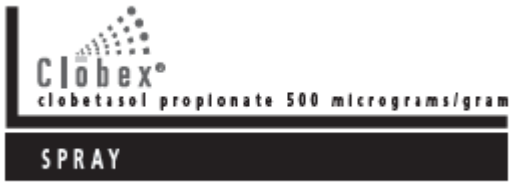

Composition

Each gram contains: Clobetasol propionate..... 0.5 mg
Vehicle (ethanol, isopropyl myristate, sodium laurilsulfate, and undecylenic acid)
q.s…….....1 gram
Excipient with known effect: One gram of Clobex spray contains 492.5 mg alcohol (ethanol 96 percent) which is equivalent to 49.25% w/w.

Pharmaceutical form and amount in drug substance per unit

Solution as a spray to be used on the skin.
1 g solution contains 0.5 mg of clobetasol propionate.
Cutaneous spray, solution. Clear colourless solution

Indications / possibilities of use

Topical treatment of moderate to severe plaque-type psoriasis, from 18 years of age on.

Posology / method of administration

Clobex cutaneous spray is intended for use on the skin, the solution should be sprayed directly onto the affected areas twice daily and then rubbed in gently until completely absorbed. Hands should be washed carefully after application. Each cycle of treatment should be limited to 4 consecutive weeks. Treatment of a lesion has to be stopped as soon as disease control is achieved; the diagnostic is to be re-evaluated if there is no improvement observed after 2 weeks.

Not more than 50g of spray-solution should be used per week. No more than 35 sprays should be involved in one application, i.e. not more than 70 sprays per day. Clobetasol propionate belongs to the most potent class of topical corticosteroids (class IV/class I) and prolonged use may result in serious undesirable effects (see Warnings and Precautions). If treatment with a local corticosteroid is clinically justified beyond 4 weeks, a less potent corticosteroid preparation should be considered. Repeated but short courses of clobetasol propionate may be used to control exacerbations.

Clobex cutaneous spray should be used neither on the face nor on intertriginous areas (axillae and genitoanal regions, see “Warnings and precautions”).

The safety and efficacy of Clobex cutaneous spray in children and adolescents under 18 years of age have not been established so far. No data are available in this context.

Contra-indications

Clobetasol propionate is contraindicated in patients who are hypersensitive to Clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation. Skin areas affected by bacterial and mycobacterial, viral, fungal, parasitic infections or ulcerous wounds. Must not be used in Children under 2 years of age Must not be applied to the eyes and eyelids (risk of glaucoma, risk of cataract).

Warnings and precautions

No children and adolescents (<18 years-old) were included in the clinical studies. The safety of Clobex cutaneous spray having not been established for this class of age, the product should therefore not be used in children and adolescents under 18 years of age. In comparison to adults, children are at a greater risk of HPA axis suppression when they are treated with topical corticosteroids (because of a higher ratio of skin surface area to body mass). They are therefore also at greater risk of adrenal insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

If signs of local intolerance appear, application should be suspended until they disappear. If signs of hypersensitivity appear, application should be stopped immediately. Hypersensitivity to corticosteroids can be observed. Clobetasol propionate is contraindicated in patients who are hypersensitive to other corticosteroids.

Topical corticosteroids should be used with caution for a number of reasons; these include post treatment rebound, relapses, development of tolerance (tachyphylaxis) and development of local or systemic toxicity such as atrophy and teliangectasia of the skin or hypothalamic-pituitary-adrenal axis suppression. 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. A careful surveillance of the patient is therefore important.

In general, treatment of large surface areas, long-term continuous therapy with corticosteroids, use of occlusive dressings can enhance absorption and lead to a higher risk of systemic effects. In such cases, medical supervision should be increased and patients are to be evaluated periodically for evidence of hypothalamic-pituitary-adrenal axis suppression.

Clobex cutaneous spray is not recommended for use on the face, intertriginous areas (axillae and genitoanal regions) and on other erosive skin surfaces, as this could increase the risk of topical adverse events such as atrophic changes, telangectasia or cortico-induced dermatitis.

