with the classification of other topical corticosteroids registered in Australia such as triamcinolone, desonide and mometasone.

Local tolerance

GLP compliant local tolerance studies were conducted with the proposed CP 0.05% shampoo formulation.

CP shampoo and shampoo vehicle applied to intact rabbit skin as a single occluded dose for 15 minutes were found to be slight irritants and irritants to the skin, respectively.

Repeat dose toxicity studies of the CP shampoo in rats and/or minipigs consistently demonstrated dermal reactions (particularly skin atrophy and thinning) at the treatment site but were generally reversible after a treatment-free period. Nonetheless, there remains a potential for local reactions at the application site in the clinical setting.

CP shampoo (applied to the eye conjunctival sac with or without rinsing) was a slight ocular irritant, suggesting CP application near the eyes should be avoided if possible.

The proposed CP shampoo formulation exhibited skin sensitisation potential in the guinea pig maximisation test.

Paediatric use

Clobetasol propionate is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

[11] Kuramoto M, Tanaka M, Ai S, Shigemi F, Takeda K, Ohguro S, Matsuura H. Reproductive effects of clobetasol-17-propionate after administration to rats during the perinatal and lactation periods. Clinical Report, 11 (1), 17-36, 1977

[12] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. <http://www.tga.gov.au/hp/medicines-pregnancy-categorisation.htm>

Nonclinical summary and conclusions

- The nonclinical data package provided to support both formulations was a hybrid submission of study reports and literature data. While pivotal sponsor studies were adequately conducted, literature studies were often constrained by summary data, precluding thorough evaluation.
- While no primary pharmacology studies were performed with the proposed CP shampoo formulation, sufficient information was provided to demonstrate that CP has potent anti-inflammatory and anti-proliferative effects that support its use for the treatment of psoriasis. CP was generally more potent than hydrocortisone (HC) but less potent than halobetasol propionate (HP) at ameliorating skin inflammation and proliferation in animal models.
- No secondary or safety pharmacology studies were performed with the proposed CP shampoo formulation. However, CP was shown to have the expected glucocorticoid effects including liver glycogen deposition, thymus involution, and androgenic/anti-estrogenic activities in rodents at daily doses between 0.1/0.25-25 mg/kg SC (similar to anticipated clinical exposure, based on BSA).
- Safety pharmacology studies assessing the major organ systems were limited but were sufficient to establish a large safety margin for potential adverse central nervous system or renal effects following topical CP spray or shampoo administration.
- Limited dermal penetration and systemic absorption of various sponsor CP formulations (including the proposed shampoo) was demonstrated when administered as proposed to intact human skin *in vitro* or rat scalp *in vivo*. No studies were conducted in psoriatic skin.
- PK studies performed with the CP shampoo formulation were limited to a skin penetration study *in vitro* and a single dose absorption study *in vivo*. While repeat-dose toxicity studies included toxicokinetic measurements, plasma concentrations were often below the limit of detection and hence of limited value.
- After skin penetration, CP absorption was rapid, with wide distribution throughout the body, followed by metabolism (primarily in the liver) and rapid elimination (primarily via biliary excretion in the faeces). Dermally applied CP (0.05%) elicited a 5 fold induction in CYP1A-mediated ethoxycoumarin-0-dealkylase activity in the skin, suggesting a potential PK interaction with co-administered drugs metabolised by CYP1A.
- No acute toxicity studies were performed with the proposed CP shampoo formulation. Nonetheless, the acute oral (LD_{50} > 3 g/kg), subcutaneous (SC) and intraperitoneal (IP) [LD_{50} = 82-414 mg/kg] toxicity of CP in rodents was low. While no IV toxicity studies were reported, SC and IP studies achieved CP exposure sufficient to elicit clinical signs of toxicity, target organ toxicity and mortality in both species.
- Repeat dose toxicity studies conducted with the CP shampoo were performed in minipigs (≤3 months) exposed topically for 15 minutes, as proposed clinically. Additional studies provided using CP lotion, ointment or cream were performed in mice (≤3 months topical) and rats (≤3 months topical; ≤6 months SC) following topical or SC daily administration.
- Typical systemic corticosteroid effects were observed in the pivotal, GLP compliant toxicity studies in rats, mini- and micropigs following repeated topical or SC CP administration. While systemic exposure was low and often below the limit of detection in these studies, typical corticosteroid immunosuppressive and anti-proliferative effects were observed, suggesting that systemic exposure was adequate to assess the toxicity profile of chronic CP administration. The duration of the repeat

dose toxicity studies was more than adequate to support the maximum proposed clinical duration of treatment (4 weeks).

- Target organs of toxicity for both species included the adrenal glands and lymphoid organs (thymus, spleen and/or lymph nodes), liver, lung, kidneys and reproductive organs. No NOAEL was established in any CP lotion study despite low relative exposure levels (generally < 0.1 on BSA). However, in the 3 month minipig CP shampoo study, a NOAEL for systemic effects was established at the highest dose, corresponding to an 8 fold safety margin(based on BSA), suggesting a better safety profile for the CP shampoo formulation and treatment regimen versus the CP lotion. The toxicity data indicate that CP does not pose a greater safety concern than other currently registered short-term use topical corticosteroids.
- Dermal reactions (including atrophy, thinning, flaking, eschar, erythema, desquamation, hyperkeratosis, parakeratosis, hyperplasia and inflammation) were observed at the treatment site in vehicle, and to a greater extent, CP treated groups following repeated topical or SC administration of CP. No NOAEL for local effects was established in any of the pivotal 3 to 9 month sponsored studies. While these changes were generally reversible and the intended clinical treatment duration is not more than 4 weeks, the results still suggest a potential for local reactions at the application site.
- CP did not demonstrate any genotoxic potential *in vitro* (Ames, fluctuation and gene conversion tests and chromosome aberration assay) or *in vivo* (mouse micronucleus test). However, only the GLP compliant sponsor clastogenicity studies were validated.
- No carcinogenicity studies were performed with the proposed CP shampoo formulation. However, the carcinogenic and photocarcinogenic potential of dermally applied CP lotion was examined in GLP compliant 2 year and 40 week studies in rats and mice, respectively. These studies are considered sufficient to support the short-term and possible intermittent use of CP. No remarkable evidence of tumourigenesis in rats or mice (in combination with low UVR irradiation) was observed following repeated dermal CP administration at doses associated with systemic and dermal toxicity (≥2-2.5 µg/kg/day; less than anticipated clinical exposure, based on BSA).
- No reproductive toxicity studies were performed with the proposed CP or shampoo formulation. However, a standard range of sponsor GLP compliant studies were performed in rats after daily dermal or twice daily SC administration of CP. No sponsor studies were performed in a second nonclinical species but literature data examining reproductive toxicity in mice, rats and rabbits following daily SC administration of CP were provided.
- There was no effect of CP on male or female mating performance in rats given a daily SC doses up to 50 µg/kg/day. However, reproductive effects, including increased seminal vesicle weights in males from 12.5 µg/kg/day and a reduction in oestrus cycles in females from 25 µg/kg/day were observed (less than the anticipated clinical CP exposure, based on BSA) . The number of viable embryos was also reduced in females given 50 µg/kg/day SC.
- Effects on embryofetal development were observed in mice rats and rabbits given dermal or SC CP during organogenesis. Fetotoxicity (increased resorptions, decreased live young, placental and fetal weights, fetal lengths, pup weights and/or anogenital distance) and fetal malformations (skeletal abnormalities, cleft palate and/or or palate irregularity, cranioschisis, retinal fold in the eyes, liver protruding into diaphragm and/or umbilical cord hernia) were observed in mice, rats and rabbits at 30 µg/kg/day SC, 50 µg/kg/day (dermal) and 3 µg/kg/day SC, respectively. No NOAEL was

established for teratology in mice or rats (lowest dose used). The NOAEL was reported as 1 µg/kg/day in rabbits.

