IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0590/022/001
Case No: 2033593

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Galderma (UK) Ltd

Meridien House, **69-71 Clarendon Road**, **Watford**, **Herts WD17 1DS**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Etrivex 500 micrograms/g cutaneous emulsion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **02/08/2007** until .

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Etrivex 500 micrograms/g cutaneous emulsion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of cutaneous emulsion contains 500 micrograms of clobetasol propionate.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cutaneous emulsion
White, fluid emulsion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Topical treatment of moderate to severe plaque-type psoriasis in adults.

4.2 Posology and method of administration

For cutaneous use.

Etrivex 500 micrograms/g cutaneous emulsion should be applied in thin layer without occlusion to the psoriasis affected areas not more than twice per day. It should be rubbed in gently until complete absorption.

The treatment duration should be adapted to the patient (see section 4.4) and limited to maximum 4 weeks. If no improvement is seen within two to four weeks, reassessment of the diagnosis may be necessary. As soon as clinical results are observed, applications should be spaced out or replaced by applications with a dermocorticoid of less potent activity. Therapy should be discontinued when the control is achieved.

Repeated courses of Etrivex 500 micrograms/g cutaneous emulsion may be used to control exacerbations.

Not more than 50 g of cutaneous emulsion should be used per week.

The safety and efficacy of Etrivex 500 micrograms/g cutaneous emulsion have not been evaluated in children; therefore, the use of Etrivex 500 micrograms/g cutaneous emulsion is not recommended in children and adolescents below 18 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), specific skin diseases (skin tuberculosis, skin diseases caused by lues), fungal or parasitic infections, acne vulgaris, rosacea or perioral dermatitis (see section 4.8).
- Etrivex 500 micrograms/g cutaneous emulsion must not be applied to the eye (risk of glaucoma) or to ulcerous wounds.

- Dermatoses in children under 2 years of age, including dermatitis and napkin eruptions.
- Perianal and genital pruritus.

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.

Treatment of large skin areas, use of large amounts of cutaneous emulsion, use of occlusive dressings or treatment of children can lead to a higher risk of systemic effects. In such cases, medical supervision should be increased and patients should be evaluated periodically for evidence of Hypothalamus-Pituitary-Adrenal (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 cutaneous emulsion is required for use in children and adolescents below 18 years of age, it is recommended that the treatment should be reviewed weekly. It should be noted that an infant's napkin may act as an occlusive dressing and therefore Etrivex 500 micrograms/g cutaneous emulsion must not be used in the napkin's area.

Patients with severe liver dysfunction and severe diabetes mellitus should be treated with special caution and closely monitored for side-effects.

Etrivex 500 micrograms/g cutaneous emulsion is not recommended for use in the face, eyelids, intertriginous areas (axillae and genitoanal regions) and on erosive skin surfaces as this could increases the risk of topical adverse events such as atrophic changes, telangiectasia or cortico-induced dermatitis.

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

Etrivex 500 micrograms/g cutaneous emulsion contains propylene glycol as excipient which may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

None reported.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of topical clobetasol propionate in pregnant women. Studies in animal have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Although not demonstrated in all epidemiological studies, a possible association between exposure to glucocorticoids during the first trimester of pregnancy and an increased risk of cleft lip with or without cleft palate in human foetuses was shown. Intrauterine growth retardation has been described in humans and animals for corticoids after systemic exposure.

As a precautionary measure, the use of topical clobetasol propionate should therefore be avoided during pregnancy. If application is clearly necessary and the potential benefit justifies the potential risk to the foetus, the duration of use should be as short as possible and the skin/mucosa area treated should be as small as possible.
Infants born of mothers who received corticoids towards the end of pregnancy are to be observed carefully for signs of hypoadrenalism.

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 cutaneous emulsion 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 cutaneous emulsion has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are: burning/stinging, skin dryness, irritation, erythema, folliculitis, pruritus, skin atrophy and telangiectasia. Their incidence is about 4%. Most adverse events are rated as mild to moderate and they are not affected by race or gender.

No serious drug-related adverse events were reported during any of the clinical trials. These undesirable effects may occur more frequently with the use of occlusive dressings.

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
Cutaneous manifestations	Common (>1/100 , < 1/10)	Skin atrophy, Telangiectasia
	Uncommon (> 1/1000, <1/100)	Burning / stinging, Skin dryness, Irritation, Erythema, Folliculitis, Pruritus

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 axis suppression. Should HPA axis suppression occur, it is likely to be transient with a rapid return to normal values. Such effects are more likely to occur when occlusive dressings are used (see sections 4.2 and 4.4).

Prolonged and/or intensive treatment (e.g. on a large body surface area) with potent corticosteroid preparations may cause local atrophic changes, such as local skin atrophy, striae, telangiectasia, erythema, purpura, contact dermatitis especially when occlusive dressings are used or when skin folds are involved.
When applied to the face, very potent corticosteroids can induce perioral dermatitis, skin atrophy or worsen rosacea (see section 4.3).
There are reports of pigmentation changes, acne, pustula eruptions and hypertrichosis with topical corticosteroids.

4.9 Overdose

Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage 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.

ATC code: D07AD01.

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Vasoconstriction studies have shown that Etrivex 500 micrograms/g cutaneous emulsion is in the very potent range of activity as compared with other topical corticosteroids. The mechanism of the anti-inflammatory activity of topical corticosteroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

5.2 Pharmacokinetic properties

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the severity of the disease, the surface treated, the vehicle, the integrity of the epidermal barrier and occlusion. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and other disease processes in the skin may increase percutaneous absorption. There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids, i.e. metabolised primarily by the liver and then excreted by the kidneys. Clobetasol propionate does not accumulate when administered to rats.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity.

In developmental toxicity studies in both the rabbit and mouse, clobetasol propionate was shown to be teratogenic when administered subcutaneously at low doses. In an embryotoxicity study performed in rats by topical route, foetal immaturity, skeletal and visceral malformations were observed at relatively low dosage levels. The relevance of these data to humans after dermal applications of clobetasol propionate is unknown.

Based on the available data there is no indication that clobetasol propionate has any genotoxic potential.
Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Propylene glycol
Liquid paraffin
PEG-6 isostearate
Carbomer copolymer
Sodium hydroxide
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

This medicinal product does not require any special storage precaution.
After first opening, do not store above 25°C.

6.5 Nature and contents of container

15 g, 30 g, 60 g or 120 g in HDPE bottles fitted with polypropylene caps.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Galderma (UK) Ltd
Meridien House
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Watford
Herts
WD17 1DS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 590/22/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2005

10 DATE OF REVISION OF THE TEXT

May 2007