



Public Assessment Report

Decentralised Procedure

Etrivex 500 micrograms/g shampoo

UK/H/872/01

Galderma (UK) Limited

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Galderma (UK) Limited a Marketing Authorisation (licence) for the medicinal product Etrivex 500 micrograms/g shampoo (Product Licence number: 10590/0052). This medicine is available on prescription only.

Etrivex shampoo contains a steroid that can help reduce redness, itchiness and inflammation of the scalp.

The data submitted in support of the application for Etrivex 500 micrograms/g shampoo raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Etrivex 500 micrograms/g shampoo
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 Article 8.3 Level 4 Chemical substance Level 5 Prescription only
Name(s) of the active substance(s) (INN)	Clobetasol propionate
Pharmacotherapeutic classification (ATC code)	Corticosteroids, dermatological preparations (D07AD01)
Pharmaceutical form and strength(s)	Viscous, translucent, colourless to pale yellow liquid shampoo. One gram contains 500 micrograms of clobetasol propionate
Reference numbers for the Mutual Recognition Procedure	UK/H/872/01/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IS, IT, LU, NL, NO, PL, PT, SE, SK
Date of start of the procedure	9 January 2006
End date of decentralised procedure	28 November 2006
Marketing Authorisation Number(s)	PL 10590/0052
Name and address of the authorisation holder	Galderma (UK) Limited Galderma House Church Lane Kings Langley Herts, WD4 8JP UK

Module 2

Summary of product characteristics

1 NAME OF THE MEDICINAL PRODUCT

Etrivex 500 micrograms/g shampoo

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of shampoo contains 500 micrograms of clobetasol propionate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Shampoo.

Viscous, translucent, colourless to pale yellow liquid shampoo with alcoholic odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of moderate scalp psoriasis in adults.

4.2 Posology and method of administration

For cutaneous use on the scalp only.

Etrivex 500 micrograms/g shampoo should be applied directly on dry scalp once daily taking care to well cover and massage the lesions. An amount equivalent to around a half tablespoon (around 7.5 ml) per application is sufficient to cover all the scalp. Etrivex 500 micrograms/g shampoo should be then kept in place without covering for 15 minutes before rinsing. Hands should be washed carefully after application. After 15 minutes, the product must be rinsed with water and / or hair can be washed by using an additional amount of regular shampoo if needed to facilitate washing. Then, hair can be dried as usual.

The 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. If no improvement is seen within four weeks, reassessment of the diagnosis may be necessary.

Repeated courses of Etrivex 500 micrograms/g shampoo may be used to control exacerbations provided the patient is under regular medical supervision.

Paediatric population

The experience in the paediatric population is limited. Etrivex 500 micrograms/g shampoo is not recommended for use in children and adolescents below 18 years of age. It is contraindicated in children under 2 years of age (see sections 4.3 and 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Skin areas affected by bacterial, viral (varicella, herpes simplex, herpes zoster), fungal or parasitic infections and specific skin diseases (skin tuberculosis, skin diseases caused by lues).
- Etrivex 500 micrograms/g shampoo must not be applied to the eye (risk of glaucoma) or to ulcerous wounds.
- Children under 2 years of age

4.4 Special warnings and precautions for use

Topical corticosteroids should be used with caution for a number of reasons including post treatment rebound relapses, development of tolerance (tachyphylaxis) and development of local or systemic toxicity. In rare instances, treatment of psoriasis with corticosteroids (or its withdrawal) is thought to have provoked generalised pustular psoriasis in case of intensive and prolonged topical use. In very rare cases, hypersensitivity to corticosteroids can be observed. This can be suspected in case of resistance to treatment.

In general, long-term continuous therapy with corticosteroids, use of occlusive moccaps or treatment of children can lead to a higher risk of systemic effects. In such cases, medical supervision should be increased and patients may be evaluated periodically for evidence of HPA axis suppression. Such systemic effects disappear when treatment is stopped. However, abrupt discontinuation can lead to acute adrenal insufficiency, especially in children. If Etrivex 500 micrograms/g shampoo is required for use in children and adolescents below 18 years of age, it is recommended that the treatment should be reviewed weekly.

Etrivex 500 micrograms/g shampoo is only intended for the treatment of scalp psoriasis and should not be used to treat other skin areas. In particular, Etrivex 500 micrograms/g shampoo is not recommended for use in the face, eyelids, intertriginous areas (axillae and genitoanal regions)

and on other erosive skin surfaces as this could increase the risk of topical adverse events such as atrophic changes, telangectasia or cortico-induced dermatitis.

If Etrivex 500 micrograms/g shampoo does enter the eye, the affected eye should be rinsed with copious amounts of water.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of topical clobetasol propionate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Etrivex 500 micrograms/g shampoo should not be used during pregnancy unless clearly necessary.

Lactation

Systemically administered corticosteroids pass into breast milk. Damage to the infant is not reported to date. Nevertheless, as there are no adequate data on the possible milk transfer of topical clobetasol propionate and its biological or clinical repercussions, Etrivex 500 micrograms/g shampoo should not be prescribed to breastfeeding women unless clearly indicated.