- Parturition difficulties and a reduced gestation index were observed in rats given 50 µg CP/kg/day SC from embryogenesis through weaning. Pre- and postnatal pup effects (including increased stillbirths, decreased live young, increased pups with no milk, decreased pup weights and weight gain, decreased pup food consumption, decreased pup survival, increased number of pups with kidney cysts and umbilical hernias) were observed at maternal doses from 25 µg/kg/day SC. However, there were no effects on the functional development, mating or fertility of the offspring. The NOAEL for pre and postnatal effects was 12.5 µg/kg/day SC (less than the anticipated clinical CP exposure, based on BSA).
- CP shampoo and its vehicle were classified as slight irritants and irritants, respectively, to the skin. CP shampoo was considered a slight ocular irritant. The CP shampoo formulation as not a skin sensitiser.

Conclusions and recommendations

The nonclinical data package provided for clobetasol propionate was a hybrid submission of study reports for the proposed CP shampoo and other CP formulations as well as literature CP studies. Study details were limited for literature data and minimal pharmacokinetic information was provided. Nonetheless, the dossier was sufficient to characterise the pharmacological and toxicological profile of clobetasol propionate.

Potent anti-inflammatory and anti-proliferative activities inherent in psoriasis treatment were observed *in vitro* and in animal models *in vivo*. The toxicity profile was well characterised with no novel safety concerns raised. While a range of systemic effects were observed at potentially low therapeutic doses, these activities are consistent with toxicological profiles and exaggerated pharmacological effects of other potent corticosteroids. Dermal reactions were observed in response to repeated exposure to the CP formulation and its vehicle. While generally reversible, the potential for local reactions in the clinical setting cannot be excluded.

Reproductive toxicity, including teratogenicity, was observed following CP exposure in three nonclinical species and pup effects were observed in rats postpartum. These findings suggest clobetasol propionate should be avoided in pregnancy and during lactation, unless clearly necessary.

There are no nonclinical objections to the registration of the proposed Clobex (0.05% w/w clobetasol propionate) shampoo formulation.

The draft Product Information and Risk Management Plan should be amended as indicated.

IV. Clinical findings

Introduction

Clinical rationale

The products are intended as treatments for psoriasis.

Scope of the clinical dossier

There were four studies that provided evaluable data regarding the pharmacokinetics of clobetasol in the shampoo formulation. Study 1.CG.03.SRE.4651 provided data with regard to dermal absorption and Study RD.06.SRE.18075, Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070 provided data with regard to systemic exposure.

There were six studies that provided pharmacodynamic data. There was one study that used the vasoconstrictor assay: Study 1.CG.03.SRE.2618 with the shampoo formulation. There were two studies of Hypo Thalamic-Adrenal (HPA) axis suppression using the shampoo formulation: Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070.

There was one "proof of concept" study: Study 1.CG.03.SRE.2577 using the shampoo formulation.

There were five pivotal efficacy studies submitted in support of CPSH. There were two studies comparing CPSH with vehicle: Study RD.06.SRE.18075 and Study RD.06.SRE.18076. There was one study comparing CPSH with vehicle and with clobetasol propionate 0.05% gel: Study RD.03.SRE.2665. There were two comparator controlled studies: Study RD.03.RDE.2638 and Study RD.03.SRE.2648. There was one additional supportive study: Study 1.CG.03.SRE.2591.

There were three studies evaluable only for safety: Study GLI.04.SRE.US10029, Study GLI.04.SRE.US10085 and Study 1.CG.03.SRE.2578.

Periodic Safety Update reports were provided for clobetasol propionate that covered the time period 29 June 2005 to 28 February 2011. Summary bridging reports were provided that covered the time period 17 March 2003 to 28 February 2010.

Paediatric data

The submission did not include paediatric data. The sponsor states: "*Clobex Shampoo and Spray have not been evaluated in children or adolescents (<18 years of age) in clinical studies to date.*"

Good clinical practice (GCP)

Each of the study reports submitted in the application contain statements of adherence to GCP.

Pharmacokinetics

Summary of pharmacokinetics

In donor skin samples, 0.06% of the administered dose of clobetasol in the shampoo formulation was absorbed following a 15 minute exposure and 19% was absorbed during a 16 hour exposure. However, the donor skin samples were healthy skin and the absorption of clobetasol by diseased skin may be greater.

The plasma samples assayed for clobetasol in subjects treated with the shampoo formulation were, with the exception of one sample, below the lower limit of quantification.

Evaluator's overall conclusions on pharmacokinetics

Exposure to Clobex shampoo in accordance with the instructions in the Product Information did not to lead to quantifiable systemic exposure to clobetasol propionate using the methods available to the sponsor.

Pharmacodynamics

Evaluator's overall conclusions on pharmacodynamics

Clobetasol propionate 0.05% in the shampoo formulation had lesser potency than the cream and scalp applications but had similar potency to a betamethasone dipropionate 0.05% cream formulation (Study 1.CG.03.SRE.2618). The TGA adopted (in 1987) EU Guideline "*Clinical Investigation of Corticosteroids Intended for Use on the Skin*"[13], comments that the vasoconstrictor assay can be used as a preliminary rough guide to anti-inflammatory activity. However, the relationship between the vasoconstrictor assay and effectiveness in treating psoriasis is not clear.

The shampoo formulation appeared to have less potential for HPA axis suppression but one subject did have evidence of HPA axis suppression and treatment emergent hypertension (Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070).

With regard to bioequivalence, the sponsor has justified the absence of pharmacokinetic data by arguing that the pharmacodynamic studies study the actual effects of systemic exposure and the presentation of pharmacodynamic studies makes the presentation of pharmacokinetic data unnecessary. However, the pharmacodynamic studies were not designed in order to demonstrate bioequivalence and did not compare the responses as ratios (90% CI). Given these deficiencies, the results, as noted above, of the vasoconstrictor assays indicate that clobetasol propionate 0.05% in the shampoo formulation had lesser potency than the cream and scalp applications (Study 1.CG.03.SRE.2618). Bioequivalence, as such, cannot be determined from the data.

Phase II studies

Evaluator's overall conclusions on Phase II studies

The Phase II studies indicated potential benefit and supported carrying the product through to Phase III. They were also useful in developing the outcome measures. However, there was limited evaluation of dosing with no evaluation of different concentrations of clobetasol propionate. There was limited evaluation of different application methods in the shampoo formulation. Some of these limitations were addressed in the Phase III studies.

Efficacy

Evaluator's conclusions on clinical efficacy for clobetasol propionate shampoo

CPSH was superior to vehicle in the treatment of scalp psoriasis. In Study RD.06.SRE.18075, CPSH was superior to vehicle for the primary efficacy outcome variable, Global Severity score, with success reported in 28 (28.3%) subjects in the CPSH group and five (10.2%) in the vehicle, p = 0.012. In Study RD.03.SRE.2665, CPSH was superior to

[13] <http://www.tga.gov.au/pdf/euguide/vol3cc26aen.pdf>

vehicle by the Total Severity score, $p < 0.05$. In Study RD.06.SRE.18076, CPSH was superior to vehicle by the analysis of primary efficacy outcome measure, Global Severity Score. At Week 4 endpoint, 40 (42.1%) subjects in the CPSH group and one (2.1%) in the vehicle had treatment success. At Week 6, 21 (23.9%) subjects in the CPSH group still had treatment success.

