Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betnovate-C 0.1% / 3% w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Betamethasone 0.1% w/w (as betamethasone valerate)
Clioquinol 3% w/w

Excipients with known effect:
chlorocresol 0.1% w/w
cetostearyl alcohol 7.2% w/w

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream
A pale yellow, homogenous, aqueous based cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Betnovate-C cream is indicated in the management of corticosteroid sensitive dermatoses, actually or potentially complicated by infection due to micro-organisms sensitive to the anti-infective contained therein.

Betnovate-C cream is indicated for the treatment of the following conditions where secondary bacterial and/or fungal infection is present, suspected or likely to occur:

- Atopic dermatitis
- Nummular dermatitis (discoid eczema)
- Prurigo nodularis
- Psoriasis (excluding widespread plaque psoriasis)
- Lichen simplex chronicus (neurodermatitis) and lichen planus
- Seborrhoeic dermatitis
- Irritant or allergic contact dermatitis
- Insect bite reactions
- Miliaria (prickly heat)
- Anal and genital intertrigo
- Otitis externa

4.2 Posology and method of administration

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice daily for up to four weeks until improvement occurs, then reduce the frequency of application or change the treatment to a less potent preparation. Allow adequate time for absorption after each application before applying an emollient.

In the more resistant lesions, such as the thickened plaques of psoriasis on elbows and knees, the effect of Betnovate-C 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 in such lesions. Thereafter, improvement can usually be maintained by regular application without occlusion.

If the condition worsens or does not improve within two to four weeks, treatment and diagnosis should be re-evaluated.

Atopic dermatitis (eczema)
Therapy with Betnovate-C 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 Betnovate-C.

Recalcitrant dermatoses
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 regime 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.

Paediatric population
Betnovate-C should not be used in children under 2 years of age.

Betnovate-C is suitable for use in children and infants (2 years and over) at the same dose as adults.

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 Betnovate-C to ensure the amount applied is the minimum that provides therapeutic benefit.

Older people
Betnovate-C is suitable for use in older people. 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.

Patients with 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, 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 substances, to clioquinol, to iodine or to any of the excipients listed in section 6.1.

Betnovate-C is contra-indicated in children under 2 years of age.

The following conditions should not be treated with Betnovate-C:

- Rosacea,
- Acne vulgaris
- Peri-oral dermatitis
- Perianal and genital pruritus
- Pruritus without inflammation
- Primary cutaneous viral infections (e.g. herpes simplex, chicken pox)
- Primary infected skin lesions caused by infection with fungi or bacteria
- Primary or secondary infections due to yeasts

4.4 Special warnings and precautions for use

Chlorocresol may cause allergic reactions. Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression
Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression can occur in some individuals as a result of increased systemic absorption of topical corticosteroids. 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 glucocorticoid insufficiency (see section 4.8).

Risk factors for increased corticosteroidal systemic effects are:

- Potency and formulation of topical corticosteroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin (e.g. on intertriginous areas or under occlusive dressings) (nappies 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.

Paediatric population
In comparison with adults, children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects.

In children under 12 years of age, long-term continuous topical therapy should be avoided where possible, as adrenal suppression can occur.

Use in Psoriasis

Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerance, risk of generalized pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases (see section 4.8). If used in psoriasis, careful patient supervision is important.

Neurotoxicity

There is a theoretical risk of neurotoxicity from the topical application of clioquinol, particularly when Betnovate-C is used for prolonged periods or under occlusion.

Application to the Face

Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematosus and severe eczema.

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.

There have been a few reports in the literature of the development of cataracts in patients who have been using corticosteroids for prolonged periods of time. Although it is not possible to rule out systemic corticosteroids as a known factor, prescribers should be aware of the possible role of corticosteroids in cataract development.

Visual disturbance

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.

Infection

Extension of infection may occur due to the masking effect of the steroid. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate systemic antimicrobial therapy.

Infection risk with occlusion

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

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.

Dilution

Products which contain antimicrobial agents should not be diluted.

