FLUTIBACT SKIN OINTMENT

Fluticasone Propionate and Mupirocin Ointment

QUALITATIVE AND QUANTITATIVE COMPOSITION

*FLUTIBACT* contains:

- Fluticasone Propionate IP 0.005 % w/w
- Mupirocin IP 2.0 % w/w

in a water-soluble ointment base

PHARMACEUTICAL FORM

Ointment

CLINICAL PARTICULARS

Therapeutic indications

*FLUTIBACT* Ointment is indicated for adults, children and infants aged three months and over for the treatment of the following steroid-responsive inflammatory disorders of the skin where secondary bacterial infections are present, suspected or likely to occur:

Atopic dermatitis (including infantile atopic dermatitis); nummular dermatitis (discoid eczemas); prurigo nodularis; psoriasis (excluding widespread plaque psoriasis.); lichen simplex chronicus (neurodermatitis) and lichen planus; seborrhoeic dermatitis; irritant or allergic contact dermatitis; discoid lupus erythematosus; an adjunct to systemic steroid therapy in generalised erythroderma; insect bite reactions; miliaria (prickly heat).

Posology and Method of Administration

*Adults, elderly, children and infants aged 3 months and over*

Ointments are especially appropriate for dry, lichenified or scaly lesions.

Apply a thin film of *FLUTIBACT* Ointment to cover the affected areas twice daily for up to 10 days depending on the response.

If the condition worsens or does not improve within 10 days, treatment and diagnosis should be re-evaluated.

The treated area may be covered by a dressing.

Do not mix with other preparations as there is a risk of dilution, resulting in a reduction in the antibacterial activity and potential loss of stability of the mupirocin in the ointment.

*Atopic dermatitis*
Therapy with topical corticosteroids should be gradually discontinued once control is achieved and an emollient continued as maintenance therapy.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical steroids especially with potent preparations.

**Children over 3 months**

Children are more likely to develop local and systemic side effects of topical corticosteroids and, in general, require shorter courses and less potent agents than adults.

Care should be taken when using FLUTIBACT Ointment to ensure the amount applied is the minimum that provides therapeutic benefit.

**Elderly**

Clinical studies of fluticasone propionate 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.

**Contraindications**

FLUTIBACT Ointment is contraindicated in:

- Hypersensitivity to any of the ingredients of the preparation
- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Pruritus without inflammation
- Perianal and genital pruritus
- Primary cutaneous viral, yeast, fungal and bacterial infections
- Secondarily infected skin lesions caused by virus, fungi and/or yeast
- Dermatoses in infants under 3 months of age, including dermatitis and nappy rash.

**Special Warnings and Special Precautions for Use**

FLUTIBACT Ointment should be used with caution in patients with a history of local hypersensitivity to corticosteroids. Local hypersensitivity reactions (see Undesirable Effects) 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 is 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 Undesirable Effects).

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.

Visual disturbance has been reported by patients using systemic and/or topical corticosteroids. If a patient has blurred vision or other visual disturbances, consider evaluation of possible causes which may include cataract, glaucoma, and central serous chorioretinopathy.

Overt suppression of the HPA-axis (morning plasma cortisol less than 5 micrograms/dL) is very unlikely to result from therapeutic use of FLUTIBACT Ointment unless treating more than 50% of an adult's body surface and applying more than 20 g per day.

Children

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression is more likely to occur.

Use in psoriasis

Topical steroids should be used with caution in psoriasis as rebound relapses, development of tolerance, 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.

Application to the face

Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes.

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.

Avoid contact with the eyes. If contaminated, the eyes should be thoroughly irrigated with water until the ointment residues have been removed.

**Concomitant infection**

Extension of infection may occur due to masking effect of the steroid.

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.

**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.

**Renal impairment**

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, *FLUTIBACT* Ointment should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

**Sensitisation Reaction**

In the rare event of possible sensitisation reaction or severe local irritation occurring with the use of *FLUTIBACT* Ointment, treatment should be discontinued, the product should be wiped off and appropriate alternative therapy for the infection instituted.

