SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DERMAMIX B CREAM
Betamethasone Valerate, Gentamicin and Miconazole Nitrate Skin Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15g contains:
Betamethasone Valerate
Eq. to Betamethasone 0.10 % w/w
Gentamicin Sulphate
Eq. to Gentamicin 0.10 % w/w
Miconazole Nitrate 2.0 % w/w

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Cream

For information on strength refer *2. Qualitative and Quantitative Composition* above.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DERMAMIX B is indicated for steroid responsive dermatosis associated with mixed infection.

4.2 Posology and Method of Administration

Creams are 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 twice daily for up to seven days, then change to another corticosteroid preparation not containing gentamicin sulphate if further treatment is required. 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 *DERMAMIX B* 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.

Treatment should not be continued for more than seven days without medical supervision. If the condition worsens or does not improve within seven days, treatment and diagnosis should be re-evaluated.

Children aged 2 years and over

DERMAMIX B is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus *DERMAMIX B* is contraindicated in neonates, infants and children less than 2 years 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 *DERMAMIX B* to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

DERMAMIX B is suitable for use in the elderly. The greater frequency of decreased hepatic and 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 impairment

Dosage should be reduced in patients with reduced renal function (see *4.4 Special Warnings and Precautions for Use*).

4.3 Contraindications

DERMAMIX B is contraindicated in children under 2 years of age.

DERMAMIX B is contraindicated in individuals with a known hypersensitivity to any of the active ingredients or to any of the excipients listed in *Section 2* above.

Due to the known ototoxic and nephrotoxic potential of gentamicin sulphate, the use of *DERMAMIX B* in large quantities or on large areas for prolonged

periods of time is contraindicated in circumstances where significant systemic absorption may occur (*see 4.2 Posology and Method of Administration*).

The following conditions should not be treated with *DERMAMIX B:*

- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Pruritus without inflammation
- Perianal and genital pruritus
- Primary cutaneous viral infections
- Primary infected skin lesions caused by infection with fungi, bacteria, or yeast
- Otitis externa when the ear drum is perforated, because of the risk of ototoxicity

4.4 Special Warnings and Precautions for Use

Hypersensitivity

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with miconazole formulations. If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued.

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 *DERMAMIX B.* If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression

Manifestations of hypercortisolism (*Cushing's syndrome*) and reversible hypothalamicpituitary-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 disturbance

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.

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.

Contact sensitisation

Extended or recurrent application may increase the risk of contact sensitisation.

Ototoxicity and nephrotoxicity

Following significant systemic absorption, aminoglycosides such as gentamicin can cause irreversible ototoxicity. Gentamicin also has nephrotoxic potential (see *4.3 Contraindications*).

Renal impairment

In renal impairment the plasma clearance of gentamicin is reduced (see *4.2 Posology and Method of Administration*).

Application to the face

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

Application to 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 (see *4.8 Undesirable Effects*).

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 skin folds and 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.

Miconazole administered systemically is known to inhibit CYP3A4/2C9, which can lead to prolonged effects of warfarin or other vitamin K antagonists. While systemic absorption is limited with topical formulations, the concomitant use of *DERMAMIX B* and warfarin or other vitamin K antagonists should be done with caution and the anticoagulant effect should be carefully monitored and titrated. Patients should be advised of the symptoms of bleeding events and to immediately stop treatment with miconazole and seek medical advice should they occur (see section *4.5 Drug Interactions*).

4.5 Drug Interactions

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

Following significant systemic absorption, gentamicin sulphate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents.

Possibility of cumulative toxicity should be considered when gentamicin sulphate is applied topically in combination with systemic aminoglycoside therapy.

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after topical application, clinically relevant interactions are rare.
However, in patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored.

4.6 Use in Special Populations

Fertility

There are no data in humans to evaluate the effect of DERMAMIX B on fertility.

Pregnancy

In animals, miconazole nitrate has shown no teratogenic effects but is foetotoxic at high oral doses. Only small amounts of miconazole nitrate are absorbed following topical administration.

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see *6. Nonclinical Properties*). The relevance of this finding to humans has not been established.