CPSH was non-inferior to clobetasol propionate 0.05% gel for the treatment of scalp psoriasis. In Study RD.03.SRE.2665, non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT. The 95% CI for the difference in treatments in change in Total Severity Score from baseline (Dermoval™ - CPSH) was 0.25 to 1.29 for the per-protocol population and 0.24 to 1.34 for the ITT. However, for some of the secondary efficacy outcome measures, clobetasol propionate 0.05% gel was superior to CPSH (Study RD.03.SRE.2665).

CPSH was superior to Calcipotriol solution 0.005%, (Dovonex/ Daivonex™), twice daily, and to Polytar®. In Study RD.03.RDE.2638, non-inferiority was demonstrated on the per-protocol analysis of Total Severity Score and superiority was demonstrated on the secondary analysis of the ITT population. The 95% CI for the difference in Day 28 Total Severity score (CPSH – calcipitriol) was -0.66 to 0.18 for the per-protocol analysis and -0.97 to -0.05 for the ITT analysis. In Study RD.03.SRE.2648, non-inferiority was demonstrated in comparison to Polytar® in the per-protocol population by the predefined criteria. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar® - CPSH) was -2.066 (-2.727 to -1.405), and the upper 95% CI was below the non-inferiority target of 1.5. Superiority was demonstrated by the secondary analysis of Total Severity score in the ITT population. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar® - CPSH) was -1.842 (-2.475 to -1.208), $p = 0.0001$.

In addition, Study 1.CG.03.SRE.2591 supported the administration method of 15 minute application to dry hair followed by lathering and rinsing.

The studies were conducted with robust and clinically relevant endpoints. The severity scores used the same components as the Psoriasis Area and Severity Index (PASI) and the Psoriasis Global Assessment (PGA). This included erythema, scaling and plaque elevation; and the % surface area affected. This is consistent with the "Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis". In addition, the studies also evaluated pruritus. The criteria used for treatment success in Study RD.06.SRE.18076 were clinically relevant. The non-inferiority criteria were clinically significant.

Evaluator's general comments on the clinical efficacy data

There were few data on the duration of response in the submission. The treatment duration was for 4 weeks at most and this reflects the treatment advice in the PI document. However efficacy assessments beyond 2 weeks after treatment cessation were not performed. This is not consistent with the "*Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis*[14]" which advises assessment up to 2 months after treatment cessation. Hence there are limited data in the submission on the duration of treatment effect or the risks of disease rebound/relapse. There were also no evaluable data for treatment in combination with other psoriasis treatments.

[14] <http://www.tga.gov.au/pdf/euguide/ewp245402en.pdf>

Safety

Patient exposure to CPSH

A total of 607 subjects were exposed to CPSH for up to 4 weeks:

Study 1.CG.03.SRE.2577, 36 subjects were treated with CPSH for 2 weeks.

Study RD.06.SRE.18075, a total of 99 subjects were exposed to CPSH for up to 4 weeks.

Study 1.CG.03.SRE.2620, 27 subjects treated with CPSH for up to 4 weeks; 14 with daily applications, and 13 with twice weekly applications.

Study RD.06.SRE.18070, there were 13 subjects exposed to CPSH 0.05% once daily for up to 4 weeks.

Study RD.03.SRE.2665, there were 63 subjects exposed to CPSH for up to 28 days, with a mean (SD) duration of treatment of 27.26 (2.16) days.

Study RD.06.SRE.18076, there were 95 subjects exposed to CPSH for up to 4 weeks.

Study 1.CG.03.SRE.2591, a total of 44 subjects were exposed to CPSH 0.05% once daily for 3 weeks.

Study RD.03.RDE.2638, there were 76 subjects exposed to daily applications of CPSH for up to 4 weeks.

Study RD.03.SRE.2648, there were 121 subjects treated with CPSH 0.05%, once daily application, for up to 4 weeks.

Study 1.CG.03.SRE.2578, there were 33 subjects with scalp seborrhoeic dermatitis that were exposed to CPSH twice weekly for 4 weeks.

Postmarketing experience

Periodic Safety Update reports were provided for clobetasol propionate that covered the time period 29 June 2005 to 28 February 2011. Summary bridging reports were provided that covered the time period 17 March 2003 to 28 February 2010.

The international birth date of clobetasol propionate was stated to be 21 February 1975. It is stated that clobetasol propionate products are marketed in 50 countries and that no action has been taken for safety reason either by the Market Authorisation Holder or any Regulatory Authority. Clobetasol propionate is available in six dosage forms: scalp lotion/emulsion/lotion, gel, shampoo, spray, cream and ointment; and in one strength: 0.05%.

During the time period 17 March 2003 to 16 September 2008 there were nine reports of serious/unlisted adverse events (AEs), six of which were medically confirmed. During the 3 year period 29 December 2006 to 28 February 2010there were 240 spontaneous reports of which ten were serious and unlisted. There were five spontaneous reports of serious/unlisted medically confirmed AEs. As of 28 February 2010 the sponsor reports 13 spontaneous reports of serious/unlisted medically confirmed AEs. From these reports glaucoma and Cushing's syndrome appear to be risks.

During the time period 1 March 2010 to 31 August 2010 there were a total of 33 spontaneous case reports, of which one was serious/unlisted: therapeutic abortion due to potential teratogenic effects of Clobex shampoo.

During the period 1September 2010 to 28 February 2011 there were 43 spontaneous reports, eleven of which were medically confirmed and two of which were serious and unlisted: shortness of breath and Cushing's syndrome. The Cushing's syndrome occurred

following 7 months of continuous treatment of Clobex shampoo at a frequency of daily to three times a week.

Evaluator's overall conclusions on clinical safety

Shampoo

There were slightly more AEs reported with CPSH than with vehicle with the excess appearing to be related to skin discomfort (Study RD.06.SRE.18076). There were significantly fewer subjects reporting AEs with CPSH than with calcipotriol: 10.5% compared with 30.7% respectively (Study RD.03.RDE.2638). However there was a higher proportion of subjects with AEs in comparison with Polytar®: 22.5% compared with 12.5% respectively, with the excess appearing to be due to skin discomfort and headache (Study RD.03.SRE.2648).

There were few SAEs, none attributable to study treatment, and no deaths reported in the studies of CPSH. Withdrawal due to AE was uncommon.

CPSH had good dermal tolerability. It caused slight irritation only and was not a sensitiser.

There were few abnormal laboratory test results and none attributed to CPSH but for most of the studies routine laboratory tests were not performed.

Postmarketing data

Glaucoma and Cushing's Syndrome appear to be rare risks associated with treatment with clobetasol propionate. Cushings Syndrome as a result of clobetasol propionate treatment may be related to prolonged usage, well in excess of the sponsor's recommendation.

General comments

The duration of follow-up from the studies was at most 2 weeks after treatment cessation, with total observation duration of 6 weeks. This was insufficient duration to evaluate rebound effects. There were also no data examining repeated short term use of CPSH. However, the postmarketing data did not indicate long-term adverse effects, excepting those associated with prolonged, inappropriate use.

The "*Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis*"[14] recommend efficacy and safety studies of one year duration for intermittent or prolonged use. However, it is not clear how these guidelines should be applied to a treatment that is for a maximum of 4 weeks.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

Shampoo

CPSH was superior to vehicle in the treatment of scalp psoriasis. In Study RD.06.SRE.18075, CPSH was superior to vehicle for the primary efficacy outcome variable, Global Severity score, with success reported in 28 (28.3%) subjects in the CPSH group and five (10.2%) in the vehicle, $p = 0.012$. In Study RD.03.SRE.2665, CPSH was superior to vehicle by the Total Severity score, $p < 0.05$. In Study RD.06.SRE.18076, CPSH was superior to vehicle by the analysis of primary efficacy outcome measure, Global Severity Score. At Week 4 endpoint, 40 (42.1%) subjects in the CPSH group and one (2.1%) in the vehicle had treatment success. At Week 6, 21 (23.9%) subjects in the CPSH group still had treatment success.