**Pseudomembranous colitis**

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. Although this is less likely to occur with topically applied mupirocin, if prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately, and the patient investigated further.

**Other General Warnings**
As with other antibacterial products, prolonged use may result in overgrowth of non-susceptible organisms.

*FLUTIBACT* is not suitable for:
- ophthalmic use,
- intranasal use,
- use in conjunction with cannulae and
- at the site of central venous cannulation.

**Interaction with Other Medicinal Products and Other Forms of Interaction**

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir, 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.

**Pregnancy and Lactation**

**Fertility**

There are no data in humans to evaluate the effect of topical corticosteroids on fertility (see *Preclinical Safety Data*).

There are no data on the effects of mupirocin on human fertility. Studies in rats showed no effects on fertility (see *Preclinical Safety Data*).

**Pregnancy**

There are limited data from the use of fluticasone propionate in pregnant women.

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. (see *Preclinical Safety Data*).

The relevance of this finding to humans has not been established.

Adequate human data on use of mupirocin during pregnancy not available. Studies in animals do not indicate reproductive toxicity (see *Preclinical Safety data*).

However, administration of *FLUTIBACT* Ointment during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. The minimum quantity should be used for the minimum duration.

**Lactation**

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. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the milk.
Adequate human and animal data on use of mupirocin during lactation are not available.

Administration of FLUTIBACT Ointment during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

If used during lactation, FLUTIBACT Ointment should not be applied to the breasts to avoid accidental ingestion by the infant.

**Effects on Ability to Drive and Use Machines**

There have been no studies to investigate the effect of FLUTIBACT 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 FLUTIBACT Ointment

**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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), including isolated reports.

**Fluticasone Propionate**

**Post-Marketing Data**

**Infections and infestations**

Very rare: Opportunistic infection.

**Immune system disorders**

Very rare: Hypersensitivity.

**Endocrine disorders**

Very rare: Hypothalamic-pituitary adrenal (HPA) axis suppression:
- Increased weight/obesity
- Delayed weight gain/growth retardation in children
- Cushingoid features (e.g. moon face, central obesity)
- Decreased endogenous cortisol levels
- Hyperglycaemia/glucosuria
- Hypertension
- Osteoporosis
- Cataract
- Glaucoma

**Skin and subcutaneous tissue disorders**

Common: Pruritus.
Uncommon: Local skin burning.
Very rare: Skin thinning, atrophy, striae, telangiectasias, pigmentation changes, hypertrichosis, allergic contact dermatitis, exacerbation of underlying symptoms, pustular psoriasis, erythema, rash, urticaria.
**Mupirocin**

**Immune system disorders:**
Very rare: Systemic allergic reactions including anaphylaxis, generalised rash, urticaria and angioedema have been reported with mupirocin ointment.

**Skin and subcutaneous tissue disorders**
Common: Burning localised to the area of application.
Uncommon: Itching, erythema, stinging and dryness localised to the area of application.
Cutaneous sensitisation reactions to mupirocin or the ointment base.

**Overdose**

**Symptoms and Signs**
Topically applied fluticasone propionate may be absorbed in sufficient amounts to produce systemic effects.

Acute overdose is very unlikely to occur, however, in the case of chronic overdose or misuse the features of hypercortisolism may appear (see Undesirable Effects).

**Treatment**

In the event of overdose, FLUTIBACT Ointment should be withdrawn gradually by reducing the frequency of application because of the risk of glucocorticosteroid insufficiency.

There is no specific treatment for an overdose of mupirocin. In the event of overdose, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

**Mechanism of Action**

**Fluticasone propionate**

Topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties. They 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.