If Clobex cutaneous spray does enter the eye, the affected eye should be rinsed with copious amounts of water.

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

Infected skin-lesions should not be treated with topical steroids. If an inflammatory lesion should become infected during the steroid-treatment, then an adequate antimicrobial therapy is indicated. The infection's expansion requires interruption of the local treatment with steroids.

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

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

Interactions
None known so far, there have been no interaction studies performed.

Pregnancy, 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 "Preclinical data"). The potential risk for humans is unknown. As a precautionary measure, Clobex cutaneous spray should not be used during pregnancy.

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 transfer of topical clobetasol propionate into the milk and its biological or clinical repercussions, Clobex cutaneous spray should not be prescribed to breastfeeding women unless clearly indicated.

Pediatrics
Use in patients between 2 and 18 years of age is not recommended and is contraindicated in children below 2 years of age.
Growth retardation may be observed in case of systemic absorption of topical corticosteroids

Effects on the ability to drive and use machines
As a topical corticosteroid, Clobex cutaneous spray has no or negligible influence on the ability to drive and use machines.

Undesirable effects
The adverse reaction most commonly reported in clinical trials was application site burning, experienced in 47.9% of subjects with Clobex cutaneous spray and in 46.7% of subjects treated with spray vehicle. Other adverse reactions were application site atrophy, telangiectasia and application site folliculitis, which occurred respectively in 3.6%, 2.8% and 2.6% of subjects treated with Clobex cutaneous spray. Most local adverse reactions were rated as mild to moderate and were not affected by age, race or gender. All these reactions usually resolved spontaneously and did not lead to treatment discontinuation.
The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data including post market experience).

System Organ Class	Frequency	Adverse reactions
Immune System Disorders	Uncommon	Hypersensitivity*
Endocrine disorders	Uncommon	Adrenal suppression* Cushing syndrome*
Eye disorders	Not known	Vision, blurred (see also section 4.4)
Skin and subcutaneous tissue disorders	Very common	Skin burning sensation (34.6%)
	Common	Folliculitis (1.7 %) Pain of skin (1.6%) Telangiectasia (1.5%) Skin atrophy (1.4%) Skin irritation (1.2%)
	Uncommon	Pruritus (0.6%) Dry skin (0.5%) Rash (0.2%) Erythema (0.1%) Allergic contact dermatitis* Psoriasis (aggravation) *

	Rare	Skin discolouration (0.04%)

*post-marketing experience

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's 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. Such effects are more likely to occur if occlusive dressings or bandages are used.

Prolonged and/or intensive treatment with potent corticosteroid preparations may cause local changes, such as local skin atrophy, striae, telangiectasia, erythema, purpura, contact dermatitis, especially with the use of occlusive dressings.

When applied to the face, very potent corticosteroids can induce perioral dermatitis, skin atrophy or worsen rosacea.

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

Overdosage

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; because of the risk of acute adrenal suppression, this should be done only under medical supervision.

Proprieties / Effects

ATC-Code: D07AD01

Mechanism of action / Pharmacodynamics

Like other topical corticosteroids, clobetasol propionate (a very potent corticosteroid of the group IV) 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 being released from membrane phospholipids by phospholipase A2.

The effect on the HPA-axis-function of treatment by Clobex cutaneous spray during 4 weeks has been investigated in two studies involving a twice daily application on patients with plaque psoriasis on at least 20% of the body-surface: 4 of 14 patients (29%) showed adrenal suppression after 4 weeks in the first study; 4 of 19 patients (21%) showed adrenal suppression after 2 weeks in the second study, 4 of 17 patients (24%) did so after 4 weeks. Suppression of the HPA-axis was defined by the occurrence of at least one of the following conditions: (1) a plasmatic cortisol-level at or below 5 µg/dl before stimulation with cosyntropin, (2) an increase of the plasmatic cortisol-level by less than 7 µg/dl 30 min. after stimulation or (3) a plasmatic cortisol-level below 18 µg/dl 30 min. after stimulation with cosyntropin. Suppression was reversible in all cases and showed no clinical symptoms.

