1. NAME OF THE MEDICINAL PRODUCT

Esapharma movate 0,5 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

0,5 mg/g gel -100 g contain:
Clobetasol propionate 0,050 g

Excipients with known effect:
Propylene glycol

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dermatoses sensible to corticosteroids, especially those more difficult and resistant ones like, for example psoriasis (excluding widespread plaque psoriasis), recalcitrant eczema, lichen planus, discoid lupus erythematosus and other skin conditions which do not respond satisfactorily to less potent steroids.
The clobetasol propionate, for its therapeutic characteristics, is indicated for the treatment of resistant dermatoses unresponsive to less potent corticosteroids. After the treatment with Esapharma movate, the recalcitrant dermatoses reduce the frequency and severity of relapses.

4.2 Posology and method of administration

Route of administration: cutaneous.
The application of the gel is indicated in all the lesions wherever they are localized. The gel is preferred for the humid and soft cutaneous surfaces due to its water dispersible vehicle.

Adults, Elderly and Children over 1 year
Apply thinly and gently rub in using only enough to cover the entire affected area once or twice a day for a maximum of 4 weeks until improvement occurs, then reduce the frequency of application or change the treatment to a less potent corticosteroid. Allow adequate time for absorption after each application before applying an emollient cream.

Repeated short courses of clobetasol propionate may be used to control exacerbations.
In more resistant lesions, especially where there is hyperkeratosis, the effect of clobetasol can be enhanced, if necessary, by occluding the treatment area with polythene film. Overnight occlusion only is usually adequate to bring about a satisfactory response. Thereafter improvement can usually be maintained by application without occlusion.
If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated.
Treatment should not be continued for more than 4 weeks without medical supervision. If continuous treatment is necessary, a less potent preparation should be used.
The maximum recommended weekly dose should not exceed 50g/week.

Atopic dermatitis (eczema)
Therapy with clobetasol propionate should be gradually discontinued once control is achieved and an emollient cream must be used as maintenance therapy.
Rebound of pre-existing dermatoses can occur with abrupt discontinuation of clobetasol propionate.

Recalcitrant eczema
Once an acute episode has been treated effectively with a continuous course of topical corticosteroid, intermittent dosing (once daily, twice weekly, without occlusion) may be considered. This has been shown to be helpful in reducing the frequency of relapse.
Application should be continued to all previously affected sites or to known sites of potential relapse. This regimen should be combined with routine daily use of emollients. The condition and the benefits and risks of continued treatment must be re-evaluated on a regular basis.

Pediatric population
Clobetasol propionate is contraindicated in children under one year of age (see section 4.3).
Children are more likely to develop local and systemic side effects of topical corticosteroids and, in general, require shorter courses and less potent corticosteroids than adults.
Care should be taken when using clobetasol propionate to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly
Clinical studies have not identified differences in responses between the elderly and younger patients. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs.
Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

Renal / Hepatic Impairment
In case of systemic absorption (when application is over a large surface area for a prolonged period) metabolism and elimination may be delayed therefore increasing the risk of systemic toxicity. Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

4.3 Contraindications

– Hypersensitivity to the active substance, to any other substance strictly related from a chemical point of view or to any of the excipients listed in section 6.1.

The following conditions should not be treated with clobetasol propionate:
• Untreated cutaneous infections
• Primary cutaneous viral infections (e.g. herpes simplex, chickenpox)
• Primary infected skin lesions caused by infection with fungi or bacteria
• Rosacea
• Acne vulgaris
• Perioral dermatitis
• Cutaneuos ulcer
• Pruritus without inflammation.
• Perianal and genital pruritus
• Dermatoses in children under one year of age, including dermatitis and nappy eruptions

Occlusive medication is contraindicated in the exuding lesions and in the patients with atopic dermatitis.
Controindicated during pregnancy and breast-feeding (see section 4.6).
The product is not for ophthalmic use.

4.4 Special warnings and precautions for use

Clobetasol propionate should be used with caution in patients with a history of local hypersensitivity to other corticosteroids or to any of the excipients in the preparation. Local hypersensitivity reactions (see section 4.8) may resemble symptoms of the condition under treatment.
Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency (see section 4.8).