Fluticasone propionate is a glucocorticoid with high topical anti-inflammatory potency but low HPA-axis suppressive activity after dermal administration. It therefore has a therapeutic index which is greater than most of the commonly available steroids.
It shows high systemic glucocorticoid potency after subcutaneous administration but very weak oral activity, probably due to metabolic inactivation. *In vitro* studies show a strong affinity, for and agonist activity at, human glucocorticoid receptors.

**Mupirocin**

Mupirocin is a novel antibiotic produced through fermentation of *Pseudomonas fluorescens*. Mupirocin inhibits isoleucyl transfer-RNA synthetase, thereby arresting bacterial protein synthesis.

Due to this particular mode of action and its unique chemical structure, mupirocin does not show any cross-resistance with other clinically available antibiotics.

Mupirocin has bacteriostatic properties at minimum inhibitory concentrations and bactericidal properties at the higher concentrations reached when applied locally.

**Pharmacodynamic Effects**

**Fluticasone propionate**

Fluticasone propionate has no unexpected hormonal effects, and no overt, marked effects upon the central and peripheral nervous systems, the gastrointestinal system, or the cardiovascular or respiratory systems.

**Mupirocin**

**Activity**

Mupirocin is a topical antibacterial agent showing *in vivo* activity against *Staphylococcus aureus* (including methicillin-resistant strains), *S. epidermidis* and beta-haemolytic *Streptococcus* species.

The *in vitro* spectrum of activity includes the following bacteria:

**Commonly Susceptible Species:**

- *Staphylococcus aureus*\(^1,2\)
- *Staphylococcus epidermidis*\(^1,2\)
- *Coagulase-negative staphylococci*\(^1,2\)
- *Streptococcus* species\(^1\)
- *Haemophilus influenzae*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Moraxella catarrhalis*
- *Pasteurella multocida*

\(^1\)Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

\(^2\)Including beta-lactamase producing strains and methicillin-resistant strains.
Resistant Species:

*Corynebacterium* species
*Enterobacteriaceae*
Gram negative non-fermenting rods
*Micrococcus* species
*Anaerobes*

*Mupirocin susceptibility (MIC) breakpoints for Staphylococcus spp.*

**Susceptible:** less than or equal to 1 microgram/ml

**Intermediate:** 2 to 256 micrograms/ml

**Resistant:** greater than 256 micrograms/ml

Resistance mechanisms

Low-level resistance in staphylococci (MICs 8 to 256 micrograms/ml) has been shown to be due to changes in the native isoleucyl tRNA synthetase enzyme. High-level resistance in staphylococci (MICs greater than or equal to 512 micrograms/ml) has been shown to be due to a distinct, plasmid encoded isoleucyl tRNA synthetase enzyme. Intrinsic resistance in Gram negative organisms such as the *Enterobacteriaceae* could be due to poor penetration into the bacterial cell.

**Pharmacokinetic Properties**

**Absorption**

Bioavailability of fluticasone propionate is very low after topical or oral administration, due to limited absorption through the skin or from the gastrointestinal tract, and because of extensive first pass metabolism.

Oral bioavailability approaches zero, due to poor absorption and extensive first pass metabolism. Therefore, systemic exposure of fluticasone propionate from any ingestion of FLUTIBACT Ointment will be low.

Mupirocin is poorly absorbed through intact human skin.

**Distribution**

Distribution studies have shown that only minute traces of orally administered compound reach the systemic circulation and that any systemically available fluticasone propionate is rapidly eliminated in the bile and excreted in the faeces.

Fluticasone propionate does not persist in any tissue and does not bind to melanin.

**Metabolism**
Pharmacokinetic data for the rat and dog indicate rapid elimination and extensive metabolic clearance of fluticasone propionate. In man too, metabolic clearance is extensive, and elimination is consequently rapid. Thus, fluticasone propionate entering the systemic circulation via the skin will be rapidly inactivated. The major route of metabolism is hydrolysis to a carboxylic acid, which has very weak glucocorticoid or anti-inflammatory activity.

