Summary of Product Characteristics

1. Name of the medicinal product
Cicloderm C Cream

2. Qualitative and quantitative composition
0.05% w/w clobetasone butyrate
1% w/w ciclopirox olamine
0.1% w/w gentamicin (as sulfate)
Excipients with known effect:
Cetostearyl alcohol
Chlorocresol
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Cream

4. Clinical particulars

4.1 Therapeutic indications
For local treatment of skin inflammations accompanied by a mycotic and/or bacterial infection.

Clobetasone butyrate is a moderately potent topical corticosteroid.

Ciclopirox (as cilclopirox olamine) is a synthetic, broad-spectrum, antifungal agent.

Gentamicin sulfate is a wide spectrum antibiotic that provides highly effective topical treatment in primary and secondary bacterial infections of the skin. Bacteria susceptible to the action of gentamicin sulfate include sensitive strains of Streptococci (group A beta-hemolytic, alphahemolytic), *Staphylococcus aureus* (coagulase positive, coagulase negative, and some penicillinaseproducing strains), and the gram-negative bacteria, *Pseudomonas aeruginosa, Aerobacter aerogenes, Escherichia coli, Proteus vulgaris and Klebsiella pneumoniae.*

4.2 Posology and method of administration

Route of administration: Cutaneous

Adults, Elderly, Children and Infants

Creams are especially appropriate for moist or weeping surfaces.

Apply thinly and gently rub in using only enough to cover the entire affected area twice and if needed even three times a day 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.

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 corticosteroids especially with potent preparations.

Duration of treatment for adults and elderly
Continuous daily treatment for longer than four weeks is not recommended. If the condition worsens or does not improve within four weeks, treatment and diagnosis should be re-evaluated.

Paediatric population

Use in children under 12 years should be on the advice of a doctor.

Care should be taken when using Cicloderm C Cream to ensure the amount applied is the minimum that provides therapeutic benefit.

Duration of treatment for children and infants

When clobetasone is used in the treatment of skin inflammations in children, extreme caution is required and treatment should not normally exceed 7 days.

If the condition worsens or does not improve within 7 days, treatment should be reviewed.

Once the condition has been controlled, the frequency of application should be reduced to the lowest effective dose for the shortest time possible.

Continuous daily treatment for longer than 4 weeks is not recommended in children.

Elderly

Clinical studies with clobetasone 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 or to any of the excipients listed in section 6.1.

The following conditions should not be treated with Cicloderm C Cream
• Untreated viral cutaneous infections.
• Rosacea
• Acne vulgaris
• Pruritus without inflammation.

4.4 Special warnings and precautions for use

Cicloderm C Cream should be used with caution in patients with a history of local hypersensitivity to other corticosteroids. 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 can be considered 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.

The use of topical antibiotics occasionally allows overgrowth of nonsusceptible organisms, ~~including fungi~~. If this occurs, or if irritation, sensitization, or superinfection develops, treatment with ~~Gentamicin Sulfate~~ Cicloderm C Cream should be discontinued and appropriate therapy instituted.

Cicloderm C Cream is not for ophthalmic use.

Keep out of reach of children.

Paediatric population

Children are more likely to develop local and systemic adverse reactions due to the use of local corticosteroids because of their higher surface area to body mass ratio and, in general, require a shorter treatment.

Particularly, in infants and toddlers the nappy can be considered as an occlusive dressing and therefore can enhance absorption.

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

Safety and effectiveness of ciclopirox in pediatric patients below the age of 10 years have not been established.

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.

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.

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.

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.

Accidental ingestion

For external use only. This and all medication should be kept out of the reach of children. In case of accidental ingestion, professional assistance should be sought or a national poison control centre contacted immediately (see section 4.9).

Cicloderm C Cream contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis) and chlorocresol which may cause allergic reactions.

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.

Topical steroid withdrawal syndrome
Long term continuous or inappropriate use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.

4.5 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see section 5.3).

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

There are no adequate or well-controlled studies with the use of ciclopirox in pregnant women. ~~Therefore, LOPROX Cream should be used during pregnancy only if the potential benefit justifies the potential risk~~ ~~to the fetus.~~

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 11, 37, 51 and 24 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 27 and 49 times the maximum recommended human dose based on body surface area comparisons, respectively).

Therefore, administration of Cicloderm C 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.

Breast-feeding

It is not known whether ciclopirox is excreted in human milk.

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

If used during lactation, Cicloderm 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 corticosteroids on fertility.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of clobetasone 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 clobetasone.

4.8 Undesirable effects

Adverse drug reactions (ADRs) of clobetasone butyrate cream are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <2/10), 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

Infections and Infestations	
Very rare	Opportunistic infection
Immune System Disorders	
Very rare	Hypersensitivity, generalised rash
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
Skin and Subcutaneous Tissue Disorders	
Very rare	Allergic contact dermatitis, urticaria, skin atrophy*, pigmentation changes*, exacerbation of underlying symptoms, local skin burning, hypertrichosis, rash, pruritus, erythema

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

Not known Withdrawal reactions - redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules. (see section 4.4)

Eye disorders

Not known	Vision, blurred (see also section 4.4)

In all controlled clinical studies with 514 patients using ciclopirox cream and in 296 patients using the vehicle cream, the incidence of adverse reactions was low. This included pruritus at the site of application in one patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in one patient and worsening of the clinical signs and symptoms in another patient using the vehicle cream.