Flammability risk

Healthcare professionals should be aware that the fabric (clothing, bedding, dressings etc.) that has been in contact with this product burns more easily and is a serious fire hazard. Patients should be warned of this risk and advised not to smoke or go near naked flames - due to the risk of severe burns. Washing clothing and bedding may reduce product build-up but not totally remove it.

Staining

Betnovate-C may stain hair, skin or fabric and the application should be covered with a dressing to protect clothing.

4.5 Interaction with other medicinal products and other forms of interactions

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.

Theoretical concerns exist that oculotoxic effects of vigabatrin may be additive with cliquinol. Vigabatrin should not be used with clioquinol.

4.6 Fertility, pregnancy and lactation

Fertility
There are no data in humans to evaluate the effect of betamethasone valerate-clioquinol on fertility.

Pregnancy
There are limited data from the use of betamethasone valerate-clioquinol in pregnant women.

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. The relevance of this finding to human beings has not been established. However, administration of betamethasone valerate-clioquinol during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus. The minimum quantity should be used for the minimum duration.

Breast-feeding
The safe use of Betnovate-C during lactation has not been established.

It is not known whether topical administration of corticosteroids could results in sufficient systemic absorption to produce detectable amounts in breast milk.

Administration of Betnovate-C during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

If used during lactation, Betnovate-C 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 Betnovate-C 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 Betnovate-C.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports.

Infections and Infestations
Very rare Opportunistic infection

Immune System Disorders
Very rare Local hypersensitivity

Endocrine Disorders
Very rare Hypothalamic-pituitary adrenal (HPA) axis suppression: (*see also Skin and Subcutaneous Tissue Disorders*) 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

Skin and Subcutaneous Tissue Disorders
Common Pruritis, local skin burning/pain of skin
Very rare Allergic contact dermatitis/dermatitis, erythema, rash, urticaria, pustular psoriasis (see section 4.4), skin thinning*/skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, alopecia*, trichorrhexis*, hair discolouration
**Skin features of hypothalamic-pituitary adrenal (HPA) axis suppression*

General Disorders and Administration Site Conditions
Very rare Application site irritation, pain

Eye disorders
Not known Vision, blurred (see also section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Topically applied Betnovate-C 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).

In the event of chronic overdosage or misuse, topical corticosteroids should be withdrawn gradually by reducing the frequency of application, or by substituting a less potent corticosteroid because of the risk of adrenal insufficiency.

Further management should be as clinically indicated or as recommended by the National Poisons Information Centre of Ireland.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code D07BC01

Mechanism of action
Betamethasone valerate is an active corticosteroid with topical anti-inflammatory activity. 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.

Clioquinol is an anti-infective agent which has both anti-bacterial and anti-fungal activity. The mechanism of action of clioquinol is not known but its action is probably due to its iodine content.

5.2 Pharmacokinetic properties

Absorption
Topical corticosteroids can be 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.

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 systematically administered corticosteroids. They are metabolised 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.

Clioquinol is excreted in the urine as glucoronide and sulphate metabolites.

5.3 Preclinical safety data

Non-clinical studies have not been conducted with Betnovate-C.
Betamethasone valerate and cliquinol individually have been evaluated in animal toxicity tests, and the following statements reflect the information available on the individual components.

Genotoxicity
Clioquinol was not mutagenic *in vitro*.

Pregnancy
Subcutaneous administration of betamethasone 17-valerate to mice or rats at doses ≥ 0.1 mg/kg/day or rabbits at doses ≥ 12 micrograms/kg/day during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

Oral administration of clioquinol to rats during pregnancy was associated with reduced foetal body weight at doses ≥ 120 mg/kg/day and delays in ossification at doses ≥ 300 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorocresol
Cetomacrogol 1000
Cetostearyl Alcohol
White Soft Paraffin
Liquid Paraffin
Sodium Dihydrogen Phosphate Dihydrate
Phosphoric Acid (for pH adjustmnet)
Sodium Hydroxide (for pH adjustment)
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Betnovate-C cream is supplied in 30 g collapsible aluminium tubes.

6.6 Special precautions for disposal and other handling

Do not dilute.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 October 1983

Date of last renewal: 27 October 2008

10 DATE OF REVISION OF THE TEXT

January 2021