CPSH was non-inferior to clobetasol propionate 0.05% gel for the treatment of scalp psoriasis. In Study RD.03.SRE.2665, non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT. The 95% CI for the difference in treatments in change in Total Severity Score from baseline (Dermoval™ - CPSH) was 0.25 to 1.29 for the per-protocol population and 0.24 to 1.34 for the ITT. However, for some of the secondary efficacy outcome measures, clobetasol propionate 0.05% gel was superior to CPSH (Study RD.03.SRE.2665).

CPSH was superior to Calcipotriol solution 0.005%, (Dovonex/ Daivonex™), twice daily, and to Polytar®. In Study RD.03.RDE.2638, non-inferiority was demonstrated on the per-protocol analysis of Total Severity Score and superiority was demonstrated on the secondary analysis of the ITT population. The 95% CI for the difference in Day 28 Total Severity score (CPSH – calcipitriol) was -0.66 to 0.18 for the per-protocol analysis and -0.97 to -0.05 for the ITT analysis. In Study RD.03.SRE.2648, non-inferiority was demonstrated in comparison to Polytar® in the per-protocol population by the predefined criteria. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar® - CPSH) was -2.066 (-2.727 to -1.405) and the upper 95% CI was below the non-inferiority target of 1.5. Superiority was demonstrated by the secondary analysis of Total Severity score in the ITT population. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar® - CPSH) was -1.842 (-2.475 to -1.208), p = 0.0001.

In addition, Study 1.CG.03.SRE.2591 supported the administration method of 15 minute application to dry hair followed by lathering and rinsing.

First round assessment of risks

Shampoo

The risks of CPSH in the proposed usage are:

- Increased risk glaucoma and raised intraocular pressure
- HPA axis suppression
- Cushing's syndrome
- Local reactions: burning and stinging

There were slightly more AEs reported with CPSH than with vehicle with the excess appearing to be related to skin discomfort (Study RD.06.SRE.18076).

There were significantly fewer subjects reporting AEs with CPSH than with calcipotriol: 10.5% compared with 30.7% respectively (Study RD.03.RDE.2638). However, there was a higher proportion of subjects with AEs in comparison with Polytar®: 22.5% compared with 12.5% respectively, with the excess appearing to be due to skin discomfort and headache (Study RD.03.SRE.2648).

There were few SAEs, none attributable to study treatment, and no deaths reported in the studies of CPSH. Discontinuation due to AE was uncommon.

CPSH had good dermal tolerability. It caused slight irritation only and was not a sensitiser.

There were few abnormal laboratory test results, and none attributed to CPSH but for most of the studies routine laboratory tests were not performed.

Exposure to Clobex® shampoo in accordance with the instructions in the PIis unlikely to lead to significant systemic exposure to clobetasol propionate.

The shampoo formulation appeared to have less potential for HPA axis suppression but one subject did have evidence of HPA axis suppression and treatment emergent hypertension (Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070).

Postmarketing data

Glaucoma and Cushing's Syndrome appear to be rare risks associated with treatment with clobetasol propionate. Cushings Syndrome as a result of clobetasol propionate treatment may be related to prolonged usage, well in excess of the sponsor's recommendation.

First round assessment of benefit-risk balance

Shampoo

The benefit-risk balance of clobetasol propionate shampoo (Clobex shampoo), given the proposed usage, was considered to be favourable.

First round recommendation regarding authorisation

It was recommended that:

Clobex Shampoo should be approved for the indication of:

> *Topical treatment of moderate to severe scalp psoriasis in adults.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

In the updated RMP Version 2 Section 1.8.1.3 Summary – Ongoing Safety Concerns, the sponsor states:

> *"In spite of the well-established use of topical clobetasol propionate 0.05%, the extensive documentation available on this active and its therapeutic class, the limited application areas on the scalp only and the limited time of application of 15 minutes, the risk of hypothalamic pituitary suppression was identified as an important identified risk and added to the Company Core Data Sheet accordingly."*

OPR reviewer comment

Subject to the evaluation of the nonclinical aspects of the Safety Specification by the Toxicology area of the OSE, it was recommended that the above summary of the Ongoing Safety Concerns was acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities[15] are proposed to monitor the Important identified risk: *Adrenal disorders: adrenal suppression/Cushing's syndrome* associated with Clobex shampoo.

[15] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones

It was considered that routine pharmacovigilance activities are satisfactory to monitor the Important identified risk: Adrenal disorders: adrenal suppression/Cushing's syndrome.

Risk minimisation activities

No additional risk minimisation activities are planned for Clobex shampoo.

OPR reviewer comment

Routine risk minimisation activities[16] were considered sufficient to monitor the safety concerns associated with Clobex shampoo.

In regard to the proposed routine risk minimisation activities, the draft PI and consumer medicine documents are considered satisfactory. However, it was recommended that the sponsor include advice in the *Dosage and Administration* section of the PI on the recommended "off treatment" duration between treatment courses.

Summary of recommendations

The OPR provided these recommendations in the context that the submitted RMP is supportive to the application;

It was recommended that the Delegate:

- Implement RMP Version 2, dated 11 May 2012 including the sponsor's response to the TGA request for information/documents (Section 31 request) and any future updates as a condition of registration.

It was recommended to the Delegate that the sponsor:

- Include advice in the *Dosage and Administration* section of the PI on the recommended "off treatment" duration between treatment courses.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator states that "most" chemistry and quality control issues have been resolved. Based on the original data set, the evaluator initially recommended a shelf life of three months only. This was because there were some outstanding manufacturing and testing issues which were to be resolved in December 2012, based on additional testing that was being conducted by Galderma. These tests were to reliably demonstrate the absence of impurities from the finished product. The results of these tests would enable the recommendation of a more realistic shelf life for this product. [The sponsor is to submit these data once registration occurs, to extend the shelf life of this product]. The open shelf life is 4 weeks.

- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[16] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The evaluator mentions that systemic bioavailability information was available from 4 clinical studies in patients with scalp psoriasis. 141 subjects were included; the issue was that there was only one plasma sample collected at the end of the 4 week dosing; the timing of the sampling was not standardised. There were 3 subjects with levels above the detection limit.

The PSC considered this submission at its 144th meeting. All outstanding issues relating to that meeting have been resolved (Recommendation 2261).

Thus, the evaluator states that the current data-set is approvable from a chemistry point of view. Lack of validation data on impurities would be addressed after the ACPM meeting with the provision of test results by Galderma. This is likely to cause the TGA to approve a more realistic shelf life for this product.

Nonclinical

The evaluator mentions that the submission was a hybrid submission, that is, consisting of evaluable studies and literature. Overall, there was evidence that CP had potent anti-inflammatory and anti-proliferative effects; it was generally more potent that hydrocortisone (HC). CP was also shown to have expected glucocorticoid effects "including liver glycogen deposition, thymus involution, and androgenic/anti-estrogenic activities in rodents at daily doses between 0.1/0.25-25 mg/kg SC (similar to anticipated clinical exposure, based on BSA)".

Safety pharmacology studies were sufficient to establish a large safety margin for potential adverse central nervous system or renal effects following administration of topical CP spray or shampoo.

There was limited dermal penetration and systemic absorption in intact human skin *in vitro* or rat scalp *in vivo*. No studies were conducted in psoriatic skin. Pharmacokinetic studies were of limited value as plasma concentrations were "often" below the limit of quantification.

