NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BETNOVATE-C betamethasone valerate 0.1% w/w and clioquinol 3% w/w cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betamethasone valerate 0.1% w/w and clioquinol 3% w/w

Excipients with known effect:

Cetostearyl alcohol

Chlorocresol

For full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

BETNOVATE-C Cream is a smooth, straw-coloured water-miscible cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BETNOVATE-C preparation is indicated for the treatment of adults, elderly and children over 1 year for the following conditions where secondary bacterial and/or fungal infection is present, suspected or likely to occur:-

- Eczema including atopic and discoid eczemas.
- Prurigo nodularis.
- Psoriasis (excluding widespread plaque psoriasis).
- Neurodermatoses including lichen simplex, lichen planus.
- Seborrhoeic dermatitis.
- Contact sensitivity reactions.
- Insect bite reactions.
- Prickly heat.
- Anal and genital intertrigo.
- Otitis externa.

4.2 Dose and method of administration

Dose

BETNOVATE-C cream is often 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 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 dermatosis

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 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 BETNOVATE-C is contraindicated in neonates and infants under 1 year of age (see 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 to ensure the amount applied is the minimum that provides therapeutic benefit.

Special populations

Elderly population

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

BETNOVATE-C is contraindicated where there is coexisting infection, otherwise concurrent antimicrobial therapy required.

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

- Rosacea.
- Acne vulgaris.
- Peri-oral dermatitis.
- Pruritus without inflammation.
- Perianal or genital pruritus.
- Primary cutaneous viral infections (e.g., herpes simplex, chickenpox).
- Hypersensitivity to any component of the preparation or to iodine.
- Primary infected skin lesions caused by infection with fungi or bacteria.
- Primary or secondary infections due to yeasts.

The use of dermal corticosteroids in the eye is contraindicated.

4.4 Special warnings and precautions for use

Hypersensitivity

BETNOVATE-C should not be used 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 section 4.8 Undesirable effects) may resemble symptoms of the condition under treatment. Local hypersensitivity reactions (see section 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 section 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 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 of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.

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.

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 section 4.8 Undesirable effects) . If used in psoriasis careful patient supervision is important.

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

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

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 is used for prolonged periods or under occlusion.

4.5 Interaction with other medicines 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of BETNOVATE-C 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 BETNOVATE-C 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 betamethasone valerate-clioquinol 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 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.

Fertility

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

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

Clinical Trial and Post-marketing Data

Adverse drug reactions (ADRs) 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.

Vascular disorders

Very rare: Dilatation of the superficial blood vessels.

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 Warnings and Precautions), 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

In very rare instances, treatment of psoriasis with corticosteroid (or its withdrawal) is thought to have provoked the pustular form of the disease.

*Skin features of HPA axis suppression

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphve.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and signs

Topically applied betamethasone valerate-clioquinol 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 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 glucocorticosteroid insufficiency.

For advice on management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Betamethasone and antiseptics, ATC code: D07BC01

Mechanism of action

Betamethasone valerate is an active topical corticosteroid which produces a rapid response in those inflammatory dermatoses that are normally responsive to topical corticosteroid therapy, and is often effective in the less responsive conditions such as psoriasis.

Clioquinol is an anti-infective agent which has both antibacterial and anticandidal activity.

Pharmacodynamic effects

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*

5.2 Pharmacokinetic properties

The following data apply to BETNOVATE-C skin preparations.

Absorption

As with other topical corticosteroids, sufficient betamethasone valerate may be absorbed to give systemic effects if applied under an occlusive dressing or when the skin is broken.

Biotransformation

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

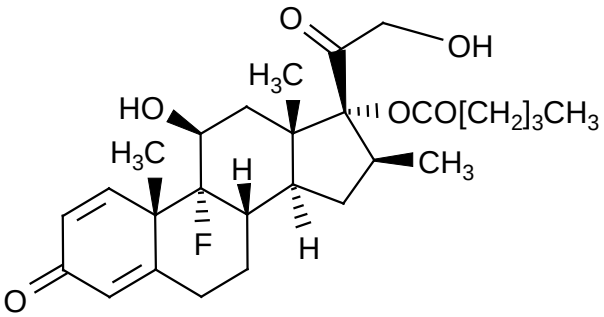
Elimination

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

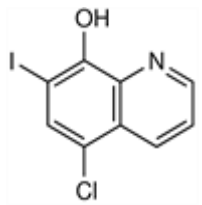
Clioquinol is excreted in the urine as glucuronide and sulphate metabolites.

Chemical Structure

Betamethasone valerate



Clioquinol



5.3 Preclinical safety data

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

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 Toxicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BETNOVATE-C Cream:

- Chlorocresol
- Cetomacrogol 1000
- Cetostearyl alcohol
- White soft paraffin (see Section 4.4 Special warnings and precautions for use)
- Liquid paraffin (see Section 4.4 Special warnings and precautions for use)
- Sodium dihydrogen phosphate dihydrate
- Phosphoric acid
- Sodium hydroxide
- Purified water

6.2 Incompatibilities

No incompatibilities have been identified.

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

BETNOVATE-C Cream: Store below 30°C.

6.5 Nature and contents of container

BETNOVATE-C Cream is supplied in a collapsible aluminium tube, internally coated with an epoxy resin based lacquer and closed with a wadless polypropylene cap.

BETNOVATE-C Cream is supplied in a 15 g tube.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

Instructions for Handling

Do not dilute.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 31 December 1969

10. DATE OF REVISION OF THE TEXT

24 August 2020

Summary table of changes

Section changed	Summary of new information
4.4	Added warning for flammability risk.
6.1	Referenced Section 4.4 Special warnings and precautions for use

Version 4.0