Risk factors for increased systemic effects are:
- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (in infants the nappy may act as an occlusive dressing)
- Increasing hydration of the stratum corneum
- Use on thin skin areas such as the face
- Use on broken skin or other conditions where the skin barrier may be impaired
- In comparison with adults, children and infants may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a greater surface area to body weight ratio compared with adults.

Pediatric population
In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.
Children are more susceptible to develop atrophic changes with the use of topical corticosteroids.
If clobetasol propionate is required for use in children, courses should be limited to only a few days and reviewed weekly.

Infection risk with occlusion
Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings. When using occlusive dressings, the skin should be cleansed before a fresh dressing is applied.

Use in Psoriasis
Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerances, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases. If used in psoriasis careful patient supervision is important.

Concomitant infection
Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate antimicrobial therapy.

Chronic leg ulcers
Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Application to the face
Application to the face is undesirable as this area is more susceptible to atrophic changes respect to other cutaneous areas.
If used on the face, treatment should be limited to only a few days.

Application to the eyelids
If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as cataract and glaucoma might result from repeated exposure. When occlusive dressings is used, the skin should be cleansed before a fresh dressing is applied to avoid bacterial infections encouraged by the warm, moist conditions caused by occlusive dressings.

In the occlusive treatments it has to be taken into account that the polythene film used can itself cause skin sensitivity.

Patients should be advised to wash their hands after the Esapharma movate application unless it is the hands that are being treated.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administered drugs that can inhibit CYP3A4 (eg ritonavir and itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

4.6. Fertility, pregnancy and lactation

Fertility
There are no data in humans to evaluate the effect of topical corticosteroids on fertility.

Pregnancy
There are limited data from the use of clobetasol propionate in pregnant women.
Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development (see section 5.3).
The relevance of this finding to humans has not been established. Administration of clobetasol propionate during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the fetus. The minimum quantity should be used for the minimum duration.

Breast-feeding
The safe use of topical corticosteroids during lactation has not been established.
It is not known whether the topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Topical administration of clobetasol propionate during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.
If used during lactation clobetasol propionate should not be applied to the breasts to avoid accidental ingestion by the infant.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of clobetasol propionate on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of topical clobetasol propionate.

4.8 Undesirable effects

Adverse drug reactions (ADRs) are listed below by MedDRA system/organ, class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Post-marketing data

Infections and Infestations	
Very rare	Opportunistic infection
Immune System Disorders	
Very rare	Local Hypersensitivity
Endocrine Disorders	
Very rare	Hypothalamic-pituitary adrenal (HPA) axis suppression: Cushingoid features: (e.g. moon face, central obesity), delayed weight gain/growth retardation in children, osteoporosis, glaucoma, hyperglycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels, alopecia, trichorrhexis
Skin and Subcutaneous Tissue Disorders	
Common	Pruritus, local skin burning /skin pain
Uncommon	Skin atrophy*, striae*, telangiectasias*
Very rare	Skin thinning*, skin wrinkling*, skin dryness*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, allergic contact dermatitis/dermatitis, pustular psoriasis, erythema, rash, urticaria
Not known (the frequency cannot be estimated from the available data)	acne
General Disorders and Administration Site Conditions	
Very rare	Application site irritation/pain

**Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk/benefit balance of the medicinal product.

4.9 Overdose

Symptoms and signs
Topically applied clobetasol propionate may be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse the features of hypercortisolism may occur (see section 4.8).
Excessive and extended use of topical corticosteroids can depress the adrenal gland function, causing a secondary hypoadrenalism and manifestations of hypercortisolism (Cushing's syndrome), in particular asthenia, adynamia, hypertension, disorders of heart rhythm, hypokalemia, metabolic acidosis.

Treatment
In the event of overdose, clobetasol propionate application should be withdrawn gradually by reducing the frequency of application or by substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The symptoms of acute hypercortisolism are generally reversible. If necessary, treat the electrolyte imbalance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **Corticosteroids, very potent (group IV)**
ATC code: **D07AD01**

Mechanism of action
Topical corticosteroids act as anti-inflammatory agents via multiple mechanisms to inhibit late phase allergic reactions including decreasing the density of mast cells, decreasing chemotaxis and activation of eosinophils, decreasing cytokine production by lymphocytes, monocytes, mast cells and eosinophils, and inhibiting the metabolism of arachidonic acid.

