For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

BETNOVATE - C SKIN CREAM

1. GENERIC NAME

Betamethasone and Clioquinol Cream BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Clioquinol I.P. 3.0 % w/w
Chlorocresol I.P. 0.1% w/w (as preservative) in a non-greasy base.

3. DOSAGE FORM AND STRENGTH

Cream

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Clioquinol I.P. 3.0 % w/w
Chlorocresol I.P. 0.1% w/w (as preservative) in a non-greasy base.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Betamethasone valerate is a potent topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses. Clioquinol is an antibacterial antifungal drug.

Topical preparations combining betamethasone valerate and clioquinol are 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

BETNOVATE - C SKIN CREAM is especially appropriate for moist or weeping surfaces.

Adults and adolescents

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 SKIN CREAM* 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 SKIN CREAM* 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 SKIN CREAM*.

Recalcitrant dermatoses

Patients who frequently relapse

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.

Children aged 1 year and over

BETNOVATE - C SKIN CREAM is suitable for use in children and infants (1 year and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus betamethasone valerate-clioquinol is contraindicated in neonates and infants under 1 year of age (see *4.3 Contraindications*).

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 SKIN CREAM* to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

BETNOVATE - C SKIN CREAM is suitable for use in the 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

BETNOVATE - C SKIN CREAM is contraindicated in children under 1 year of age.

The following conditions should not be treated with *BETNOVATE - C SKIN CREAM*:

- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Pruritus without inflammation
- Perianal or genital pruritus
- Primary cutaneous viral infections
- 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

Hypersensitivity

BETNOVATE - C SKIN CREAM should be used with caution in patients with a history of hypersensitivity to betamethasone, clioquinol or to any of the excipients in the preparation, or to iodine. Local hypersensitivity reactions (see *4.8 Undesirable Effects*) may resemble symptoms of the condition under treatment.

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 glucocorticosteroid insufficiency (see *4.8 Undesirable Effects*).
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.

Visual Disturbances

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 or central serous chorioretinopathy.

Use in children

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.

In children under 12 years, long-term continuous topical corticosteroid 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 generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases (see *4.8 Undesirable Effects*). If used in psoriasis careful patient supervision is important.

Dilution

Products which contain antimicrobial agents should not be diluted.

Neurotoxicity

There is a theoretical risk of neurotoxicity from the topical application of clioquinol, particularly when *BETNOVATE - C SKIN CREAM* 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.

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.

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.

Flammability risk

BETNOVATE - C SKIN CREAM contains paraffin. Instruct patients not to smoke or go near naked flames due to the risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

Staining

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

4.5 Drug 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 clioquinol. Vigabatrin should not be used with clioquinol.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Children aged 1 year and over

BETNOVATE - C SKIN CREAM is suitable for use in children and infants (1 year and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus betamethasone valerate-clioquinol is contraindicated in neonates and infants under 1 year of age (see *4.3 Contraindications*).

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 SKIN CREAM* to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

BETNOVATE - C SKIN CREAM is suitable for use in the 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.

Pregnancy and Lactation

Fertility

There are no data in humans to evaluate the effect of *BETNOVATE - C SKIN CREAM* on fertility.

Pregnancy

There are limited data from the use of *BETNOVATE - C SKIN CREAM* in pregnant women.

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see *6 Nonclinical Properties*). The relevance of this finding to human beings has not been established. However, administration of *BETNOVATE - C SKIN CREAM* 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.

Lactation

The safe use of *BETNOVATE - C SKIN CREAM* during lactation has not been established.

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

Administration of *BETNOVATE - C SKIN CREAM* 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 SKIN CREAM* 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 SKIN CREAM* 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 *BETNOVATE - C SKIN CREAM.*

4.8 Undesirable Effects

Clinical Trial and Post-marketing Data

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.

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	Pruritus, local skin burning/pain of skin
Very rare	Allergic contact dermatitis/dermatitis, erythema, rash, urticaria, pustular psoriasis (see *4.4 Special Warnings and Precautions for Use*), skin thinning*/skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, alopecia*, trichorrhexis*, hair discoloration

General Disorders and Administration Site Conditions

Very rare	Application site irritation/pain

**Skin features of hypothalamic-pituitary-adrenal (HPA) axis suppression.*

4.9 Overdose

Symptoms and signs

Topically applied *BETNOVATE - C SKIN CREAM* 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 appear (see *4.8 Undesirable Effects*).

Treatment

In the event of chronic overdose 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 Centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Betamethasone valerate

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

The mechanism of action of clioquinol is not known but its action is probably due to its iodine content.

5.2 Pharmacodynamic Properties

ATC code
D07BC01 Betamethasone and antiseptics

Betamethasone valerate

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

Clioquinol

Clioquinol has antibacterial and antifungal action against *Staphylococcus aureus*, *Staphylococcus epidermidis, Escherichia coli* and *Candida albicans*. It has weak activity against *Staphylococcus pyogenes* and no activity against *Pseudomonas*.

5.3 Pharmacokinetic Properties

Absorption

Betamethasone valerate

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.

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

Betamethasone valerate

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

Elimination

Betamethasone valerate

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

Clioquinol

Clioquinol is excreted in the urine as glucuronide and sulphate metabolites

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Non-clinical studies have not been conducted with *BETNOVATE - C SKIN CREAM.*

Betamethasone valerate and clioquinol 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.*

Reproductive Toxicology

Pregnancy

Betamethasone valerate

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.

Clioquinol

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.

7. DESCRIPTION

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Clioquinol I.P. 3.0 % w/w
Chlorocresol I.P. 0.1% w/w (as preservative) in a non-greasy base.

List of Excipients

Chlorocresol (as preservative)
Cetomacrogol 1000
Cetostearyl alcohol
White soft Paraffin
Liquid Paraffin
Sodium Dihydrogen Phosphate dihydrate
Phosphoric acid or Sodium hydroxide (for pH adjustment)
Purified water

For important information about some of these excipients see *4.4 Special Warnings and Precautions for Use.*

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

No incompatibilities have been identified.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Aluminium tube in a carton.

All presentations may not be marketed in India.

8.4 Storage and Handling Instructions

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

Do not dilute

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or their patient's parents) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *BETNOVATE - C SKIN CREAM*. Patients (and/or their patient's parents) may also be informed about posology, method of administration and storage/handling information as applicable

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing License number is indicated on the labels and packaging.

12. DATE OF REVISION

18th September 2020

Trade marks are owned by or licensed to the GSK group of companies.

Version: BEVC/PI/IN/2020/01

Adapted from Betamethasone 17-valerate-Clioquinol GDS 12 / IPI 04 dated 11 May 2020