Acute oral toxicity was low in rodents.

The evaluator mentions that "repeat dose toxicity studies conducted with the CP spray were primarily performed in rats (≤3 months) and minipigs (≤9 months) exposed topically twice daily, as proposed clinically. Repeat dose toxicity studies conducted with the CP shampoo were performed in minipigs (≤3 months) exposed topically for 15 minutes, as proposed clinically".

Typical systemic corticosteroid effects were observed though the systemic exposure was low supporting the suggestion that systemic exposure was adequate to assess the toxicity profile of chronic administration.

In relation to the CP shampoo, based on a 3 month mini-pig CP shampoo study, a NOAEL for systemic effects was established at the highest dose corresponding to an 8 fold safety margin.

Repeat topical or SC administration of CP showed greater dermal reactions with CP than vehicle only. These changes were generally reversible.

No genotoxicity was demonstrated *in vitro* or *in vivo*.

Carcinogenicity studies were conducted with CP lotion in 2 year and 40 week studies in rats and mice, respectively. These were considered acceptable for short term and intermittent use of CP. There was no evidence of tumorogenesis (exposure less than with anticipated clinical exposure).

Reproductive effects (rats given daily SC dose of 50 µg) were seen in males (increased weight of seminal vesicles) and reduction of oestrus cycles in females. Number of viable embryos reduced in females given 50 µg/kg/SC.

There was foetal toxicity and malformations seen in mice, rats and rabbits (see *Nonclinical Findings*). No NOAEL was established for teratology in mice or rats. NOAEL was 1µg/kg/day.

The evaluator also mentions that "parturition difficulties and a reduced gestation index were observed in rats given 50 µg CP/kg/day SC from embryogenesis through weaning. Pre- and postnatal pup effects....were observed at maternal doses from 25 µg/kg/day SC".

There were adequate data to qualify isopropyl myristate (IPM) for use as excipient in the formulation at the proposed concentration.

Several PI amendments were recommended.

Overall, the evaluator recommends approval from a nonclinical point of view.

Clinical

Please note that the efficacy aspects of the clinical evaluation report that deals with the spray formulation can be ignored for the purposes of making a recommendation on this submission.

Pharmacokinetics

Four studies are discussed by the evaluator. One *in vitro* study that examined donor samples of skin where clobetasol was administered, showed 0.06% of the administered dose was absorbed after 15 minutes and 19% after 16 hours of exposure. However, this was a study on healthy skin samples and may not reflect the pharmacokinetics in diseased skin.

The plasma samples assayed for clobetasol in subjects with the shampoo formulation were generally below the lower limit of quantification.

Pharmacodynamics

There were two studies of the vasoconstrictor effect: 1) *Study T100-01003* and 2) *Study CG. 03. SRE.2618.* The latter examined clobetasol shampoo and the former the spray. These studies were conducted on healthy volunteers who were preselected for being vasoconstrictor assay "responders". The evaluator acknowledged that the vasoconstrictor assay can be used as a preliminary guide to anti-inflammatory activity (as stipulated in the EU document, "clinical investigation of corticosteroid intended for use in skin"). The evaluator mentions that the relationship of the effectiveness of this assay in treating psoriasis is not clear.

Studies of pituitary adrenal axis suppression: There were four such studies. The evaluator mentions that, "w*ith the spray formulation, around 25% of subjects had some indication of HPA suppression after 4 weeks of treatment (Study D02-0204-03 and Study TI01-01009). The shampoo formulation appeared to have less potential for HPA axis suppression but one subject did have evidence of HPA axis suppression and treatment emergent hypertension (Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070)*".

Efficacy

There were two Phase II, 'proof of concept' studies, only one (1.CG.03.SRE.2577) relating to the shampoo formulation. This study is discussed in detail in the clinical evaluation report (CER).

Study 1.CG.03.SRE. 2577 was a single centre randomised, investigator masked study of clobetasol propionate 0.05% after different short contact application times in scalp psoriasis. Dermal foaming gel and clobetasol proprionate vehicle were comparators. There was a two week treatment period followed by a two week follow up. There were 60 subjects enrolled. The evaluator notes that different strengths were not included in these studies. There was a greater global improvement with active treatment; (this was the primary efficacy endpoint).

Pivotal efficacy studies

Efficacy studies with CP Shampoo:

Study RD.06.SRE.18075 was a multicentre, randomised double blind parallel group study of CP shampoo 0.05% versus vehicle in subjects with scalp psoriasis. Subjects over the age of 12 with moderate to severe scalp psoriasis (defined as global severity 3) were eligible to enroll.

The treatments were applied once daily to the affected areas of the scalp and rinsed after 15 minutes. The study duration was 4 weeks.

The primary efficacy outcome measure was treatment success as measured by the Global Severity score (success rate was defined as the proportion of subjects with a Global Severity score of clear or minimal). The secondary endpoints were total severity score, erythema, plaque thickening, scalp surface area of involvement, global assessment of improvement by the investigator and patient.

Sample size calculations took into account a 2: 1 randomisation. A total of 148 subjects were randomised: 99 to the CP shampoo (CPSH) group and 49 to the vehicle group. There were 55% females. The demographic characteristics were similar between groups.

In relation to the primary efficacy outcome, the evaluator mentions that, "*CPSH was superior to vehicle. Success was reported in 28 (28.3%) subjects in the CPSH group and five (10.2%) in the vehicle, p = 0.012. By Global Severity score seven (7.1%) subjects in the CPSH group and one (2.0%) in the vehicle were clear at Week 4, p = 0.005 (Table 7.1.2.1.7)*".

Secondary efficacy endpoints reflected similar findings.

Study RD.03.SRE. 2665 was also a multicentre, randomised, investigator blinded, active and vehicle controlled study. This study recruited those of the ages of 18 and over with moderate to severe scalp psoriasis that affected at least 15% of the scalp surface area.

Here, CP shampoo, vehicle and clobetasol propionate 0.05% gel (Dermoval gel) topical were used once daily for 4 weeks.

The primary efficacy endpoints were global severity score and total severity score on each quarter of the scalp. Secondary endpoints were erythema, desquamation, plaque thickening, pruritus, global assessment of improvement.

The study was designed to test non-inferiority of CPS shampoo versus Dermoval and superiority versus vehicle.

A total of 144 subjects were enrolled in the study: 63 in the CPS shampoo group, 61 in the Dermoval group and 20 in the vehicle group.

The following is extracted from the evaluation report: "*Non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT. The 95% CI for the difference in*

treatments in change in Total Severity Score from baseline (Dermoval™ - CPSH) was 0.25 to 1.29 for the per-protocol population and 0.24 to 1.34 for the ITT (Table 7.1.2.2.4). CPSH was superior to vehicle, p < 0.05. At Week 4, Global Severity Score was similar for CPSH and Dermoval™, mean (SD) score 1.7 (1.3) for CPSH and 1.1 (1.0) for Dermoval™."

In general, in relation to the secondary endpoints, Dermoval was superior to CPS shampoo. Both the actives were superior to vehicle.

Study RD.06.SRE.18076 was a multicentre randomised vehicle controlled double blind parallel group study of subjects with moderate to severe scalp psoriasis in those aged 12 years and older. CP shampoo or vehicle was applied once daily and rinsed after 15 minutes; the treatment duration was 4 weeks. The efficacy endpoints were as for the previous studies.

A total of 142 subjects were randomised: 95 to CP shampoo and 47 to vehicle. (There were 2 subjects between the ages of 12-17 who were in the active treatment group).

