SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mibetin 1 mg/g + 0.5 mg/g Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of cream contains 1 mg gentamicin (as 1.67 mg gentamicin sulfate) and 0.5 mg betamethasone (as 0.64 mg betamethasone dipropionate).

Excipients with known effect
Each gram of cream contains 72 mg of cetostearyl alcohol, 1.7 mg of methyl parahydroxybenzoate and 0.3 mg of propyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream,
homogeneous white cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mibetin cream is indicated for localised inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids and associated with infection with gentamicin sensitive pathogens.

4.2 Posology and method of administration

Posology
Mibetin cream is applied once or twice daily. Frequency should be reduced as the clinical symptoms improve.

Paediatric population
Mibetin cream is applied once daily in children.
Mibetin cream is contraindicated in newborns and infants less than 1 year old.

Method of administration
Mibetin cream is applied thinly to the diseased skin areas and lightly rubbed in.

The treated skin area should be no more than 10% body surface area. In children, Mibetin cream should only be used in the short term and over small areas. In general, increased caution must be exercised when treating children with corticosteroid preparations, as there may be increased absorption of the corticosteroid through the child's skin compared to adults.
Treatment under an occlusive dressing should also be avoided due to the risk of possible absorption of betamethasone dipropionate.

In particular, Mibetin cream is intended for use on greasy skin or for treatment of weeping skin conditions.

Duration of use
Duration of treatment with Mibetin cream should not exceed 10 days in adults and 7 days in children.
If needed and clinically justified, further treatment should be administered as monotherapy with a glucocorticoid (if necessary, with a less potent topical glucocorticoid) or an antibiotic.

4.3 Contraindications

Hypersensitivity to the active substances, methyl parahydroxybenzoate, propyl parahydroxybenzoate or to any of the excipients listed in section 6.1 or in cases of hypersensitivity to other medicinal substances of the glucocorticoid type or aminoglycoside antibiotic type.

Mibetin cream is contraindicated during pregnancy (see section 4.6).
Furthermore, Mibetin cream must not be used in the following cases:
- viral infections including vaccination reactions and chickenpox,
- tuberculosis and syphilis of the skin,
- viral infections of the skin (e.g. herpes simplex, herpes zoster),
- rosacea and rosacea-like dermatitis,
- perioral dermatitis,
- dermatomycosis,

- ophthalmological disorders,
- concomitant systemic use of aminoglycoside antibiotics, due to the risk of toxic serum levels,
- advanced renal impairment,
- babies and infants less than 1 year old.

Mibetin cream is not intended for use in the auditory canal, eyes or on mucous membranes.

Airtight occlusive dressings must not be used.

4.4 Special warnings and precautions for use

Gentamicin-containing products such as Mibetin cream should be carefully selected for each individual treatment. They should only be used if the response to antiseptic measures is slow to appear, response is insufficient or antiseptic therapy is contraindicated.

In some cases gentamicin may cause irreversible partial or total deafness when given systemically or when applied topically to open wounds or large areas of damaged skin. This effect is dose-related and is enhanced by renal and/or hepatic impairment and is more likely in the elderly.

Prolonged use may lead to skin sensitisation and the emergence of resistant organisms. Cross sensitivity with other aminoglycoside antibiotics may occur.

There have been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A > G mutation, including cases where the patient's aminoglycoside serum levels were within the recommended range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation. Mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

In the facial area Mibetin cream should be applied with particular caution.
As absorption of the active substances is possible, long-term treatment and/or use on large skin areas should be avoided.

The adverse reactions reported for systemically administered glucocorticoids, including impaired adrenocortical function, may also occur with externally applied glucocorticoids after systemic absorption. This particularly applies to infants and children.

Systemic absorption of topically applied glucocorticoids generally increases with the potency of the glucocorticoids, duration of use, the extent of treated body surface areas and in the treatment of intertriginous skin areas.

The topical use of gentamicin in skin infections engenders the risk of allergic reactions. Gentamicin is a contact allergen with an individual sensitisation frequency of approximately 1.4% with increasing tendency. The risk of sensitisation increases with increasing duration of therapy. Between gentamicin and other aminoglycosides, such as neomycin and kanamycin, there is a group allergy. Topically acquired gentamicin allergy excludes subsequent systemic use of gentamicin and other aminoglycosides (see also sections 4.3 and 4.8).