Mupirocin is suitable only for topical application. Following i.e. or oral administration, or if mupirocin is absorbed (e.g. through broken/diseased skin) mupirocin is rapidly metabolised to inactive monic acid.

**Elimination**

In all test animal species the route of excretion was independent of the route of administration of fluticasone propionate. Excretion is predominantly faecal and is essentially complete within 48 hours.

Mupirocin is rapidly eliminated from the body by metabolism to its inactive metabolite monic acid which is rapidly excreted by the kidney.

**Special Patient Populations**

*Elderly patients:* No restrictions unless there is evidence of moderate or severe renal impairment (see *Special Warnings and Special Precautions for Use*).

**Preclinical Safety Data**

**Carcinogenesis**

*Fluticasone propionate*

Long-term topical and oral studies in animals to investigate the carcinogenic potential of fluticasone propionate did not show any evidence of carcinogenicity.

*Mupirocin*

Carcinogenicity studies with mupirocin have not been conducted.

**Genotoxicity**

*Fluticasone propionate*

Fluticasone propionate was not shown to be mutagenic in a range of *in vitro* bacterial and mammalian cell assays.

*Mupirocin*

Mupirocin was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* (Ames assay). In a Yahagi assay, small increases in *Salmonella typhimurium* TA98 were observed at highly cytotoxic concentrations. In an *in vitro* mammalian gene mutation assay (MLA), no increase in mutation frequency was observed in the absence of metabolic activation. In the presence of
metabolic activation, small increases in mutation frequency were observed at highly cytotoxic concentrations. However, no effects were observed in, yeast cell assays for gene conversion/mutation, an in vitro human lymphocyte assay or in an in vitro unscheduled DNA synthesis (UDS) assay. Furthermore, an in vivo mouse micronucleus assay (chromosome damage) and a rat Comet assay (DNA strand breakage) were negative, indicating the small increases observed at highly cytotoxic concentrations in vitro do not translate to the in vivo situation.

Reproductive Toxicology

Fertility

Fluticasone propionate

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 micrograms/kg per day and to males up to 100 micrograms/kg per day (later reduced to 50 micrograms/kg per day) had no effect upon mating performance or fertility.

Mupirocin

Mupirocin administered subcutaneously to male rats 10 weeks prior to mating and to female rats 15 days prior to mating until 20 days post coitum at doses up to 100 mg/kg/day had no effect on fertility.

Pregnancy

Fluticasone propionate

Subcutaneous administration of fluticasone propionate to mice (150 micrograms/kg/day), rats (100 micrograms/kg/day) or rabbits (300 micrograms/kg/day) during pregnancy produced foetal abnormalities including cleft palate. Oral administration did not produce foetal abnormalities, consistent with the low bioavailability of fluticasone propionate by the oral route.

Mupirocin

In embryo-foetal development studies in rats there was no evidence of developmental toxicity at subcutaneous doses up to 375 mg/kg/day.

In an embryo-foetal development study in rabbits at subcutaneous doses up to 160 mg/kg/day, maternal toxicity (impaired weight gain and severe injection site irritation) at the high dose resulted in abortion or poor litter performance. However, there was no evidence of developmental toxicity in foetuses of rabbits maintaining pregnancy to term.

PHARMACEUTICAL PARTICULARS

List of Excipients
Polyethylene Glycol 400, Polyethylene Glycol 3350.

**Incompatibilities**

No incompatibilities have been identified.

**Shelf-Life**

The expiry date is indicated on the label and packaging.

**Special Precautions for Storage**

Store at a temperature not exceeding 25°C. Do not freeze.

Keep out of reach of children.

**Nature and Contents of Container**

Aluminium tube in a carton.

All pack presentations may not be marketed in the country.

**Instructions for Use/Handling**

For External Use only. Wash your hands after application.

Any product remaining at the end of treatment should be discarded.

There are no other special requirements for use or handling of this product.

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