4.7 Effects on ability to drive and use machines

As a topical corticosteroid, Etrivex 500 micrograms/g shampoo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

During clinical development of Etrivex 500 micrograms/g shampoo, in a total of 558 patients receiving Etrivex 500 micrograms/g shampoo, the most commonly reported adverse drug reaction was skin discomfort. Its incidence was about 5%. Most adverse events were rated as mild to moderate and they were not affected by race or gender. Clinical signs of irritation were uncommon (0.5%). No serious drug-related adverse events were reported during any of the clinical trials.

If signs of local intolerance appear, application should be suspended until they disappear. If signs of hypersensitivity appear, application should be stopped immediately.

The table below reports the adverse reactions related to treatment by body system and by absolute frequency:

Body System	Incidence	Adverse reactions
Skin and subcutaneous tissue disorders	Common ($\geq 1/100$, $< 1/10$)	Skin discomfort Acne/folliculitis
	Uncommon ($\geq 1/1000$, $<1/100$)	Local signs of irritation Pruritus Urticaria Telangiectasia Skin atrophy
Eye disorders	Common ($\geq 1/100$, $< 1/10$)	Eye stinging/burning

As a class attribution, prolonged use of topical corticosteroids, treatment of extensive areas or use of large amounts can result in sufficient systemic absorption to produce the features of hypercortisolism (Cushing syndrome) or of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression. Should HPA axis suppression occur, it is likely to be transient with a rapid return to normal values. However, as Etrivex 500 micrograms/g shampoo is to be kept in place for only 15 minutes before rinsing, systemic absorption is seldom observed (see section 5.2) and therefore, the risk of appearance of HPA axis suppression is very low compared to non rinsed potent corticosteroids products. No HPA axis suppression has been observed during clinical trials with Etrivex 500 micrograms/g shampoo.

Prolonged and/or intensive treatment with potent corticosteroid preparations may cause local atrophic changes, such as local skin atrophy, striae, telangiectasia, erythema, purpura, contact dermatitis. When applied to the face, very potent corticosteroids can induce perioral dermatitis, skin atrophy or worsen rosacea. During development of Etrivex 500 micrograms/g shampoo, skin atrophy was assessed using ultrasound measurement of skin thickness in a specific clinical trial involving 13 patients. After 4 weeks of treatment with Etrivex 500 micrograms/g shampoo, no skin thinning was observed.

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

4.9 Overdose

Acute overdose is very unlikely to occur, however, in the case of chronic overdose or misuse, the features of hypercortisolism may appear and in this situation, treatment should be discontinued gradually. However, because of the risk of acute adrenal suppression, this should be done under medical supervision.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids, Very Potent (Group IV)

ATC code: D07AD01

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of topical corticosteroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

5.2 Pharmacokinetic properties

In vitro liberation –penetration studies on human skin showed that only a small percentage (0.1 %) of the applied dose of Etrivex Shampoo can be found in the epidermis (including the stratum corneum) when applied for 15 minutes and then rinsed. The very low topical absorption of clobetasol propionate from Etrivex Shampoo when applied according to the recommended clinical use (15 minutes before rinse off) resulted in negligible systemic exposure in animal studies and in clinical trials. Available clinical data revealed that only 1 of 141 subjects had a quantifiable clobetasol propionate plasma concentration (0.43 ng/ml).

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

5.3 Preclinical safety data

Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single, repeated dose toxicity and genotoxicity. The carcinogenicity of clobetasol has not been studied.

In rabbits, Etrivex Shampoo was slightly irritating to the skin and eyes, but no delayed-type hypersensitivity was seen on guinea pigs' skin.

In developmental toxicity studies in the rabbit and the mouse, clobetasol propionate was shown to be teratogenic when administered subcutaneously at low doses. In a topical embryotoxicity study of clobetasol in the rat, foetal immaturity and skeletal and visceral malformations were observed at relatively low dosage levels. In addition to malformations, studies in animals exposed to high systemic levels of glucocorticoids during pregnancy have also shown other effects on the offspring, such as intrauterine growth retardation.

The clinical relevance of the effects of clobetasol and other corticosteroids in developmental animal studies is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Coco alkyl dimethyl betaine
Sodium laurethsulfate
Polyquaternium-10
Sodium citrate
Citric acid monohydrate
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years
Shelf life after first opening: 4 weeks

6.4 Special precautions for storage

Store in the original container

6.5 Nature and contents of container

The product is packaged in high density polyethylene (HDPE) bottles fitted with polypropylene screw closures. Bottles contain 15 ml, 60 ml or 125 ml of shampoo.