Pharmacodynamic effects
Topical corticosteroids, have anti-inflammatory, antipruritic, and vasoconstrictive properties. Esapharma movate contains a corticosteroid (clobetasol propionate); it has been demonstrated to have a high topic activity through the "vasoconstriction bioassay test" of McKenzie, confirmed through many clinical tests.
The steroid systemic activity is the following:

- The clobetasol propionate demonstrated to be always more active than the betamethasone alcohol in the mouse independently from the carrier and the administration route; in particular the active substance, respect the standard, is 2 times more potent if administrated orally, and 11 times subcutaneously;
- The clobetasol propionate demonstrate to be 5 times more active than the betamethasone alcohol in the anti-granulomatous activity test in the mouse;
- In the rat the anti-inflammatory activity of the clobetasol propionate is similar or minor than the betamethasone one, depending on the administration route.

The clobetasol propionate has no estrogen, androgen and anabolic activity either in the mouse or in the rat and it has no antigonadropic activity in the rat.

The clobetasol propionate demonstrated anti-estrogen activity either in the mouse or in the rat.

In the rabbit it has progestinic activity higher or equal than the progesterone one (respectively administrated subcutaneously and orally); its activity is comparable to the one of fluocinolone 16-17 acetonide.

The topic activity has been studied in the man through the vasoconstriction test. The clobetasol propionate vasoconstriction index resulted to be 1869, assuming equal to 100 the fluocinolone acetonide activity.

5.2 Pharmacokinetic properties

Absorption
Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.
In the absorption patch tests on the dog with treatments for 10 days at high doses (0.1 g/Kg, corresponding to 35 mg of active ingredient in a man of 70 Kg), no adrenal activity modification occurred, evaluated on the base of the cortisol plasmatic levels.

The cortisol variation demonstrates the potential systemic absorption: the entity of the absorption is correlated to the dimension of the cutaneous surface treated, to cutaneous alteration level and to the treatment duration.

Mean peak plasma clobetasol propionate concentrations of 0.63 ng/ml occurred in one study eight hours after the second application (13 hours after an initial application) of 30 g clobetasol propionate 0.05% ointment to normal individuals with healthy skin. Following the application of a second dose of 30 g clobetasol propionate gel 0.05% mean peak plasma concentrations were slightly higher than the ointment and occurred 10 hours after application.
In a separate study, mean peak plasma concentrations of approximately 2.3 ng/ml and 4.6 ng/ml occurred respectively in patients with psoriasis and eczema three hours after a single application of 25 g clobetasol propionate 0.05% ointment.

Distribution
The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary due to the fact that circulating levels are well below the level of detection.

Metabolism
Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolized, primarily in the liver.

Elimination
Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

5.3 Preclinical safety data

Carcinogenesis / Mutagenesis

Carcinogenesis
Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Genotoxicity
Clobetasol propionate was not mutagenic in a range of *in vitro* bacterial cell assays.

Reproductive Toxicology

Fertility
The effect of topical clobetasol propionate on fertility has not been evaluated in animals.

Pregnancy
Subcutaneous administration of clobetasol propionate to mice (≥100 micrograms/kg/day), rats (400 micrograms/kg/day) or rabbits (1 to 10 micrograms/kg/day) during pregnancy produced fetal abnormalities including cleft palate and intrauterine growth retardation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Carbomer
Titanium dioxide
Sodium hydroxide
Purified water

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months.
Shelf life after the first opening: 6 months.

6.4 Special precautions for storage

No labelling storage conditions is required

6.5 Nature and contents of container

Collapsible aluminum tube internally coated with epoxyphenolic resin based lacquer, provided with polypropylene screw cap.
Pack sizes: 30 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The gel must not be diluted.

7. MARKETING AUTHORISATION HOLDER

Esapharma SpA
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20066 Melzo (Milano)
Italy

8. MARKETING AUTHORISATION NUMBER(S)

FDA/SD. 191-11951