SUMMARY OF PRODUCT CHARACTERISTICS

Gentalene-C Cream
(Betamethasone Dipropionate, Gentamicin Sulfate & Clotrimazole Cream)

1. NAME OF THE MEDICINAL PRODUCT

Gentalene-C Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains:	
Betamethasone Dipropionate USP equivalent to Betamethasone	0.05% w/w
Gentamicin Sulfate USP equivalent to Gentamicin	0.10% w/w
Clotrimazole USP	1.0% w/w
Preservative:	
Chlorocresol BP	0.10% w/w
Cream base	q.s.

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Topical Cream

Description: White to off white, smooth, homogenous cream filled in properly printed Aluminium collapsible tubes and Further packed in properly Printed cartons.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications [1, 2, 5, 8]

Gentalene-C cream is indicated in patients 17 years and older for the topical treatment of the following dermal infections: tinea pedis, tinea cruris and tinea corporis due to *Epidermophyton floccosum, Trichophyton mentagrophytes, Trichophyton rubrum* and; candidiasis due to *Candida albicans*; particularly those accompanied by local inflammation and/or pruritus, and bacterial infections.

4.2 Posology and method of administration [1, 2, 8, 9]

Gentalene-C cream should be applied to the affected area as a thin film twice a day. Cream should not be used with occlusive dressings. This cream should not be applied to the diaper area if the patient requires diapers or plastic pants as these garments may constitute occlusive dressing.

Gentalene-C cream should not be used longer than 2 weeks in the treatment of tinea corporis or tinea cruris and; amounts greater than 45 g per week of **Gentalene-C cream** should not be used. If a patient with tinea corporis or tinea cruris shows no clinical improvement after 1 week of treatment, the diagnosis should be reviewed.

Gentalene-C cream should not be used longer than 4 weeks in the treatment of tinea pedis and amounts greater than 45 g per week of **Gentalene-C cream** should not be used. If a patient with tinea pedis shows no clinical improvement after 2 weeks of treatment, the diagnosis should be reviewed.

Gentalene-C cream should be used for at least two weeks to treat candida infections. Treatment should be reviewed if symptoms do not improve within 7 days.

Topical betamethasone dipropionate, one of the components of this cream, is a super- high potency topical corticosteroid. As with other highly active corticosteroid, therapy should be discontinued when control is achieved.

4.3 Contraindications [1, 2, 3, 5, 6]

Gentalene-C cream is contraindicated in:

- Patients who are hypersensitive to clotrimazole, betamethasone dipropionate, gentamicin sulfate, other corticosteroids or to any of the excipients listed in section 6.1.

Gentalene-C cream contains betamethasone dipropionate, as one of the components, which is contraindicated in:

- Rosacea and acne vulgaris
- Perioral dermatitis, perianal and genital pruritus
- Viral infections of the skin, e.g. Herpes simplex, chicken pox
- Gravitational ulcers

Hypersensitivity to the active substance(s) or to any of the excipients

4.4 Special warnings and precautions for use [1, 2, 3, 4, 5, 8, 9, 11]

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Gentalene C Cream can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or after withdrawal of treatment. Factors that predispose to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test.

Betamethasone 0.05% cream lowered adrenal corticosteroid secretion, although plasma cortisol levels did not go below the lower limit of the normal range. In a reported open- label paediatric study of subjects aged 3 months to 12 years of age, few subjects reported evidence of HPA axis suppression. The proportion of subjects with adrenal suppression in the reported study was progressively greater, the younger the age group.

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Cushing's syndrome and hyperglycemia may also occur with topical corticosteroids. These events are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.

Paediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios.

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing. If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

Use of topical corticosteroids may increase the risk of posterior subcapsular

cataracts and glaucoma. Cataracts and glaucoma have been reported in post marketing experience with the use of topical corticosteroid products, including topical betamethasone products (see section 4.8).
Avoid contact of **Gentalene-C cream** with eyes. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.
The use of **Gentalene-C cream** in the treatment of diaper dermatitis is not recommended.