However, gentamicin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity.

Thus, the use of *DERMAMIX B* is not recommended in pregnancy.

Lactation

Topically applied miconazole is minimally absorbed into the systemic circulation, and it is not known whether miconazole is excreted in human breast milk.

The safe use of betamethasone valerate with gentamicin and miconazole 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.

Thus, use of *DERMAMIX B* is not recommended in lactation.

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *DERMAMIX B* on driving performance or the ability to operate machinery.

4.8 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 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000), very rare (<1/10,000 including isolated reports) and Not Known (cannot be estimated from the available data).

Infections and Infestations

Very rare	Opportunistic infection

Immune System Disorders

Very Rare	Local hypersensitivity
Not Known	Anaphylactic reaction

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

Uncommon Skin inflammation

Very rare Allergic contact dermatitis/dermatitis, erythema, rash, urticaria, pustular psoriasis (*see also 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*

Not Known Angioedema

General Disorders and Administration Site Conditions

Uncommon Application site reactions (including application site irritation, burning, pruritus, reaction NOS and warmth)

Very Rare Pain

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

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities

4.9 Overdose

Symptoms and signs

Topically applied betamethasone valerate and gentamicin sulphate 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 *4.8 Undesirable Effects*).

Excessive use can result in skin irritation, which usually disappears after discontinuation of therapy. In case of accidental ingestion, stomach irritation may occur.

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.

Consideration should be given to significant systemic absorption of gentamicin sulphate *(*see *4.4 Special Warnings and Precautions for Use, 4.5 Drug Interactions).* If this is suspected, use of the product should be stopped and the patient's general status, hearing acuity, renal and neuromuscular functions should be monitored. Blood levels of gentamicin sulphate should also be determined. Haemodialysis may reduce the serum level of gentamicin sulphate.
DERMAMIX B is intended for cutaneous use, not for oral use. If accidental ingestion of large quantities of the product occurs, use appropriate supportive care.

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 and Pharmacodynamic Properties

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

Gentamicin sulphate

Gentamicin is mixture of antibiotic substances produced by the growth of *Micromonospora Purpurea*. It is a bactericidal antibiotic which acts by

inhibiting protein synthesis. It has greater antibacterial activity than streptomycin, neomycin or kanamycin.

Gentamicin exerts a number of effects on cells of susceptible bacteria. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effect is inhibition of protein synthesis at the level of the 30s ribosomal subunit.

Miconazole Nitrate

Miconazole nitrate is an imidazole antifungal agent and may act by interfering with the permeability of the fungal cell membrane. It possesses a wide antifungal spectrum and has some antibacterial activity.

5.1 Pharmacokinetic Properties

Betamethasone valerate

Absorption

Topical corticosteroids can be systematically 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 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.

Gentamicin sulphate

Absorption

Topical application of gentamicin has been reported to occur from wounds and inflamed skin. It is poorly absorbed from the gastrointestinal tract when administered orally.

Distribution

Absorbed gentamicin distributes to tissues. Aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney.

Metabolism and Elimination

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration.

Miconazole nitrate

Absorption
There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.

Distribution

Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells (10.6 %).

Metabolism and Elimination

The small amount of miconazole that is absorbed is eliminated predominately in faeces as both unchanged drug and metabolities.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Chlorocresol
White Soft Paraffin
Cetostearyl Alcohol
Glyceryl Monostearate
Liquid Paraffin

Glycerol
Sodium Hydroxide
Purified Water
Phosphoric Acid

6.2. Incompatibilities

No relevant data available.

6.3. Shelf Life

24 months

6.4. Special Precautions for storage

Store at temperature below 30°C. Do not freeze.

Keep out of reach of children.

For external use only.

6.5. Nature and contents of container

Collapsible aluminum tube having a screw threaded neck finish sealed with an aluminum membrane. Each tube is supplied with a white polyethylene screw cap which has a piercing tip to puncture open the aluminum membrane on the neck.

6.6. Instructions for use and handling

Keep away from the reach of children

7 MARKETING AUTHORISATION HOLDER

BEL-EA PHARMACY LTD

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD6865/13209

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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