PRODUCT MONOGRAPH

[Pr] SANDOZ OPTICORT

Framycetin Sulfate 5 mg/mL
Gramicidin 0.05 mg/mL and
Dexamethasone (as Dexamethasone Sodium Metasulphobenzoate) 0.5 mg/mL

Antibiotic - Corticosteroid

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[Pr] Sandoz Opticort
Ophthalmic/Otic Solution
Framycetin Sulfate 5 mg/mL
Gramicidin 0.05 mg/mL
and Dexamethasone
(as Dexamethasone Sodium Metasulphobenzoate) 0.5 mg/mL

THERAPEUTIC CLASSIFICATION

Antibiotic - Corticosteroid

ACTIONS AND CLINICAL PHARMACOLOGY

Gramicidin is a polypeptide antibiotic; its mechanism of action is mediated through alteration of the cation component of the bacterial cell wall.

Framycetin sulfate, also known as neomycin B, is an aminoglycoside antibiotic which forms the major component of neomycin sulfate and has similar actions and uses.

Aminoglycosides are taken up into sensitive bacterial cells by an active transport process which is inhibited in anærobic, acidic, or hyperosmolar environments. Within the cell, they bind to the 30S and to some extent to the 50S subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is imperfectly understood, and other mechanisms may contribute, including effects on membrane permeability.

In general, neomycin is active against many ærobic gram-negative bacteria and some ærobic gram-positive bacteria. Bacterial strains susceptible to neomycin include: *Escherichia coli*, *Hæmophilus influenzæ*, *Moraxella lacunata*, indole-positive and indole-negative *Proteus*, *Staphylococcus aureus*, *S. epidermidis* and *Serratia*. Neomycin is only minimally active against streptococci. *Pseudomonas æruginosa* is generally resistant to the drug. The drug is inactive against fungi, viruses, and most anaerobic bacteria.

Natural and acquired resistance to neomycin have been demonstrated in both gram-negative and gram-positive bacteria. There is partial cross-resistance between neomycin and other aminoglycosides; cross-resistance occurs frequently between kanamycin, neomycin and paromomycin.

Dexamethasone is a synthetic glucocorticoid used principally as an anti-inflammatory or immunosuppressant drug. Dexamethasone exerts marked anti-inflammatory activity at the tissue level and effectively supresses inflammation in many disorders of the anterior segment of the eye. Dexamethasone has 7 times the anti-inflammatory potency of prednisolone. Like other glucocorticoids, dexamethasone also has antiallergic, antitoxic, antishock, antipyretic and immunosuppressive properties. Dexamethasone has practically

no water and salt-retaining properties and is, therefore, particularly suitable for use in patients with cardiac decompensation or hypertension. Because of the long biological half-life (36 to 54 hours), dexamethasone is especially suitable in conditions where a continuous glucocorticoid action is desired.

Corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and to a lesser extent albumin. The corticosteroid binding globulin has a high affinity but a low binding capacity, while the albumin has a low affinity but a high binding capacity. Only unbound corticosteroid has pharmacological effects or is metabolized. Corticosteroids are metabolized mainly in the liver but also in the kidney, and are excreted in the urine.

INDICATIONS

Eye: Sandoz Opticort is indicated for blepharitis and infected eczema of the eyelid; allergic, infective and rosacea conjunctivitis; rosacea keratitis; scleritis and episcleritis; iridocyclitis and other inflammatory conditions of the anterior segment of the eye.

Ear: Sandoz Opticort is indicated for the treatment of otitis externa (acute and chronic) and other inflammatory and seborrheic conditions of the external ear.

Sandoz Opticor contains antibacterial ingredients, framycetin and gramicidin. To reduce the development of drug-resistant bacteria and maintain the effectiveness of framycetin and gramicidin, Sandoz Opticor should only be used for the authorized indication.

CONTRAINDICATIONS

Sandoz Opticort is contraindicated in patients with known hypersensitivity to any of its ingredients or to other aminoglycosides and polypeptide antibiotics (see COMPOSITION).

Eye:

- Herpes simplex and other viral diseases of the cornea and conjunctiva; tuberculosis and fungal diseases of the eye; trachoma.
- Acute purulent, untreated infections of the eye, which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid.
- Known hypersensitivity to any of the ingredients.

Ear:

- Viral and fungal infections.
- Acute purulent, untreated infections.
- Perforation of the eardrum because of the risk of ototoxicity.
- Known hypersensitivity to any of the ingredients.