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

The use of topical antibiotics occasionally allows overgrowth of non-susceptible organisms, including fungi. If this condition occurs, or if irritation, sensitization or superinfection develops, treatment with **Gentalene-C cream** should be discontinued and appropriate therapy instituted.

Instruct patients not to smoke or go near naked flames - 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.

Information for Patients

- Use **Gentalene-C cream** as directed by the physician. It is for external use only.
- Avoid contact with the eyes, mouth, or intravaginally.
- Advise patients to report any visual symptoms to their healthcare providers.
- Do not use **Gentalene-C cream** on the face or underarms.
- Do not use more than 45 grams of **Gentalene-C cream** per week.
- When using **Gentalene-C cream** in the groin area, patients should use the medication for 2 weeks only, and apply the cream sparingly. Patients should wear loose-fitting clothing. Notify the physician if the condition persists after 2 weeks.
- Do not use **Gentalene-C cream** for any disorder other than that for which it was prescribed.
- Do not bandage, cover or wrap the treatment area unless directed by the physician.
  Avoid use of **Gentalene-C cream** in the diaper area, as diapers or plastic pants may constitute occlusive dressing.
- Report any signs of local adverse reactions to the physician. Advise patients

that local reactions and skin atrophy are more likely to occur with occlusive use or prolonged use.
- This medication is to be used for the full prescribed treatment time, even though the symptoms may have improved. Notify the physician if there is no improvement after 1 week of treatment for tinea cruris or tinea corporis, or after 2 weeks for tinea pedis.

Paediatric Use

The Use of Gentalene C Cream in the Treatment of Patients under 17 Years of Age or Patients with Diaper Dermatitis is not Recommended.

Betamethasone and Clotrimazole Combination

Adverse events consistent with corticosteroid use have been reported in pediatric patients treated with combination of betamethasone and clotrimazole cream. In reported open-label studies, pediatric patients (aged 12 - 16 years old) using combination of betamethasone and clotrimazole cream for treatment of tinea pedis reported adrenal suppression as determined by cosyntropin testing. In another reported open-label study, pediatric patients (aged 12 - 16 years old) using combination of betamethasone and clotrimazole cream for treatment of tinea cruris reported adrenal suppression as determined by cosyntropin testing.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of hypothalamic-pituitary-adrenal (HPA) axis suppression when they are treated with topical corticosteroids. They are, therefore also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Pediatric patients may be more susceptible than adults to skin atrophy, including striae, when they are treated with topical corticosteroids.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids.

Gentamicin Sulfate

Gentamicin sulfate as a cream has been used successfully in children over one year of age, as well as in adults.

Geriatric Use

Betamethasone and clotrimazole combination

Reported clinical studies of combination of betamethasone and clotrimazole cream did not include sufficient numbers of subjects aged 65 and over to

determine whether they respond differently from younger subjects. However, greater sensitivity of some older individuals cannot be ruled out. The use of combination of betamethasone and clotrimazole cream under occlusion, such as in diaper dermatitis, is not recommended.

Post-marketing adverse event reporting for betamethasone and clotrimazole cream in patients aged 65 and above includes reports of skin atrophy and rare reports of skin ulceration. Caution should be exercised with the use of corticosteroid-containing topical products on thinning skin.

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

Gentalene-C cream contains cetostearyl alcohol and propylene glycol
Gentalene-C cream contains cetostearyl alcohol and propylene glycol which may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction [5, 6, 8, 10]

Betamethasone
Drug interactions have not been reported with topical forms of betamethasone.

Clotrimazole
It has been reported that concomitant medication with vaginal clotrimazole and oral tacrolimus (FK-506 immunosuppressant) might lead to increased tacrolimus plasma levels, and similarly with sirolimus. Patients should thus be thoroughly monitored for symptoms of tacrolimus or sirolimus overdosage, if necessary by determination of the respective plasma levels.