The risk of local skin infections may be increased with topical glucocorticoid use.

Occasionally, prolonged or extensive topical use of antibiotics leads to colonisation by non-sensitive pathogens, including fungi. In this case, or at the onset of skin irritation, allergic reactions or superinfections, treatment with gentamicin should be discontinued and suitable therapy initiated.

Systemic absorption of topically applied gentamicin may be increased during treatment of extensive skin areas, particularly over prolonged periods or in the presence of skin fissures. Under these circumstances, caution must be exercised, especially in children, as there is a possibility that systemic adverse reactions may occur even after local use of gentamicin.

Due to the neuromuscular blocking effect of aminoglycosides upon systemic absorption, caution is advised in patients with myasthenia gravis, Parkinson's disease, other diseases with muscular weakness or concomitant use of other medicinal products with neuromuscular blocking effects.

Visual disturbances may occur with systemic and topical (including intranasal, inhalation and intraocular) use of corticosteroids. If a patient presents with symptoms such as blurred vision or other visual disturbances, referral of the patient to an ophthalmologist should be considered to evaluate possible causes of such visual disturbance; among others, these include cataract, glaucoma or rare diseases, e.g. central serous chorioretinopathy (CSC), which have been reported after the use of systemic or topical corticosteroids.

Topical steroid withdrawal syndrome
Long term 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.

Mibetin cream contains methyl parahydroxybenzoate and propyl parahydroxybenzoate (E218 and E216) and cetostearyl alcohol. Methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic

reactions (possibly delayed). Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Mibetin cream should not be applied to wounds or leg ulcers.

If latex condoms are used concurrently during treatment with Mibetin cream in the genital or anal region, their tear resistance may be reduced by the white soft paraffin and liquid paraffin excipients, thereby compromising the safety of such condoms.

The label will state strong steroid.

4.5 Interaction with other medicinal products and other forms of interaction

Due to possible mutual inactivation, Mibetin cream should not be applied concomitantly with other topical dermatological agents.
Gentamicin is incompatible with amphotericin B, heparin, sulfadiazine and beta-lactam antibiotics (e.g. cephalosporins).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Mibetin cream in pregnant women.
Gentamicin penetrates the placental barrier and attains measurable concentrations in foetal tissue and amniotic fluid. Studies in animals have shown reproductive toxicity (see section 5.3).

Betamethasone showed embryotoxic and teratogenic effects in animal studies after systemic and topical administration. In animal studies with other glucocorticoids, embryotoxic and teratogenic effects including cleft palate, skeletal abnormalities, as well as intrauterine growth disorders and embryolethality were observed.. In human foetuses, there may be an increased risk of oral cleft formation with systemic use of glucocorticoids during the first trimester.

Animal studies have shown that glucocorticoid administration at subteratogenic doses during pregnancy contributes to an increased risk of intrauterine growth retardation, cardiovascular disease and/or metabolic diseases in adulthood, as well as to a permanent change in glucocorticoid receptor density, neurotransmitter turnover and behaviour.

Mibetin cream is therefore contraindicated for use during pregnancy (see section 4.3).

Breastfeeding

Gentamicin is excreted in human milk in small amounts. There are no data on the excretion of betamethasone dipropionate in human milk. Other glucocorticoids are excreted in human milk. If extensive or long-term use is required, Mibetin cream should not be used during breastfeeding. Contact between the infant and treated skin areas must be avoided.

Fertility
No studies on the effect on human fertility have been conducted with Mibetin cream.

4.7 Effects on ability to drive and use machines

Mibetin cream has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions from post-authorisation experience

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
not known (cannot be estimated from the available data)

Organ class	Frequency	Adverse reactions
Endocrine disorders	Not known	Suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome in children
Metabolism and nutrition disorders	Not known	Decreased weight gain in children
Eye disorders	Not known	Blurred vision (see also section 4.4)
Vascular disorders	Not known	Intracranial hypertension in children
Skin and subcutaneous tissue disorders	Not known	Burning, pruritus, irritation, dryness, folliculitis, hypertrichosis, steroid acne, acne-like rash, changes in skin pigmentation, rosacea-like (perioral) dermatitis, allergic contact dermatitis,

		maceration of the skin, skin atrophy, striae, miliaria, erythema, hypersensitivity, skin discoloration 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)
Musculoskeletal and connective tissue disorders	Not known	Growth retardation in children