1 g of shampoo corresponds to 1 millilitre of shampoo.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Galderma (UK) Limited
Galderma House
Church Lane
Kings Langley
Herts, WD4 8JP

8 MARKETING AUTHORISATION NUMBER(S)

PL 10590/0052

9 DATE OF FIRST AUTHORISATION

26 February 2007

10 DATE OF REVISION OF THE TEXT

28 November 2006

Module 3

Product Information Leaflet

Etrivex 500 micrograms/g shampoo

clobetasol propionate

SHAMPOO



Etrivex 500 micrograms/g shampoo
Clobetasol propionate

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You might need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What is Etrivex 500 micrograms/g shampoo and what it is used for
2. Before you use Etrivex 500 micrograms/g shampoo
3. How to use Etrivex 500 micrograms/g shampoo
4. Possible side effects
5. How to store Etrivex 500 micrograms/g shampoo
6. Further information

1. What is Etrivex 500 micrograms/g Shampoo and what it is used for

Etrivex shampoo contains the active substance called clobetasol propionate; it belongs to a group of medicines called topical corticosteroids (or steroids). Topical corticosteroids are further classified into groups depending on their strength; clobetasol propionate is a very strong corticosteroid. "Topical" means that it should only be applied to the surface of the skin. Topical steroids reduce the redness, itchiness and inflammation associated with skin conditions.

Scalp psoriasis is caused by the skin cells of your scalp being produced too quickly. Etrivex shampoo is used to treat scalp psoriasis of moderate intensity in adults.

2. Before you use Etrivex 500 micrograms/g shampoo

Do not use Etrivex 500 micrograms/g shampoo

- if you have been told that you are allergic (hypersensitive) to Clobetasol propionate or any of the other ingredients in Etrivex shampoo. Please check by reading the list of ingredients below. If you answer yes, you must inform your doctor before starting treatment.
- If you have bacterial, viral, fungal or parasitic skin infections such as cold sores, varicella (chicken pox), herpes zoster (shingles), impetigo (type of rash on the face), ringworm, athlete's foot, thrush, skin tuberculosis or skin disease caused by syphilis.
- If you have ulcerous wounds (weeping wounds) on your scalp
- In children under two years old
- Do not apply Etrivex shampoo in the eyes (risk of glaucoma which is high pressure in the eye)

Take special care with Etrivex 500 micrograms/g shampoo

- If this product has been prescribed for a child or adolescent below 18 years of age, you must check with your doctor every week before continuing to use this product.
- When using Etrivex shampoo, it must only be used on the scalp, do not use it as a regular shampoo or on other areas of the body and do not use Etrivex shampoo as a shower gel, body wash or bath foam.
- When treating the scalp with Etrivex shampoo you must not cover the area being treated, for example: a shower cap must not be used as it may make the active substance pass through the skin and affect the other parts of the body.
- When using Etrivex shampoo, avoid contact with the face, eyelids, axillae (armpits), erosive skin (chapped skin) surface and genital regions. Rinse off immediately with water if any product runs from the scalp.
- If you get Etrivex shampoo in your eye(s), wash the affected eye thoroughly with water. If any irritation persists, please seek advice from your doctor.
- If you do not notice an improvement of your scalp psoriasis, please see your doctor.

Using other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without a prescription.

Pregnancy and Breast-feeding:

Ask your doctor or pharmacist for advice before taking any medicine. Do not use Etrivex shampoo if you are pregnant or breastfeeding unless your doctor clearly tells you to.

Driving and using machines:

Etrivex shampoo has no or very little influence on the ability to drive and use machines.

3. How to use Etrivex 500 micrograms/g Shampoo

Always use Etrivex Shampoo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual daily dose per application is an amount equivalent to around a half tablespoon (around 7.5 ml) sufficient to cover the entire scalp.

Unless your doctor has instructed otherwise, wash your hands and apply Etrivex Shampoo directly to your dry scalp once daily taking care to well cover and massage the affected areas. Avoid using large amounts of Etrivex Shampoo, only use enough to cover your scalp when dry. Wash your hands carefully after application. Leave the product to work for 15 minutes without covering, and then add water, rinse and dry your hair as usual. Your regular shampoo can be used if more shampoo is required to wash your hair. Do not add more of Etrivex shampoo to your hair.

Your doctor will tell you how long you need to use Etrivex shampoo for to control your scalp psoriasis. Treatment should not normally continue for more than 4 weeks. However, if your scalp psoriasis is significantly improved before the end of treatment, please see your doctor. On the contrary, if no improvement is seen by the end of the treatment, please tell your doctor. This treatment needs careful supervision; you should let your doctor review your progress at regular intervals. Do not use Etrivex shampoo for longer than your doctor tells you.

Nonetheless, your doctor may ask you to use Etrivex shampoo again in the future following a period of no use.

If this product has been prescribed for children or adolescents between the ages of 2 and 18 years, the instructions given by your doctor must be followed. You must check with the doctor every week before continuing treatment.

If you have used Etrivex shampoo for much longer than you should, please see your doctor. This product is for use on the scalp only. Do not swallow it. If you accidentally do so, small amounts are not harmful. If you are not sure, seek immediate medical advice.