Clotrimazole cream may cause damage to latex contraceptives. Consequentially patients should be advised to use alternative precautions for at least five days after using this product.

Gentamicin Sulfate
Following drug interactions have been reported with systemic gentamicin:

- Antibacterials: increased risk of nephrotoxicity with cephalosporins notably cephalothin.

- Gentamicin has been known to potentiate anticoagulants such as warfarin and phenindione.
- Antifungals: increased risk of nephrotoxicity with amphotericin B.
- Cholinergics: antagonism of effect of neostigmine and pyridostigmine.
- Cyclosporin, cisplatin: increased risk of nephrotoxicity.
- Cytotoxics: increased risk of nephrotoxicity and possible risk of ototoxicity with cisplatin.
- Diuretics: increased risk of ototoxicity with loop diuretics (e.g. ethacrynic acid and furosemide).
- Muscle relaxants: effect of non-depolarising muscle relaxants such as tubocurarine enhanced. Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anesthesia.
- Indomethacin possibly increases plasma concentrations of gentamicin in neonates.
- Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.
- Concurrent use of the Botulinum Toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

4.6 Pregnancy and Lactation [1, 2, 3, 4, 5, 8, 9, 11]

Pregnancy

Betamethasone and Clotrimazole Combination

There are no reported data on topical betamethasone dipropionate or clotrimazole use in pregnant women to identify associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

An increased risk of low birth-weight infants was reported with the use of greater than 300 grams of potent or very potent topical corticosteroid during pregnancy. Advise pregnant women that betamethasone and clotrimazole combination cream may increase the risk of having a low birth-weight infant and to use betamethasone and clotrimazole combination cream on the smallest area of skin and for the shortest duration possible.

There have been no reproduction studies reported in animals or humans with the combination of clotrimazole and betamethasone dipropionate. In a reported animal reproduction study, betamethasone dipropionate caused malformations (i.e., umbilical hernias, cephalocele, and cleft palate) in pregnant rabbits when given by the intramuscular route during organogenesis. The reported data do not allow the calculation of relevant comparisons between the systemic exposure of clotrimazole and/or betamethasone dipropionate reported in the animal studies

to the systemic exposure that would be expected in humans after topical use of betamethasone and clotrimazole combination cream.

The reported background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have been reported for a background risk of birth defect, loss, or other adverse outcomes.

Betamethasone
An increased risk of low birth-weight infants was reported with the use of greater than 300 grams of potent or very potent topical corticosteroid during pregnancy.

Betamethasone dipropionate has been reported to cause malformations in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities reported included umbilical hernias, cephalocele and cleft palate. There are no reported data on betametasone use in pregnant women to identify a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Clotrimazole
Reported studies in pregnant rats treated during organogenesis with intravaginal doses up to 100 mg/kg revealed no evidence of fetotoxicity due to clotrimazole exposure.

No increase in fetal malformations was reported in pregnant rats receiving oral (gastric tube) clotrimazole doses up to 100 mg/kg/day during gestation Days 6 to 15. However, clotrimazole dosed at 100 mg/kg/day has been reported to be embryotoxic (increased resorptions), fetotoxic (reduced fetal weights), and maternally toxic (reduced body weight gain) to rats. Clotrimazole dosed at 200 mg/kg/day has been reported to be maternally lethal, and therefore fetuses were not evaluated in this group. Also in this study, doses up to 50 mg/kg/day had reported no adverse effects on dams or fetuses. However, in the reported combined fertility, embryofetal development, and postnatal development study with rats, 50 mg/kg clotrimazole was associated with reduced maternal weight gain and reduced numbers of offspring reared to 4 weeks. Oral clotrimazole doses of 25, 50, 100, and 200 mg/kg/day were not reported to cause malformations in pregnant mice. No evidence of maternal toxicity or embryotoxicity was reported in pregnant rabbits dosed orally during organogenesis with 60, 120, or 180 mg/kg/day.