With use over long periods (more than 4 weeks) and/or large areas (approximately 10 % of body surface area or more) and especially under occlusion, the following may occur: skin maceration, skin atrophy, telangiectasia, striae, steroid acne, miliaria, folliculitis, hypertrichosis, pigmentation changes and perioral dermatitis.
Transient mild irritation (erythema, pruritus) caused by gentamicin usually does not require discontinuation of treatment.
If severe irritation, sensitisation or superinfection occurs, treatment should be discontinued and appropriate therapy initiated.
Topical use of gentamicin may lead to impaired wound granulation.
Furthermore, oto-, vestibular- and nephrotoxic effects may occasionally occur even after external use of gentamicin, particularly with repeated use of gentamicin on extensive wounds. Treatment with gentamicin caused transient irritation (erythema and pruritus).
Methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).
Paediatric population:
Suppression of the hypothalamic-pituitary-adrenal axis manifests in children as a low plasma cortisol level and lack of response to ACTH stimulation.
Intracranial hypertension manifests as bulging fontanelles, headache and a bilateral papillary oedema.
Children are more susceptible than adult patients to glucocorticoid-induced suppressive effects on the hypothalamic-pituitary-adrenal axis and to exogenous glucocorticoid effects, due to the larger skin surface area to body weight ratio.
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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Mibetin cream should only be used at the recommended dosage.

Symptoms of overdose
Excessive or extensive use of topical glucocorticoids (chronic overdose or misuse) may lead to suppression of the hypothalamic-pituitary-adrenocortical function resulting in secondary adrenocortical insufficiency. Furthermore, symptoms of excessive glucocorticoid use may occur, including Cushing's syndrome. Excessive or extensive use of topical antibiotics may lead to wound colonisation by fungi or non-susceptible pathogens.

Treatment
If Mibetin cream has been accidentally ingested, or if used in excessive amounts or over excessively long periods of time, a physician should be informed immediately. Appropriate symptomatic treatment must be initiated.
As a rule, acute symptoms of hypercorticism are reversible. Electrolyte disturbances must be treated as appropriate.
In cases of chronic toxicity, gradual discontinuation of the glucocorticoid is recommended.
If colonisation with non-susceptible pathogens occurs, treatment with Mibetin cream should be discontinued and appropriate therapy initiated.

If a dose has been omitted, users should make up for it as soon as possible and then resume their normal dosing regimen.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids, dermatological preparations; Corticosteroids, potent, combinations with antibiotics
ATC code: D07CC01

Information on betamethasone
Betamethasone dipropionate is a synthetic glucocorticoid and is topically applied. Betamethasone is classed as a potent corticosteroid.

Betamethasone, a derivative of prednisolone, shows high glucocorticoid activity and only minor mineralocorticoid activity. Glucocorticoids for topical use, such as betamethasone dipropionate, are indicated primarily for their anti-inflammatory, antipruritic and vasoconstrictive action for the treatment of glucocorticoid-sensitive skin conditions.

The McKenzie vasoconstriction assay is among the tests that can be used for the pharmacodynamic comparison of efficacy between betamethasone dipropionate and various known fluorinated topical glucocorticoids. In one test, betamethasone dipropionate showed a significantly higher blanching rate ($p < 0.05$) than fluocinolone acetonide, fluocortolone caproate, flumethasone pivalate and betamethasone valerate.

Information on gentamicin
Gentamicin is an antibiotic from the aminoglycoside group. It represents a mixture of the structurally very similar homologues gentamicin C_1, C_{1a} and C_2.

Mechanism of action

For gentamicin, the mechanism of action is based on disruption of protein biosynthesis via interaction with ribosomal RNA, followed by faulty amino acid incorporation during translation. This results in a bactericidal effect.

Pharmacokinetic/pharmacodynamic relationship

Efficacy largely depends on the ratio between maximum achieved concentration (C_{max}) on site of action and minimum inhibitory concentration (MIC) of the pathogen.