If you forget to use Etrivex shampoo, do not use a double dose on the next application to make up for a forgotten dose. Go back to your regular schedule. If you miss several doses, tell your doctor.

If you stop using Etrivex shampoo, please see your doctor. It may be that worsening of the disease occurs when treatment with Etrivex shampoo is stopped, especially if it has been used for a long time. Tell your doctor if you observe such a worsening of your skin conditions.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Etrivex shampoo can have side effects, although not everybody gets them.

- The following are common side effects affecting less than 1 in 10 people: skin discomfort, acne and eye burning or stinging.
- The following are uncommon side effects affecting fewer than 1 in a 100 people : irritation, itching, urticaria, visible small vessels or thinning skin around the treated areas.

These are generally of a mild to moderate.

- If you have a burning sensation or redness to the areas that have been treated, do not use Etrivex shampoo until these symptoms have disappeared.
- Stop using the medicine and tell your doctor as soon as possible if you find your condition gets worse during treatment (this is more likely to happen if you have been using Etrivex shampoo longer than prescribed) or if you experience swelling of the eyelids, face or lips as you may be allergic to the product or have a skin infection.
- Using large amounts or keeping the product on the scalp for more than 15 minutes may:
 - cause the skin to become thinner so that it can damage more easily
 - allow the active substance to pass through the skin ; this can affect other parts of the body especially in children, and during pregnancy
- Repeated courses of topical steroids over a long time may sometimes cause acne, pustular eruptions (big pimples) and changes in hair growth and skin colour. Striae (stretch marks), purpura (bruising), surface veins, erythema (skin redness) and contact dermatitis (local allergic reactions) may become noticeable
- If you have rosacea (severe flushing of skin on and around the nose) the application of Etrivex shampoo on the face may cause your rosacea to worsen.
- Application of Etrivex shampoo on the face may induce perioral dermatitis (spotty red rash around the mouth).
- Application of Etrivex Shampoo to the skin may cause thinning of skin and therefore it should never be used on the face or on other areas of the skin than the scalp.
- If you have any unusual discomfort that you do not understand, tell your doctor as soon as possible.

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. How to store Etrivex 500 micrograms/g Shampoo

Keep out of the reach and sight of children.

Do not use Etrivex Shampoo after the expiry date which is stated on the bottle and the carton. The expiry date refers to the last day of that month.

Store in the original plastic bottle.

Discard the bottle 4 weeks after first opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Etrivex Shampoo contains:

The active substance is clobetasol propionate

Each gram (millilitre) of Etrivex Shampoo contains 500 micrograms of the active ingredient Clobetasol propionate.

The other ingredients are: ethanol, coco alkyl dimethyl betaine, sodium laureth sulfate, polyquaternium-10, sodium citrate, citric acid monohydrate and purified water.

What Etrivex Shampoo looks like and contents of the pack:

Etrivex Shampoo is a thick, semi transparent liquid shampoo with an alcoholic smell that is colourless to pale yellow in appearance.

Etrivex shampoo is available on prescription from your doctor in white high density polyethylene (HDPE) plastic bottles fitted with polypropylene screw closures. Bottles contain 15 ml, 60 ml or 125 ml of shampoo (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder:

Galderma (UK) Ltd.

Kings Langley,

Herts,

WD4 8JP,

UK.

PL 10590/0052

PA 590/23/1

Manufacturer:

Laboratoires Galderma,

Z.I.- Montdésir

74540, Alby-sur-Chéran

France.

This medicinal product is authorised in the Member States under the following names:

United Kingdom, Italy, Ireland and Portugal: Etrivex 500 micrograms/g shampoo

France, Germany, Belgium, Poland, Spain, Hungary, The Netherlands, Sweden, Denmark, Austria, Luxembourg, Iceland, Czech Republic, Norway, Greece, Slovakia and Finland: Clobex 500 micrograms/g shampoo

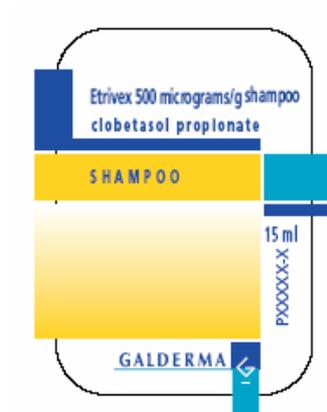
This leaflet was last approved in November 2006.