The evaluator mentions that "*CPSH was superior to vehicle by the analysis of primary efficacy outcome measure. At Week 4 endpoint, 40 (42.1%) subjects in the CPSH group and one (2.1%) in the vehicle had treatment success (Table 7.1.2.3.4). At Week 6, 21 (23.9%) subjects in the CPSH group still had treatment success. There was no apparent significant effect of subgroup on success rate*". All secondary endpoints also showed statistically significant change favouring the CPS shampoo.

Study RD.03. RDE.2638 was a multicentre, randomised investigator blinded parallel group comparator controlled study on subjects with moderate to severe scalp psoriasis (age 12 years and older).

The study treatments were CP Shampoo 0.05% once daily versus calcipotriol solution 0.005% (Daivonex) twice daily for 4 weeks. The primary efficacy endpoints were total severity score and global severity score. The secondary endpoints were erythema, plaque thickening, desquamation, pruritus scalp surface area involved and global assessment of improvement.

This study was designed as a non-inferiority study.

A total of 151 subjects were enrolled; 76 in the CPS shampoo group and 75 in the calcipotriol group.

Primary outcome: Non-inferiority was demonstrated in the per-protocol analysis in relation to the total severity score. This is also demonstrated relating to the global severity score. It is stated that in relation to the secondary endpoints, erythema, plaque thickening, desquamation and pruritus were 'more favourable' in the CP shampoo group, though not statistically tested.

Study RD.03. SRE. 2648 was similar in design to the previous studies where Poly Tar Liquid (twice per week) was used as comparator. Subjects were randomised on a 3: 1 basis.

Some 162 subjects were randomised to treatment: 121 to CP shampoo and 41 to Poly Tar.

The evaluator mentions that "N*on-inferiority was demonstrated in the per-protocol population by the predefined criteria. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar® - CPSH) was -2.066 (-2.727 to -1.405), and the upper 95% CI was below the non-inferiority target of 1.5 (Table 7.1.2.5.4)*."

Superiority was demonstrated by the secondary analysis of Total Severity score in the Intention-to-Treat (ITT) population. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar® - CPSH) was -1.842 (-2.475 to -1.208), p = 0.0001. This was confirmed by the analysis of Global Severity score: mean (SD) at Week 4: 1.9 (1.0) for CPSH and 3.0 (1.0) for Polytar®, p = 0.0001. As in the other studies, the secondary

endpoints reflected similar findings, that is, superiority of CPS shampoo over the comparator.

Another efficacy study, ***1. CG.03. SRE.2591***, is also discussed where the CP shampoo is compared to Daivonex scalp lotion. This tested contact for various periods of time with the scalp (1- to 15 minutes). This study supported the finding of 15 minutes contact time.

Overall efficacy conclusion

The evaluator mentions that there was clinically and statistically significant superiority of CPSH over placebo in relation to Overall Disease Severity. The effect persisted for 4 weeks. CPSH was non-inferior to clobetasol propionate 0.05% gel for the treatment of scalp psoriasis that is in Study RD.03.SRE.2665, non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT.

The evaluator mentions that there were no data on cessation of treatment beyond two weeks; the EU Guidelines mentions the provision of data after stopping treatment. In addition, there were no data on combination with other treatments.

Safety

Some 607 patients were exposed for up to 4 weeks. CP shampoo reported less AEs than calcipotriol (10% versus 30.7%). In comparison to Polytar, it was higher (22.5% versus 12.5%). It had good dermal tolerability and was not a sensitiser.

Risk management plan

Routine pharmacovigilance activities were proposed by the sponsorand were considered satisfactory by the TGA. The sponsor states that the PI will be amended to include precautionary statements that treatment of large surface areas, long term continuous therapy, use of occlusive dressings can enhance absorption and lead to higher risk of systemic effects, including HPA axis suppression. Regular monitoring for this is recommended. The following statement is also recommended "*Patients applying doses of Clobex in excess of 50g (corresponding to 60ml)/week should be carefully monitored*."

Overall conclusions of the evaluator

The evaluator recommended approval of the shampoo as it had a positive risk benefit profile.

Risk-benefit analysis

Delegate considerations

The quality data posed a significant question in relation to the recommendation to register this product with a shelf life of three months. This is not a practical duration that would enable the product to reach retail pharmacy shelves.

At the time of this overview, the quality was inadequate to support a realistic shelf life.

The data set is adequate in terms of nonclinical and clinical data.

This data set provides evidence of efficacy of the CP Shampoo in moderate to severe psoriasis. The efficacy is objectively defined based on a global severity scale. Efficacy has been demonstrated versus vehicle, where superiority to vehicle was shown. CP shampoo was also non-inferior to clobetasol gel and calcipotriol.

The total number of subjects exposed to CP shampoo, of the ages of 12-17 is not provided in the clinical evaluation report. The sponsor should submit this (from the efficacy studies) in their pre-ACPM response.

The data set support efficacy for 4 weeks only. There are no data on relapses and re-treatment. Similarly, there are no long term data on safety in relation to local or systemic toxicity; there are no data on the development of tolerance.

Should this submission be approved, the PI should include the studies conducted versus calcipotriol and Poly tar. There should also be a statement that there are no data beyond 4 weeks. There is a precautionary statement regarding the occurrence of HPA suppression and this is satisfactory.

Question to the ACPM

Should this submission be recommended for rejection, based on the current data set and the sponsor requested to re-submit with complete data to support a realistic shelf life?

The Committee's advice was requested.

The Delegate recommended that the sponsor re-submit this submission with adequate Quality data to support a realistic shelf life. Based on the present data-set, this submission should be rejected as there are inadequate quality data.

Response from sponsor

This Pre-ACPM response is in relation to a Category 1 registration application dated 30 May 2011 for the registration of Clobex Spray and Shampoo. During the evaluation process, Galderma elected to withdraw Clobex Spray from the application on 23 October 2012 as the company was unable to provide the requested pharmacokinetic absorption data.

Clobex Shampoo has been demonstrated as an effective and well tolerated topical treatment for moderate to severe scalp psoriasis with up to 8 years of clinical experience as a registered product internationally. Clobetasol propionate is currently prescribed in Australia as an extemporaneously compounded product due to its recognised effectiveness to treat the symptoms of moderate to severe psoriasis. It is considered to be a valuable treatment option for a patient population which frequently experiences significant discomfort and difficulties associated with social acceptance. The availability of Clobex in Australia as a treatment option is supported by dermatologists who currently prescribe compounded clobetasol propionate to alleviate the symptoms of psoriasis.

Galderma wishes to address the issues raised in the Delegate's proposed actions dated 1 November 2012 relating to the PQuality data, Product Information and Consumer Medicine Information amendments and Clinical data.

1. Quality data

Following the TGA evaluation of the Clobex shampoo registration application, Galderma performed a new stress stability study on Clobex Shampoo 0.05%. Results of this stress stability data, originally expected in December 2012, are now available and presented below.

The objective of this study was to generate additional data in order to demonstrate the stability indicating nature of the current analytical procedure used for the determination of Clobetasol propionate and related substances in Clobex Shampoo (Method AC.02.ATP.0241.R01.2).

The study was conducted on Clobex Shampoo 0.05% and Clobex Shampoo placebo. The following degradation conditions were applied:

- Heat exposure: Clobex Shampoo 0.05% and Placebo packaged in amber glass vials closed with chlorobutyl cap and aluminum capsule. Samples stored at 70°C for 7 and 14 days and others kept under refrigerated conditions and used as control.
- Light exposure: Clobex Shampoo 0.05% and Placebo stored in quartz cells and exposed to light in a Suntest chamber under International Conference on Harmonization (ICH) conditions. Samples protected with aluminum placed in the Suntest chamber and used as control.
- Oxidative conditions: Clobex Shampoo 0.05% and Placebo aliquots treated with 10% hydrogen peroxide and stored at room temperature for 24 hours. Untreated samples were used as control.
- Basic conditions: Clobex Shampoo 0.05% and Placebo aliquots adjusted at pH around 9-10 using sodium hydroxide and stored at room temperature for 24 hours with untreated samples as control.
- Acidic conditions: Clobex Shampoo 0.05% and Placebo aliquots adjusted at pH around 2-3 using hydrochloric acid and stored at room temperature for 24 hours with untreated samples as control.