Reported data from the use of clotrimazole in pregnant women is limited. Animal

studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of clotrimazole during the first trimester of pregnancy.

No human studies of the effects of clotrimazole on fertility have been reported, however animal studies have not reported any effects of the medicine on fertility.

Gentamicin Sulfate
Use of aminoglycosides during pregnancy may damage the eighth cranial nerve of the fetus.

Teratogenic effects - Gentamicin has been reported to depress body weights, kidney weights, and median glomerular counts in newborn rats when administered systemically to pregnant rats in daily doses approximately 500 times the maximum recommended ophthalmic human dose. No adequate and well-controlled studies have been reported in pregnant women. Gentamicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding
Betamethasone
There are no reported data regarding the excretion of betamethasone dipropionate in breast milk, the effects on the breastfed infant, or the effects on milk production after topical application of betamethasone dipropionate cream to women who are breastfeeding.

It is possible that topical administration of large amounts of betamethasone dipropionate could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for betamethasone dipropionate cream and any potential adverse effects on the breastfed infant from betamethasone dipropionate cream or from the underlying maternal condition.

To minimize potential exposure to the breastfed infant via breast milk, use betamethasone dipropionate cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply betamethasone dipropionate cream directly to the nipple and areola to avoid direct infant exposure.

Clotrimazole
There are no reported data regarding the excretion of clotrimazole into breast

milk, the effects on the breastfed infant, or the effects on milk production after topical application to women who are breastfeeding.

Gentamicin Sulfate
Safety of gentamicin for use in lactation has not been established. In the absence of gastrointestinal inflammation the amount of gentamicin ingested from the milk is unlikely reported to result in significant blood levels in breast-fed infants. Gentamicin should only be used in lactation when considered essential by the physician, after careful assessment of the potential risks and benefits.

4.7 Effects on ability to drive and use machines [8, 12]

Gentalene C Cream has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects [1, 2, 3, 5]

Adverse reactions reported for combination cream preparation containing clotrimazole and betamethasone in reported clinical trials were paresthesia, rash, edema, and secondary infection.

The following local adverse reactions have been reported with topical corticosteroids: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, skin atrophy, striae, miliaria, capillary fragility (ecchymoses), telangiectasia, and sensitization (local reactions upon repeated application of product).

Ophthalmic adverse reactions of blurred vision, cataracts, glaucoma, increased intraocular pressure, and central serous chorioretinopathy have been reported with the use of topical corticosteroids, including topical betamethasone products.

Adverse reactions reported with the use of clotrimazole are as follows: erythema, stinging, blistering, peeling, edema, pruritus, urticaria, general irritation of the skin, allergic reactions (syncope, hypotension, dyspnoea), discomfort/pain, rash, genital peeling, pelvic pain, abdominal pain, burning, vaginal hemorrhage.

In patients with dermatoses treated with gentamicin sulfate, irritation (erythema and pruritis) that did not usually require discontinuance of treatment has been reported in a small percentage of cases. There was no reported 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.

Gentamicin may cause nephrotoxicity when given systemically. However, it is likely that systemic absorption following topical administration does not constitute a comparable risk.

4.9 Overdose [6, 7, 12]

The percutaneous absorption of corticosteroids can occur when large amounts of corticosteroids are applied or when occlusive dressings are used. Toxic effects may include ecchymosis, peptic ulceration, hypertension, delayed wound healing, decreased resistance to infection, hirsutism, acne, oedema, and muscle weakness. No specific antidote is available. Treatment should be the slow withdrawal of the drug bearing in mind the possibility of adrenal suppression.

No risk of acute intoxication has been reported with clotrimazole as it is unlikely to occur following a single dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion. There is no specific antidote. However, in the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). Gastric lavage should be carried out only if the airway can be protected adequately.