Module 4

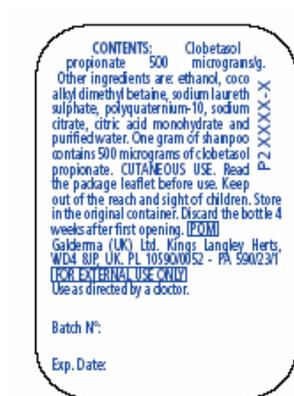
Labelling

15ml bottle:

Front



Back

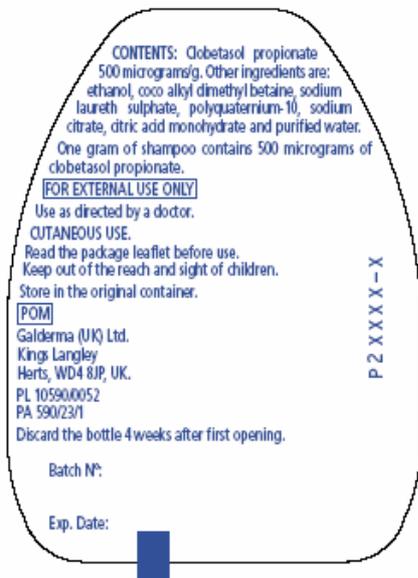


60ml bottle:

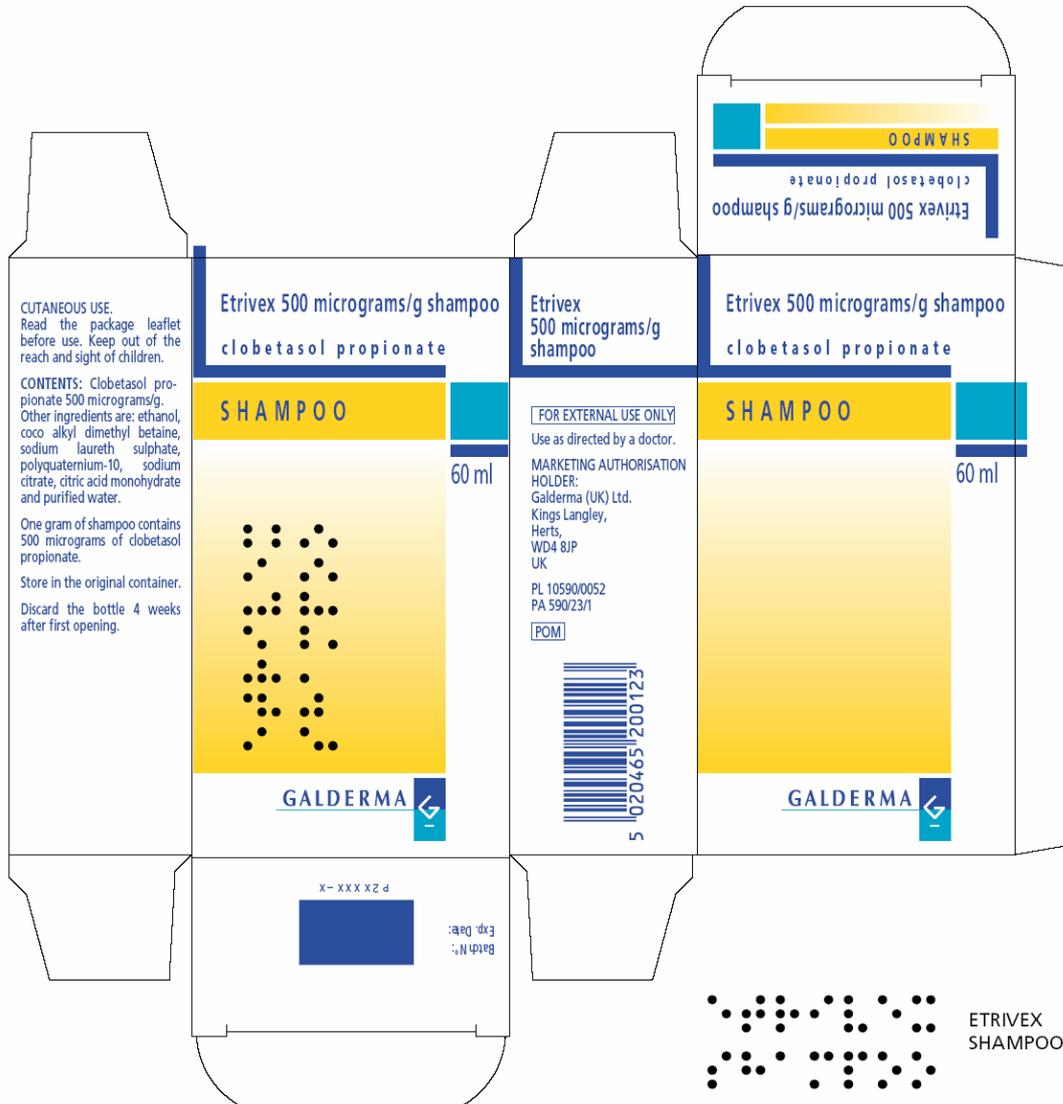
Front



Back

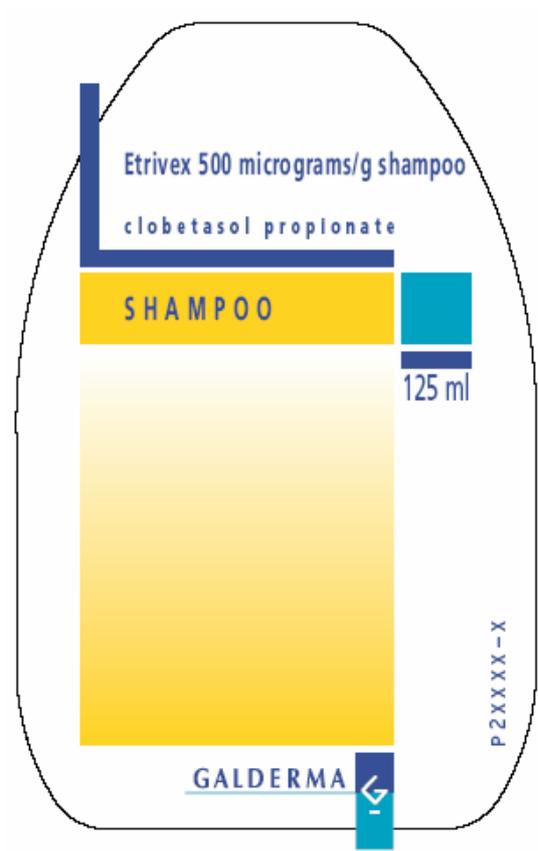


Carton label 60ml:

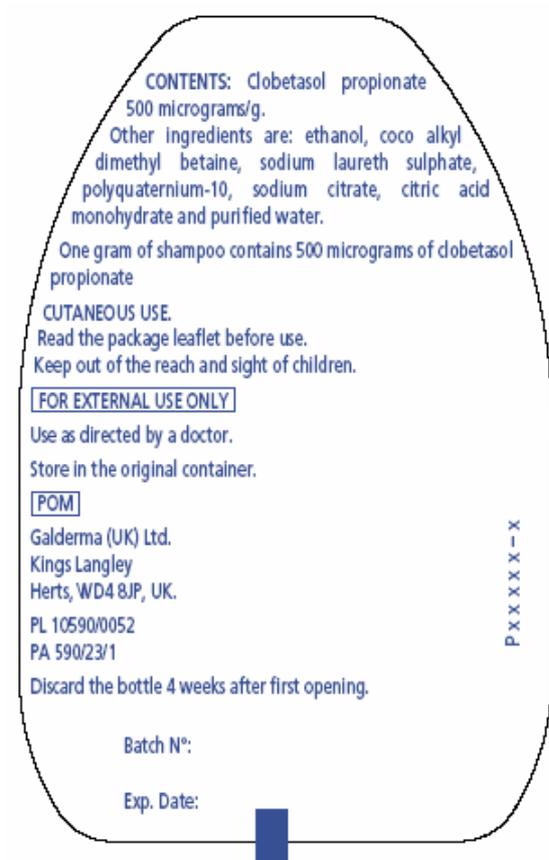


125ml bottle:

Front

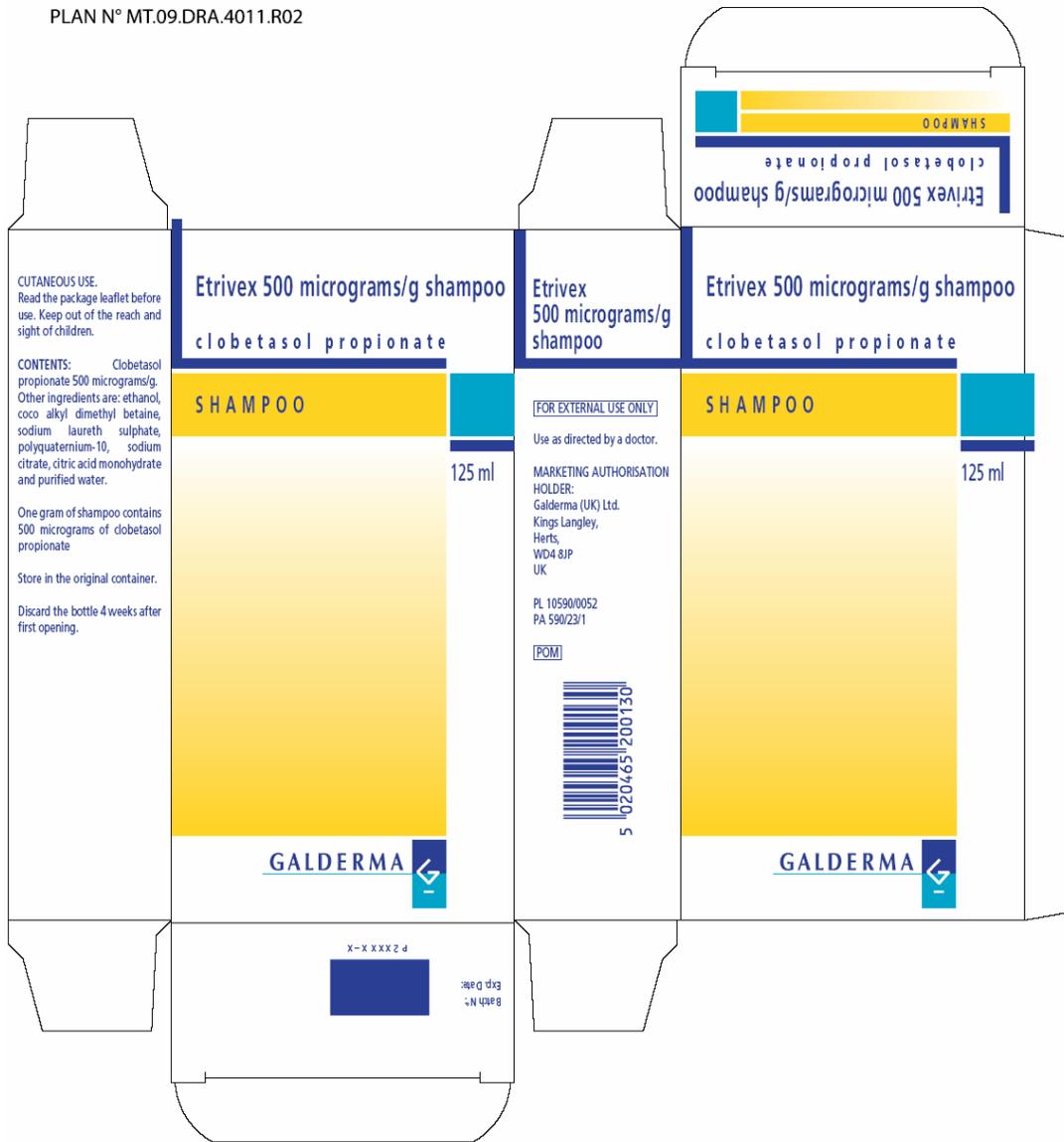


Back



Carton label 125ml:

ETUI VERTICAL 70x34x142
NOUVELLE GAMME 125ML
PLAN N° MT.09.DRA.4011.R02



Module 5

Scientific discussion during initial procedure

I. RECOMMENDATION

Based on the review of the data and the Applicant's responses to questions raised by the RMS and CMSs on quality, safety and efficacy, the RMS considered that the application for Etrivex 500 micrograms/g shampoo in the treatment of scalp psoriasis was approvable.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Clobetasol propionate (CP) is a very potent corticosteroid currently licensed in the EU as a topical treatment for corticoid responsive dermatosis, such as eczema and psoriasis. It is currently available as a cream, ointment, solution, lotion and gel.

Psoriasis is a chronic inflammatory dermatosis affecting 1 to 3% of the population of Western Europe and North America. It involves the scalp in approximately 50% of patients. The scalp is also the sole site of involvement for 25% of patients with psoriasis. In addition to the physical discomfort, it can cause social embarrassment and distress.

Topical corticosteroids are probably the most frequently used treatments for moderate to severe scalp psoriasis and, generally, potent or very potent preparations are recommended. Current formulations (creams, ointments, lotions, gels and foams) are sometimes felt to be inconvenient by patients and compliance is frequently unsatisfactory.

II.2 About the product

Etrivex shampoo is intended to be used in treatment of scalp psoriasis.

The applicant has developed a product containing the very potent corticosteroid, CP, to be applied topically once a day as a shampoo for up to four weeks. The shampoo is applied to the dry scalp with a short contact time of just 15 minutes, without the necessity to avoid unaffected areas, and is then rinsed off. The shampoo has a texture and smell similar to that of other commercially available products normally used for washing hair. In addition to its "convenient" application, the short contact duration (15 minutes) minimises corticosteroid side effects, with an acceptable efficacy profile.

Like other topical corticosteroids, CP has anti-inflammatory and antipruritic properties, although its exact mechanism of action is unclear.

II.3 General comments on the submitted dossier

This application concerns a known active substance (CP) in a new pharmaceutical form (shampoo) and it has been submitted under article 8(3) of Directive 2001/83/EC.

The dossier contains new quality, preclinical and clinical data based on the product and is of a satisfactory standard.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All clinical studies were performed in compliance with the International Conference on Harmonisation of Good Clinical Practice (GCP) and in accordance with the ethical principles laid down in the Declaration of Helsinki.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to CP are of sufficient quality in view of current European regulatory requirements.

The control tests and specifications for the drug substance are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The manufacturing process has been described with relevant in-process controls. Process validation has been conducted on production scale batches at the proposed manufacturing site.

Relevant certification has been provided for the pharmacopoeia and non-pharmacopoeia excipients.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guidelines. The control tests and specifications for the drug product are adequately drawn up.

The proposed shelf-life of 3 years for the drug product, with a shelf life of 4 weeks after first opening, is considered acceptable.

III.2 Preclinical aspects

Pharmacology

Like other corticosteroids, CP exerts marked anti-inflammatory and anti-proliferative effects in various animal models. Also CP was found to be associated with a number of local adverse effects on the skin, principally due to its antiproliferative effects on keratinocytes and fibroblasts leading to skin thinning and atrophy. Depending on the extent of percutaneous absorption, topical corticosteroid preparations may also induce HPA axis suppression. These local and systemic effects have been extensively studied during the Phase II clinical programme with CP shampoo.