Based on the results generated, the following considerations are noted:

- Light exposure: Clobex Shampoo is totally degraded in ICH extreme degradation conditions. Only two additional peaks were reported (RRT 0.64 and RRT 1.09). Mass balance is not reached, which can be explained by the fact that some of the impurities do not absorb in UV. This is not considered a critical point as the formulation is protected by its primary packaging.
- Acidic and oxidative conditions: This study confirms that no degradation was induced by acid treatment or oxidative condition for Clobex Shampoo.
- Basic conditions: Around 16% degradation is reported for Clobex Shampoo treated with sodium hydroxide. Related compound A significantly increases and two additional peaks are reported (RRT 0.68 (Clobetasol) and RRT 0.75). Mass balance is reached up to 99.7%. This confirms that in basic conditions, the content in Clobetasol 17-propionate decreases and in parallel impurities are observed.
- Heat exposure: Clobex Shampoo presents a degradation of around 10%. Related compound A is observed and increases with study duration. Three additional peaks are reported (RRT 0.08, RRT 0.76 (Clobetasol propionate related compound B) and RRT 1.18). Mass balance was found at 98.8% after 7 days at 70°C. The content in Clobetasol 17-propionate decreases and in parallel impurities are observed. This is confirmed by the results obtained after 14 days at 70°C.

In conclusion, the packaging protects the formulation from its high sensitivity to light. The absence of sensitivity of the formulation is confirmed in acidic and oxidative conditions. The results obtained in basic and heat conditions prove the stability indicating nature of the method.

The sponsor considers that the stability data presented were obtained using suitable analytical methods and support 36 months of shelf life.

2. Product Information and Consumer Medicine Information amendments

The proposed Product Information, Consumer Medicine Information and product labels have been amended to reflect the changes noted by the evaluators and the TGA Delegate.

The PCE's comments regarding the measurement of the recommended dose of Clobex Shampoo have been noted. The sponsor commits to add a measuring device with Clobex Shampoo. The sponsor proposes to address this concern by means of a variation submission to the TGA in early 2013. The *Dosage and Administration* information in the PI and CMI will be amended at that time to reflect this change.

The section "*Use in children*" in the Product Information has been amended.

3. Clinical data

Subjects aged from 12 to 17 years old have been included in three efficacy studies. Studies 18075 and 18076 were the two vehicle-controlled Phase III studies in subjects aged 12 years and older with moderate to severe scalp psoriasis. Study 2638 was an active-controlled Phase III study and also enrolled subjects 12 years and older with moderate to severe scalp psoriasis. The table below summarises the number of patients aged from 12 to 17 years old receiving clobetasol propionate (CP) shampoo in each study.

Table 3. Study details

Efficacy study number	Title	Number of subjects from 12 to 17 years old	
		Treated with CP shampoo	Control-group
Study 18075	A randomized, double-blind, parallel group evaluation of clobetasol propionate shampoo, 0.05% versus its vehicle – an efficacy and safety study in subjects with scalp psoriasis	N=3	N=3
Study 18076	A randomized, double-blind, parallel group evaluation of clobetasol propionate shampoo, 0.05% versus its vehicle – an efficacy and safety study in subjects with scalp psoriasis	N=2	N=2
Study 2638	Parallel group comparison of 4-week treatment with clobetasol 17-propionate 0.05% shampoo versus calcipotriol solution 0.005% - an efficacy and safety study in subjects with scalp psoriasis	N=1 (+ one 10 years old subject)	N=2

In the efficacy clinical development program, 6 subjects from 12 to 17 years old were exposed to CP shampoo in efficacy studies. One 10 year old subject was also enrolled in Study 2638 (protocol violation) and exposed to CP shampoo. Safety study 18070 was specifically designed to address the risk of HPA axis suppression in the 12 to 17 years population where 19 subjects were exposed.

The section "Use in children" of the Product Information has been amended as follows:

"The experience in the paediatric population is limited. CLOBEX shampoo is not recommended for use in children and adolescents below 18 years of age. 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"

Off-treatment duration

Psoriasis is a chronic, relapsing, inflammatory skin disease. Treatment of localised psoriasis such as scalp psoriasis usually relies on topical treatments. The initial clearing phase mostly requires the use of high potency corticosteroids such as clobetasol propionate (CP). Once a marked improvement is observed, the strength of the corticosteroid and/or the frequency of application are gradually reduced over several weeks (transition phase), until complete clearance. At this time, the treatment is often discontinued. Patients are usually instructed to resume treatment as soon as the disease reappears. Alternatively, a maintenance treatment may be recommended to increase the duration of the remission, particularly in patients who experience frequent relapses.

Maintenance treatment typically relies on vitamin D3 analogues or intermittent use of corticosteroids[17,18] However, there are no available data comparing the efficacy and safety of intermittent treatment (as needed) versus continuous maintenance treatment in the long term management of psoriasis. This is classically a decision taken by the physician, in agreement with the patient, based on the disease severity and history and the impact of the disease and treatment on the patient's quality of life.

There are, in particular, limited data concerning the impact of repeated treatments with topical corticosteroids on HPA axis suppression in psoriasis patients. One reason, as mentioned above, is the absence of a treatment algorithm on which to base the analysis, as long term management is decided by the physician on a case by case basis. Another reason may be technical: the repeated administration of cosyntropin to perform regular (e.g. monthly) HPA axis stimulation tests could in itself prevent the suppression to happen.

What is known is that laboratory HPA axis suppression is frequently observed after two to four weeks of treatment with high potency corticosteroids. Our review of available data concerning various CP formulations revealed that laboratory HPA axis suppression can be observed in up to 71% of patients (depending on the dose and duration of treatment but also on the criteria used to define HPA axis suppression) (see Table 4, below). However, it is important to note that laboratory HPA axis suppression following treatment with leave-on CP formulations is usually transient and readily reversible after cessation of treatment.

[17] Katz H.I. *et al*., Intermittent corticosteroid maintenance treatment of psoriasis : a double-blind multicentre trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. Dermatologica 1991; 183:269-274

[18] Del Rosso J.& Friedlander S.F. Corticosteroids: Options in the era of Steroid Sparing therapy. J Am Acad Dermatol 2005 53 s50-8