Systemic absorption of gentamicin may occur following application to large denuded areas of the body (especially in cream form). Serum concentrations of 1

µg/ml may be achieved and 2 to 5% of the applied dose is excreted in the urine. Calcium salts given intravenously have been reported to be used to counter the neuromuscular blockade cause by gentamicin.

5. PHARMACOLOGICAL PROPERTIES [1, 2, 3, 4, 5, 12]

5.1 Pharmacodynamic properties

Betamethasone
Betamethasone dipropionate is a corticosteroid. Corticosteroids play a role in cellular signalling, immune function, inflammation, and protein regulation; however, the precise mechanism of action for the treatment tinea pedis, tinea cruris and tinea corporis is unknown.

Vasoconstrictor Assay: Studies reported with betamethasone cream, 0.05% indicated that it is in the high range of potency as demonstrated in vasoconstrictor studies in healthy subjects when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

Clotrimazole
Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity.

Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane. Clotrimazole has a broad antimycotic spectrum of action *in vitro* and *in vivo*, which includes dermatophytes, yeasts, moulds, etc. Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062 – 8.0 µg/mL substrate.

The mode of action of clotrimazole is primarily fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. *In vitro* activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive. In addition to its antimycotic action, clotrimazole also acts on gram-positive microorganisms (Streptococci/Staphylococci/ *Gardnerella vaginalis*) and gram-negative micro- organisms (Bacteroides). *In vitro* clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci (with the exception of Enterococci) in concentrations of 0.5 – 10 µg/mL substrate. Primarily resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been

reported in very isolated cases under therapeutic conditions. Clotrimazole has been reported to be active against most strains of the following dermatophytes, both *in vitro* and in clinical infections: *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*.

Drug Resistance: Strains of dermatophytes having a natural resistance to clotrimazole have not been reported. Resistance to azoles, including clotrimazole, has been reported in some *Candida* species. No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*.

Gentamicin Sulfate
Gentamicin sulfate is a wide spectrum bactericidal antibiotic that provides highly effective topical treatment in primary and secondary bacterial infections of the skin. 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 it's most important effect is inhibition of protein synthesis at the level of the 30s ribosomal subunit. Topical gentamicin sulfate may clear infections that have not responded to treatment with other topical antibiotic agents. In primary skin infections such as impetigo contagiosa, treatment 3 or 4 times daily with topical gentamicin sulfate usually clears the lesions promptly. In secondary skin infections, topical gentamicin sulfate aids in the treatment of the underlying dermatoses by controlling the infection. Bacteria susceptible to the action of gentamicin sulfate include sensitive strains of *Streptococci* (group A beta hemolytic, alpha-hemolytic), *Staphylococcus aureus* (coagulase positive, coagulase negative, and some penicillinase-producing strains), and the gram-negative bacteria, *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, and *Klebsiella pneumoniae*.

5.2 Pharmacokinetic properties

Betamethasone
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier and the use of occlusive dressings.

Topical corticosteroids can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption of topical corticosteroids. Occlusive dressings substantially reported to increase the percutaneous absorption of topical corticosteroids (see section 4.2).

Once absorbed through the skin the pharmacokinetics of topical corticosteroids are reported to be similar to systemically administered corticosteroids. Corticosteroids are reported to bound to plasma proteins in varying degrees, are metabolized primarily in the liver and then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also reported to be excreted into the bile.

Clotrimazole
Pharmacokinetic investigations after dermal application have reported that clotrimazole is minimally absorbed from the intact or inflamed skin into the human blood circulation.

The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 µg/mL, suggesting that clotrimazole applied topically on the skin is unlikely to lead to measurable systemic effects or side effects.

Pharmacokinetic investigations after vaginal application have reported that only a small amount of clotrimazole (3 – 10%) is absorbed. Due to the rapid hepatic metabolisation of absorbed clotrimazole into pharmacologically inactive metabolites the resulting peak plasma concentrations of clotrimazole after vaginal application of a 500 mg dose were less than 10 ng/mL, suggesting that clotrimazole applied intravaginally is unlikely to lead to measurable systemic effects or side effects.