Mechanisms of resistance

Resistance to gentamicin may be based on the following mechanisms:

- Enzymatic inactivation: enzymatic modification of aminoglycoside molecules is the most common mechanism of resistance. For this, acetyltransferases, phosphotransferases or nucleotidyltransferases are responsible, which are mostly plasmid-encoded.
- Reduced penetration and active efflux: these mechanisms of resistance are found mainly in *Pseudomonas aeruginosa*.
- Change in target structure: modifications within the ribosomes occur as a cause of resistance. These arise either through mutation or methyltransferase formation. Gentamicin is largely cross-resistant to other aminoglycoside antibiotics.

There is a widespread cross-resistance between Gentamicin and other aminoglycoside antibiotics.

Breakpoints

Gentamicin is tested using the standard dilution series. The following minimum inhibitory concentrations for sensitive and resistant microorganisms have been established:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Pathogen	0B**Susceptible**	**Resistent**
Enterobacterales (systemic infections)	(≤ 2 mg/l) [1)]	(> 2 mg/l) [1)]
Enterobacterales (urinary tract infections)	≤ 2 mg/l	> 2 mg/l
***Acinetobacter* spp.** (systemic infections)	(≤ 4 mg/l) [1)]	(> 4 mg/l) [1)]
***Acinetobacter* spp.** (urinary tract infections)	≤ 4 mg/l	> 4 mg/l
Staphylococcus aureus (systemic infections)	(≤ 1 mg/l) [1)]	(> 1 mg/l) [1)]
Non-species specific limits*	≤ 0,5 mg/l	> 0,5 mg/l

[1)] The limits are based on epidemiological cut-off values (ECOFF), that separate wild type isolates and those with **reduced** suscebility**.**

* Limits mainly based on pharmacokinetic in serum.

These data are mainly based on the actual pharmacokinetic serum values obtained. However, these EUCAST breakpoints do not have any relevance for topical gentamicin preparations, as application of the cream/ointment results in topical antibiotic concentrations that are 250 to 500-fold above these breakpoints. Due to the high antibiotic concentrations at the site of action, development of resistance is unlikely with topical use of Mibetin cream. In a multicentre *in vitro* study to determine the resistance status of skin germs to gentamicin, all of the *S. aureus* isolates and *S. pyogenes* isolates tested were found to be sensitive at a concentration of 128 mg/L or more. Therefore, since concentrations of up to 1,000 mg/L are achieved with the cream or ointment formulation, no *S. aureus* and *S. pyogenes* strains with resistance to gentamicin could be found.

The prevalence of acquired resistance for individual species may vary locally and over time. Therefore, local information on the resistance situation is required - especially for the adequate treatment of severe infections. If, based on the local resistance situation, the efficacy of gentamicin is questionable, expert therapeutic advice should be sought. Particularly in the case of serious infections or treatment failure, a microbiological diagnosis should be sought, with detection of the pathogen and its susceptibility to gentamicin.

5.2 Pharmacokinetic properties

The pharmacokinetics of topically applied glucocorticoids after penetration of the skin is similar to that of systemically administered glucocorticoids.

Betamethasone dipropionate

Absorption

The extent of percutaneous absorption of topical corticosteroids depends on different factors like the vehicle, skin integrity and application of occlusive dressings. As topical corticosteroids are absorbed by normal intact skin, inflamed skin and/or other skin diseases may increase percutaneous absorption. Particularly, occlusive dressings increase the percutaneous absorption of topical corticosteroids.

Distribution, Biotransformation, Elimination

Glucocorticoids are bound to plasma proteins to varying degrees, metabolised mainly in the liver and usually excreted via the kidneys.

When betamethasone dipropionate is administered intravenously to rodents, the substance and its metabolites are excreted with the faeces. The substance is thus metabolised in the liver and excreted with the bile.

Betamethasone 17-propionate and 6β-hydroxybetamethasone 17-propionate were found as the main metabolites.

In human trials, a temporary decrease in plasma cortisol levels was found only to occur upon administration of over 60 g gentamicin/betamethasone cream per day on large surfaces of the body over a period of 4 weeks for psoriasis or atopic eczema.