Table 4. Incidence of HPA axis suppression with various CP products

Study	Clobetasol Propionate 0.05% Product	Daily dose (prescribed)	Duration of treatment before test	Criteria to define HPA axis suppression	Incidence of HPA suppression
Glaxo Study No. TME-112 (NDA 20-340)	Temovate Cream	3g	4 days	Pre-stimulation serum cortisol level ≤10 µg/100 mL and/or 60-minute post-stimulation serum cortisol level ≤18 µg/100 mL.	4/6 (67%)
	Temovate E® Emollient Cream	3g	4 days		2/6 (33%)
Glaxo Study No. TME-102 (NDA 20-337)	Temovate Gel	3g	4 days	Pre-stimulation serum cortisol level ≤10 µg/100 mL and/or 60-minute post-stimulation serum cortisol level ≤18 µg/100 mL.	3/7 (43%)
	Temovate Cream	3g	4 days		5/7 (71%)
Connetics Study CPCD.C.003 (NDA 21-142)	Olux Foam	7g	1 week 2 weeks	Pre-stimulation serum cortisol level ≤5 µg/100 mL or 30-minute post-stimulation serum cortisol level ≤18 µg/100 mL.	3/13 (23%) 3/13 (23%)
	Temovate Ointment	7g	1 week 2 weeks		3/13 (23%) 5/13 (38%)
Connectics Study CPE.C.201 (NDA 22-013)	Primolux Foam	≤ 7.2g (max 50g/week)	2 weeks	30-minute post-stimulation serum cortisol level ≤18 µg/100 mL.	2/12 (17%)
Galderma study CR.U9708	Clobex lotion	7.2g	1 week 2 weeks 4 weeks	Pre-stimulation serum cortisol level ≤10 µg/100 mLand 60-minute post-stimulation serum cortisol level ≤18 µg/100 mL.	3/11 (27%) 2/11 (18%) 2/11 (18%)
	Temovate E® Emollient Cream	7.2g	1 week 2 weeks 4 weeks		0/11 (0%) 0/11 (0%) 1/11 (8%)

For all marketed formulations of CP globally, it is agreed that the dose should not exceed 50 g/week and that treatment should be limited to a maximum of 4 consecutive weeks and restricted to adults. There are currently no other restrictions, such as minimal duration between two courses of treatment, for the safe use of leave-on CP formulations in psoriasis. There have been published case reports in which adrenal insufficiency has been recorded after stopping treatment with potent topical corticosteroids but these were invariably secondary to prolonged use (over four continuous weeks) of excessive doses and frequently in the paediatric population.[19]

The scalp is a common site of disease involvement during psoriasis which is difficult to treat as the application of creams or ointments directly onto lesions is hampered by the overlying hair. Other types of formulations such as lotions, gels and foams may leave the hair sticky and greasy. Due to the limitations of current therapies, compliance with treatments for the scalp is frequently low. In order to provide patients with scalp psoriasis and the physicians who treat them a more convenient and efficient topical treatment, Galderma has developed Clobex shampoo.

Clobex Shampoo meets two objectives:

- To reduce the systemic distribution of CP while maintaining clinical efficacy, through the strategy of short contact corticosteroid therapy (duration of application of 15 minutes followed by a thorough rinsing of the hair and scalp)

[19] Tempark T.et al. Exogenous Cushing's syndrome due to topical corticosteroid application: case report and review literature. Endr (2010) 38:328-334

- To provide a product which is easy to integrate in the daily routine as it is easy to apply to the hairy scalp and easy to rinse off, due to its formulation as a shampoo.

The short contact therapy is based on the rationale that after application of very potent corticosteroids, cutaneous receptors to corticosteroids might be saturated in a short time and that longer periods of exposure might not be needed for efficacy, but might result in higher systemic exposure.[20] As illustrated *in vitro* (Study 1.CG.03.SRE.4651), the short contact reduces the possibility of systemic absorption of CP. The percentage of absorption of CP following Clobex shampoo application on human skin was compared to that of Temovate Scalp, a US marketed formulation of CP. The application of 10 mg of Clobex shampoo on human skin for 15 minutes followed by rinsing resulted in 0.1% penetration of the applied dose. When 10 mg of Temovate® Scalp was applied for 16 hours, 7% of the applied dose penetrated (70 times more).

Galderma has conducted two studies to assess the effect of Clobex shampoo on the HPA axis, using an Adrenocorticotropic Hormone (ACTH) stimulation test, one in adults (Study 2620[21]) and the other in adolescents (Study 18070). Both studies evaluated the effect of daily applications for 4 weeks in subjects with moderate to severe scalp psoriasis and concluded that no evidence of HPA axis suppression was observable using this regimen.

Regarding post marketing data, two cases of HPA axis suppression have been reported with Clobex shampoo. In these two cases, the product had been used for an excessive duration of 3 months and 4 months. Therefore, according to all available data, Galderma does not expect any case of HPA axis suppression if the product is used according to recommendations described in the PI.

Conclusion

It has been demonstrated that Clobex Shampoo is effective and can be safely used for the treatment of moderate to severe scalp psoriasis with a maximum treatment duration of 4 consecutive weeks. Systemic exposure appears to be lower than that obtained with currently marketed leave-on CP formulations as illustrated by the absence of HPA axis suppression in the trials. However, as for all marketed topical corticosteroids formulations, duration of treatment and the decision to resume treatment remains a physician's decision, based on several parameters such as the disease severity, history and the impact on quality of life.

These conclusions are also consistent with the recommendation by the TGA nonclinical and clinical evaluators who reported a positive risk benefit profile for Clobex Shampoo. The safety and effectiveness of the product is further supported by extensive clinical experience internationally.

The availability of Clobex Shampoo as a treatment option for moderate to severe scalp psoriasis would address a need of prescribers and patients with an effective, well tolerated and easily administered formulation which would be expected to improve patient compliance and quality of life.

[20] Stoughton R.B.& Wullich K. Relation of Application time to Bioactivity of a Potent Topical Glucocorticoide formulation. J Am Acad Dermatol 1990 Vol 22 p1038

[21] Andres P.A. *et al,* Short-term Safety Assessment of clobetasol Propionate 0.05% Shampoo: Hypothalamic-Pituitary Adrenal Axis Suppression, Atrophogenicity, and ocular Safety in Subjects with Scalp Psoriasis Journal Drugs. Dermatol 2006 5(4) p328-32 Also presented as Study 2620

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile for the following indication:

Topical treatment of moderate to severe scalp psoriasis

In making this recommendation, the ACPM noted that the issues associated with the quality and stability of the product had been addressed to the satisfaction of the TGA.

The ACPM expressed concern that the potential for safety issues in regard to reproducibility of the recommended dose was high and agreed with the Pharmaceutical Subcommittee (PSC) that a simple and reliable dispenser device to deliver a measured dose was required. In particular, due to the nature of the condition, patients may be exposed to consistently high doses; therefore due consideration should be given to the potential of lengthy withdrawal period in terms of Hypo Thalamic-Adrenal (HPA) axis suppression.

In addition, the ACPM expressed concern that in view of the long term nature of this condition and risk profile, the submission of only 4 week treatment data is inadequate.

The ACPM advised that the amendments to the Product Information (PI) and Consumer Medicine Information (CMI) should include the following:

- Statements in the *Dosage and Administration / Precautions* sections of the CMI to ensure patients are aware of the appropriate response to eye irritation, (for example, first aid processes), as the current wording is inadequate.
- A statement in the *Precautions* section of the PI and CMI to ensure prescribers and patients have due regard for the safety concerns associated with the potential long term and large volume use of this product.

The ACPM advised that the sponsor should be required to conduct studies on use over 12 months, including duration of effect, interval to retreatment and surveillance mechanisms for HPA axis suppression as a condition of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Clobex Clobetasol propionate 500 microgram/g Shampoo Application Bottle, indicated for:

Topical treatment of moderate to severe scalp psoriasis in adults.

Specific conditions applying to these therapeutic goods

1. The implementation in Australia of the Clobex Clobetasol propionate 500 microgram/g shampoo Risk Management Plan included with submission PM-2011-

01596-3-51, identified as the EU RMP Version 2 dated 11 May 2012, and any subsequent revisions as agreed with the TGA and its Office of Product Review.

2. It is a further condition of registration that the sponsor submits the results of clinical studies on use over 12 months, including duration of effect, interval to re-treatrnent and surveillance mechanisms for HPA axis suppression, to the TGA as soon as the data become available.
3. Prior to these goods being available for marketing the sponsor is required to submit to the TGA the specifications of a simple and reliable dispensing device, to be supplied with the product that allows for reproducibility of the recommended dose.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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