Gentamicin Sulfate
Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and on instillation into, and irrigation of, wounds, body-cavities (except the urinary bladder), and joints.

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. Gentamicin is reported to be 70-85% bound to plasma albumin.

Reported effective plasma concentration is 4 - 8ug/ml. The reported volume of distribution is 0.3 l/kg. At steady state at least 70% of a dose may be recovered in the urine in 24 hours and urine concentrations in excess of 100 micrograms/mL may be achieved. However, gentamicin and the other aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney, although the relative degree to which this occurs may vary with different aminoglycosides.

Release from these sites is slow and small amounts of aminoglycosides may be detected in the urine for up to 20 days or more after treatment stops. Small amounts of gentamicin appear in the bile.

5.3 Preclinical safety data [1, 9]

Betamethasone and Clotrimazole Combination
Long-term animal studies have not been reported to evaluate the carcinogenic potential of the combination of clotrimazole and betamethasone dipropionate or either component individually.

Betamethasone
Betamethasone was reported to be negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*) and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was reported to be positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay.

Reported reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular route and in mice up to 33 mg/kg by the intramuscular route reported no impairment of fertility except for dose-related increases in fetal resorption rates in both species.

Clotrimazole
In a reported combined study of the effects of clotrimazole on fertility, embryofetal development, and postnatal development, male and female rats were dosed orally (diet admixture) with dose levels of 5, 10, 25, or 50 mg/kg/day from 10 weeks prior to mating until 4 weeks postpartum. No adverse effects on the duration of estrous cycle, fertility, or duration of pregnancy were reported.

Gentamicin Sulfate
There are no reported carcinogenicity or impairment of fertility studies on gentamicin. Aminoglycoside antibiotics have been reported to be non-mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White soft paraffin, Cetostearyl alcohol, Cetomacrogol 1000, Light liquid paraffin, Propylene glycol, Chlorocresol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Do not freeze.
Keep all medicines out of the reach of children.

6.5 Nature and contents of container

30g cream packed in Alu tube and such 1 tube packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Limited (a SUN PHARMA company)
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8. MARKETING AUTHORISATION NUMBER(S)

A4-3975

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30-12-1999

10. DATE OF REVISION OF THE TEXT

November 2023

REFERENCES

1. Prescribing Information of LOTRISONE® Cream, Merck Sharp & Dohme Corp., USA, June 2019.
2. Prescribing Information of DIPROLENE® AF Cream, Merck Sharp & Dohme Corp., USA, May 2019.
3. Prescribing Information of GENTAMICIN SULFATE CREAM, E. FOUGERA & CO., Melville, New York 11747, USA, May 2012.
4. Brayfield A. Martindale: The Complete Drug Reference, Gentamicin Sulfate, 39th Edition, Pharmaceutical Press, London. 2017. page no. 309-311.
5. Medsafe Data Sheet of CANESTEN™, Bayer New Zealand Ltd, Auckland, September 2017.
6. Medsafe Data Sheet of BIVATE™, Douglas Pharmaceuticals Ltd, December, 1998.
7. Fernanando R and Jayakody RL. Gentamicin sulfate (monograph). International Programme on Chemical Safety (IPCS).1994.
8. Summary of Product Characteristics of Boots Antifungal Cream, Teva UK Limited, UK, February 2020.
9. Prescribing Information of GARAMYCIN (gentamicin sulfate) ointment, Fera Pharmaceuticals, LLC, USA, September 2010.
10. Summary of Product Characteristics of Gentamicin 40 mg/ml Injection, Hospira UK Ltd., February 2021.
11. Summary of Product Characteristics of Genticin Eye/Ear drops, Amdipharm Limited, UK, May 2021.
12. Summary of Product Characteristics of Canesten Antifungal Cream, Bayer plc, UK, July 2018.

Information compiled in November 2023