The effects on the CNS and renal systems observed in the safety pharmacology studies only occurred at very high dose levels and using the parenteral route of administration leading to a greater systemic exposure than via the proposed clinical dose and route.

Pharmacokinetics

There was no new information for the distribution, metabolism and excretion of CP.

In vitro, the amounts of CP recovered in human epidermis, including stratum corneum, were higher for Temovate Scalp Application after 16 hours of application than for CP Shampoo after 15 or 30 minutes of application. However, the concentrations of CP in the receptor liquid in both formulations were all below the lower LOQ. In vivo, the percutaneous absorption of CP in the rat was lower than after application of Dermovate Scalp.

Toxicology

CP has potent anti-inflammatory and antiproliferative action both under experimental and therapeutic conditions. Etrivex 500 micrograms/g Shampoo is a short-application therapy in order to reduce systemic exposure whilst local efficacy remains high.

In vitro studies using human skin and in vivo studies in rats showed that very low amounts of clobetasol from CP shampoo 0.05% penetrate into or through skin during the recommended duration of application of the product followed by rinsing. Plasma CP levels have been monitored in four clinical studies and show that systemic exposure to CP from CP shampoo is very low, if it occurs at all.

The toxic effects reported in toxicity studies using the topical or subcutaneous route in the rat were those usually associated with steroid administration. These effects occurred at dose levels that exceeded those that could be achieved under therapeutic conditions. A repeated dose topical study in mini-pigs with CP shampoo 0.05% showed that even after application for 13 consecutive weeks, only minimal irritation and slight to moderate skin atrophy occurred. There was no systemic exposure or toxicity detected in this study.

The reproductive toxicity studies revealed that the teratogenic potential of CP is similar to other corticosteroids, with induction of cleft palate in all species at high dose levels. Recent

epidemiological studies are reported to show a slight association between the use of systemic corticosteroids during the first trimester and the occurrence of cleft lip, with or without cleft palate. As a precautionary measure, the use of topical CP should, therefore, be avoided during pregnancy. As there are no adequate data on the possible milk transfer of topical CP, the shampoo should not be prescribed to breastfeeding women unless clearly indicated.

The eye and skin irritation study and the sensitisation study showed that CP shampoo 0.05% had slight irritating properties but did not elicit delayed type hypersensitivity.

Non-compensial ingredients were tested with the drug product in the 13 week mini-pig study and in a 13 week dermal rat toxicity study with the vehicle. Only minimal skin irritation was reported.

III.3 Clinical aspects

Pharmacokinetics

Absorption of CP was negligible after application of the shampoo, consequently, its distribution, metabolism and excretion have not been discussed.

Pharmacodynamics

The pharmacodynamic activity of the CP shampoo was assessed in a vasoconstrictor assay in humans. This study compared CP shampoo with other well known corticosteroids and confirmed the classification of CP Shampoo as a 'very potent' corticosteroid topical preparation.

Two studies were performed to assess the effect of CP Shampoo on the HPA axis and the results of these studies showed no evidence of HPA axis suppression when CP shampoo is used under the proposed dosage.

Clinical efficacy

Efficacy data was collected from:

- two Phase II studies in patients with scalp psoriasis designed to examine efficacy and tolerability of different scalp conditions and different contact times before rinsing
- two Phase III vehicle-controlled studies designed to show superiority of CP Shampoo over the shampoo vehicle
- three Phase III studies with active-comparator controls. Two were designed to show non-inferiority of CP Shampoo over Daivonex Solution[®] and Polytar[®] Liquid and provided for a pre-planned switch to a demonstration of superiority if non-inferiority was established. The third was designed to show non-inferiority versus Dermoval[®] Gel and superiority versus Shampoo vehicle.

Overall, efficacy has been demonstrated for CP shampoo in moderate to severe scalp psoriasis.

Clinical safety

A total of 900 subjects with scalp psoriasis participated in the phase II and III trials. Four hundred and fifty-one subjects received CP shampoo at the proposed dosage for 4 weeks: 115, vehicle; 61, Dermoval gel; and 40, Polytar liquid. A total of 558 patients received CP shampoo in the phase II and III trials. Any adverse events (AEs) amongst the 900 subjects were recorded and it was concluded that, overall, the safety profile of Etrivex shampoo is acceptable.

Products similar to Etrivex shampoo are currently licensed in several countries, including the USA, and post-marketing surveillance has not revealed safety concerns.

5. Overall conclusion

QUALITY

The important quality characteristics of Etrivex 500 micrograms/g shampoo are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

Pharmacology studies have shown the anti-inflammatory and anti-proliferative properties of this product. The pharmacokinetic data submitted are satisfactory for an application of this type.

Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY

Clinical studies have demonstrated the efficacy of Etrivex 500 micrograms/g shampoo in the treatment of moderate scalp psoriasis

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

Module 6. Steps take after initial procedure

No further steps have yet been taken following initial procedure.