In patients with dermatoses treated with gentamicin sulfate, irritation (erythema and pruritus) that did not usually require discontinuance of treatment has been reported in a small percentage of cases. There was no evidence of irritation or sensitization, however, in any of these patients patch-tested subsequently with gentamicin sulfate on normal skin. Possible photosensitization has been reported in several patients but could not be elicited in these patients by reapplication of gentamicin sulfate followed by exposure to ultraviolet radiation.

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. . Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
Side effects can also be reported to the following email: safety@trima.co.il

4.9 Overdose

Symptoms and signs

Topically applied clobetasone 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).

Treatment

In the event of overdose, clobetasone 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 centere, where available.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code

D07AB Corticosteroids, moderately potent (group II)
D07AB30 Combinations of corticosteroids
D01AE Other antifungals for topical use
D01AE Combinations
D06AX Other antibiotics for topical use
D06AX07 Gentamicin

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.

Ciclopirox is a hydroxypyridone antifungal agent that acts by chelation of polyvalent cations (Fe or Al), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Gentamicin sulfate is a wide spectrum antibiotic that provides highly effective topical treatment in primary and secondary bacterial infections of the skin. Bacteria susceptible to the action of gentamicin sulfate include sensitive strains of Streptococci (group A beta-hemolytic, alphahemolytic), *Staphylococcus aureus* (coagulase positive, coagulase negative, and some penicillinaseproducing strains), and the gram-negative bacteria, *Pseudomonas aeruginosa, Aerobacter aerogenes, Escherichia coli, Proteus vulgaris and Klebsiella pneumoniae.*

Pharmacodynamic effects

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

Clobetasone butyrate has little effect on hypothalamo-pituitary-adrenal function. This was so even when clobetasone butyrate cream was applied to adults in large amounts under whole body occlusion.

Clobetasone butyrate is less potent than other available corticosteroid preparations and has been shown not to suppress the hypothalamo-pituitary-adrenal axis in patients treated for psoriasis or eczema.

Pharmacological studies in man and animals have shown that clobetasone butyrate has a relatively high level of topical activity accompanied by a low level of systemic activity.

5.2 Pharmacokinetic properties

Absorption and Distribution

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.

A single application of 30g clobetasone butyrate 0.05% ointment to eight patients resulted in a measurable rise in plasma clobetasone butyrate levels during the first three hours but then the levels gradually decreased. The maximum plasma level reached in the first three hours was 0.6ng/ml. This rise in levels was followed by a more gradual decline with plasma levels of clobetasone butyrate falling below 0.1ng/ml (the lower limit of the assay) after 72 hours. The normal diurnal variation in plasma cortisol levels was not affected by the application of clobetasone butyrate ointment.

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 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.

Pharmacokinetic studies in men with tagged ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.

Penetration studies in human cadaverous skin from the back, with ~~LOPROX®~~ ciclopirox cream with tagged ciclopirox showed the presence of 0.8 to 1.6% of the dose in the stratum corneum 1.5 to 6 hours after application. The levels in the dermis were still 10 to 15 times above the minimum inhibitory concentrations.

Autoradiographic studies with human cadaverous skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and PhotoDraize study conducted in a total of 142 healthy male subjects showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photo-contact sensitization due to ciclopirox cream.

5.3 Preclinical safety data

Genotoxicity and Carcinogenesis

Conventional *in vitro* and *in vivo* genotoxicity studies with clobetasone reveal no hazard for humans.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical clobetasone.

A 104-week dermal carcinogenicity study in mice was conducted with ciclopirox cream applied at doses up to 1.93% (100 mg/kg/day or 300 mg/m /day). No increase in drug related neoplasms was noted when compared to control.

The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation

(positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe^{3+},
with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An *in vitro* cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

Reproductive toxicity

Topical application of clobetasone to rats at doses of 0.5 or 5 mg/kg/day, and subcutaneous administration to mice at doses ≥3 mg/kg/day or rabbits at doses ≥30 µg/kg/day during pregnancy resulted in foetal abnormalities including cleft palate, intrauterine growth retardation and foetal loss.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85 mg/kg/day ciclopirox (approximately 1.2 times the maximum recommended human dose based on body surface area comparisons). **6. Pharmaceutical particulars**

6.1 List of excipients
Purified water
Glycerol
Glyceryl monostearate
Propylene glycol
Cetostearyl alcohol
Beeswax (white)
SE glyceryl monostearate (acid stable)
Dimethicone
Citric acid anhydrous
Chlorocresol

6.2 Incompatibilities
None stated.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store in a cool place, below 25°C.

6.5 Nature and contents of container
White to off-white homogeneous cream, packed in a 15 g or 30 g tube.

6.6 Special precautions for disposal and other handling
Patients should be advised to wash their hands after applyingCicloderm C, unless it is the hands that are being treated.

7. Manufacturer:
Trima, Israel Pharmaceutical Products Maabarot Ltd., Maabarot 4032000, Israel.

8. Marketing authorisation holder
Trima, Israel Pharmaceutical Products Maabarot Ltd., Maabarot 4023000, Israel.

9. Marketing authorisation number(s)
068.06.27821.00

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