Gentamicin sulfate

The active substance gentamicin can be administered parenterally or topically. It is not indicated for oral use due to minimal enteral absorption. The metabolism of

topically applied antibiotics after penetration of the skin basically follows the same pattern as for parenterally administered antibiotics.

Upon intramuscular administration of 1 mg gentamicin/kg body weight, mean peak gentamicin concentrations of 3.5-6.4 mg/L are measured after 30-60 minutes. The half-life is approximately 2 hours during the first 8-12 hours, after which gentamicin is slowly released from deep compartments with a half-life of 100-150 hours. Excretion is exclusively renal by glomerular filtration in unchanged and biologically active form.

Absorption
Following topical application of gentamicin preparations, the dermal absorption rate of gentamicin on intact skin is about 2% of the applied amount from a 0.1% cream preparation and approximately 0.5% from a 0.1% ointment preparation.
From wounds, an average of 6.9 µg gentamicin is absorbed per cm^2 of wound surface from a cream preparation and 1.5 µg from an ointment preparation. These active substance doses can result in serum concentrations up to 1 µg/mL, equivalent to approximately 10% of the minimum toxic level. For burn injuries, serum levels have been found to be between 3 and 4.3 µg/mL following topical gentamicin therapy.

Due to the enzymatic mechanism of resistance, which is significant for aminoglycosides, there are numerous instances of partial one-sided resistance, but also complete parallel resistance between germs and the various aminoglycoside antibiotics.

5.3 Preclinical safety data

Acute toxicity
Like all aminoglycoside antibiotics, gentamicin is potentially oto- and nephrotoxic. Non-clinical data reveal no special hazard for humans based on conventional studies on the acute toxic potential of betamethasone dipropionate.

Chronic toxicity
Betamethasone dipropionate
Studies on the chronic and subchronic toxicity of betamethasone dipropionate showed dose-dependent symptoms of a glucocorticoid overdose upon oral and dermal administration (e.g. increased serum glucose and cholesterol levels, decrease in lymphocytes in peripheral blood, bone marrow depression, atrophic changes in the spleen, thymus and adrenal glands, as well as decreased body weight gain).

Gentamicin sulfate
With regard to the subacute and chronic toxicity of gentamicin, there is a series of data on systemic effects. Like all aminoglycoside antibiotics, gentamicin is also potentially ototoxic and nephrotoxic. Previous *in vitro* tests with gentamicin did not reveal any clinically relevant genotoxic potential.

Mutagenicity
In previous studies, gentamicin and glucocorticoids showed no mutagenic effects. There are no long-term studies examining carcinogenic potential.

Toxicity to reproduction
Betamethasone dipropionate showed teratogenic effects in animal trials (e.g. cleft palate, skeletal abnormalities, subnormal weight, embryolethality). Studies on peri- and postnatal toxicity, as well as fertility, have not been performed.

Gentamicin showed transplacental renal toxicity in rats after IM administration of very high doses (75 mg/kg BW) at different times during gestation. In guinea pigs, daily IM administration of 4 mg/kg BW gentamicin from days 48 to 54 of gestation led to transient transplacental renal toxicity. Other aminoglycosides are known to potentially lead to inner ear damage in the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, white soft (containing all-rac-α-tocopherol)
Liquid paraffin
Cetostearyl alcohol
Macrogol cetostearyl ether 20
Methyl parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate (E 216)
Sodium dihydrogen phosphate dihydrate
Phosphoric acid solution
Sodium hydroxide solution
Purified water

6.2 Incompatibilities

Acidic- and in particular basic pH conditions lead to decomposition of the glucocorticoid.
Gentamicin sulfate is incompatible with anionic excipients (e.g. aqueous hydrophilic ointment DAB 10).
Due to possible mutual inactivation, Mibetin cream should not be applied concomitantly with other topical dermatological agents (see also section 4.5).

6.3 Shelf life

36 months

The shelf life after first opening is 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. The product is unaffected by refrigerated storage for short periods of time. Long-time refrigerated storage of the product is not foreseen.

6.5 Nature and contents of container

Aluminium tube with internal protective lacquer and a HDPE screw cap with piercing device.

Before using the cream for the first time the aluminium membrane has to be pierced by the spike on the outer side of the screw cap.

15 g cream
20 g cream
25 g cream
30 g cream
50 g cream
60 g cream

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 49452/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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