Clinical efficacy

The efficacy of Clobex cutaneous spray in psoriasis has been demonstrated in two randomized, vehicle controlled clinical trials, which were identical in design. The studies were conducted in patients aged 18 years and older, with moderate to severe plaque psoriasis. Patients were treated twice daily for up to 4 weeks with either Clobex cutaneous spray or vehicle spray.

Patients were evaluated on their Overall Disease Severity, a 5-point scale based on scaling, erythema, and plaque elevation that classified subjects as clear, almost clear, with mild, moderate, or severe/very severe psoriasis. The median percent body surface area (BSA) at baseline was 6% for the two studies. The numbers of patients scored as clear or almost clear at Weeks 2 and 4 are presented in the following Table.

		Study 1		Study 2	
		CLOBEX	Vehicle	CLOBEX	Vehicle
		N=60	N=60	N=60	N=60
Week 2	Clear Almost Clear	1 (2%) 32 (53%)	0 (0%) 1 (2%)	0 (0%) 28 (47%)	0 (0%) 0 (0%)
Week 4	Clear Almost Clear	15 (25%) 32 (53%)	0 (0%) 2 (3%)	18 (30%) 31 (52%)	0 (0%) 1 (2%)

Pharmacokinetics

No specific study was performed (in vivo or in vitro) with Clobex cutaneous spray.

In vitro studies in human skin with different formulations of clobetasol propionate demonstrated that clobetasol propionate was recovered mainly in the epidermis (including stratum corneum) showing a potentially low systemic exposure after topical application.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including disease severity, the area treated, the vehicle used, 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 metabolic pathways similar to systemically administered corticosteroids, i .e. metabolised primarily by the liver and then excreted by the kidneys.

A clinical PK study conducted on 20 subjects with plaque psoriasis showed that after twice daily repeated topical applications, clobetasol plasma concentrations were low but quantifiable. Subjects were treated on psoriasis involved Body Surface Area ranging from 10% to 18%; and the amount of formulation per application ranged from 1.1g to 3.4 g. Steady state conditions were achieved by two weeks of treatment; and after four weeks treatment the mean peak plasma concentrations (Cmax) was 132.5 pg/mL and the mean AUC0-12h was 864.3 pg.h/mL.

Preclinical data

Clobetasol propionate had no carcinogenic potential when applied topically to rats for 2-years. Clobetasol propionate showed no mutagenic potential in in vitro or in vivo tests.

When administered subcutaneously to rats, clobetasol propionate reduced the viability of embryos and reduced maternal reproduction capacities. In developmental toxicity studies in rats and rabbits, clobetasol propionate was shown to be teratogenic when administered topically or subcutaneously. In a topical embryotoxicity study of Clobetasol propionate in rats, foetal immaturity and skeletal and visceral malformations were observed at relatively low dosage levels. In a study on development and peri/post-natal reproduction toxicity in rats, clobetasol propionate administered by the SC route decreased pup survival, increased foetal immaturity and increased skeletal and visceral malformations.

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

Additional information

Shelf-life and recommended storage conditions

Do not store above 30°C.

Keep out of the sight and reach of children.

Discard after the expiry date (Exp. Date) shown on the pack.

Do not refrigerate or freeze.

Shelf life after first opening: 3 months.

Store in the original package

Instructions for use and handling

The bottle contains a highly flammable solution.

Do not use near a naked flame. Do not expose to temperatures higher than 50ºC or to direct sunlight.

Pack-sizes

Bottles (with spray pump) containing 60 ml or 120 ml solution.

Not all pack sizes may be marketed.

Manufacturer

Laboratoires Galderma

Z.I. Montdésir

74540 Alby-sur-Chéran

France

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Dec 2022