WARNINGS

Eye Use

Visual disturbance may be associated 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). Extended ophthalmic use of corticosteroids may increase intra-ocular pressure in some individuals in such cases, intra-ocular pressure should be checked regularly. In conditions causing thinning of the cornea, topical steroids may cause perforation. Cataract has occurred after prolonged treatment with topical steroids.

Prolonged ophthalmic use of corticosteroids may result in increased intraocular pressure in some individuals. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored. In diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical preparations containing corticosteroids. Protracted use of topical corticosteroids in the eye may result in the development of posterior subcapsular cataracts. Acute anterior uveitis may occur in susceptible individuals, primarily blacks. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Although corticosteroids are contraindicated in acute viral infection of the cornea caused by herpes simplex, there may be occasion to employ steroids in the healing stage to prevent scarring; however, this must only be done with great caution and close observation. In patients with a history of herpetic infection of the cornea, reactivation of the disease may occur with the use of topical ophthalmic or otic corticosteroids.

The use of steroids after cataract surgery may delay healing and increase the incidence of filtering blebs.

"Ear Use"

When Sandoz Opticort is used locally in the ear, the potential eight cranial nerve toxicity should be considered. Animal studies have shown that some aminoglycosides (e.g. gentamicin) applied topically to the external ear canal may be absorbed since they have been detected in the serum and urine after this route of administration.

PRECAUTIONS

Eye

The drug should be discontinued if there are signs of sensitivity to any of its ingredients. Patients are advised to inform the physicians of the prior use of corticosteroids.

Extended ophthalmic use of corticosteroids may increase intra-ocular pressure in some

individuals; in such cases, intra-ocular pressure should be checked regularly. In conditions causing thinning of the cornea, topical steroids may cause perforation. Cataract has occurred after prolonged treatment with topical steroids.

Use in Obstetrics
The safety of prolonged use of topical steroids during pregnancy has not been substantiated. The benefits of use should be weighed against possible adverse effects to the fetus.

Use in Children
Although it is unlikely that infants will be treated with Sandoz Opticort for prolonged periods, there is a risk of adrenal suppression, even without occlusive dressings, after prolonged treatment of these patients with topical steroids.

"Ear Use"
To minimize the risk of ototoxicity, the following precautions are suggested:
Sandoz Opticort should be used for the shortest duration possible; the patient should be precisely instructed regarding the dosage and duration of therapy. Treatment should be discontinued if hearing loss, tinnitus, vertigo, or imbalance is noted. The use of Sandoz Opticort should be reassessed, with respect to ototoxicity, 5-7 days after start of treatment and thereafter, on a regular basis.

Aminoglycosides antibiotics may cause irreversible, partial or total deafness when applied topically to open wounds or damaged skin. This effect is aggravated by renal or hepatic impairment and by prolonged duration of treatment. The treatment should not be continued after resolution of symptoms.

Susceptibility/Resistance

Development of Drug Resistant Bacteria
Prescribing Sandoz Opticort in the absence of the authorized indications is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth
The use of Sandoz Opticort may promote the selection of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

ADVERSE REACTIONS (see Precautions)

Eye disorders: perforation of the cornea, increased intra-ocular pressure; ocular hypersensitivity manifested by increased ocular hyperemia, edema and burning/stinging of the eye; blurred vision, chorioretinopathy.

Adverse reactions reported with other steroid-anti-infective combinations include: allergic sensitization due to the antibiotic component; elevation of intraocular pressure

with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, filtering blebs following cataract surgery, secondary ocular infection from pathogens including herpes simplex and delayed wound healing due to the steroid component.

Corticosteroid-containing preparations can also cause anterior uveitis or perforation of the globe. Mydriasis, defects in visual acuity and visual fields, loss of accommodation and ptosis have also been reported following corticosteroid therapy.

Eye: The possibility of ototoxicity following otic application should be kept in mind and the patient monitered accordingly on a regular basis (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Rare cases of ototoxicity (hearing loss, tinnitus, vertigo, imbalance, ataxia or oscillopsia) in the presence of tympanic membrane perforation or tympanoplasty tubes have been reported with the use of aminoglycoside-containing otic preparations. Ototoxicity was primarily vestibular and was generally associated with prolonged treatment duration. However, ototoxicity with treatment durations of 5 to 7 days has also been reported. In some instances, patients have not recovered from their symptoms (hearing loss , tinnitus, vertigo, imbalance, ataxia or oscillopsia).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Dexamethasone
Symptoms: Excessive prolonged use of topical corticosteroids can suppress pituitary-adrenal function resulting in secondary adrenal insufficiency, and produce manifestations of hypercorticism, including Cushing's disease.

Treatment: Appropriate symptomatic treatment of corticosteroid overdosage is indicated. Acute hypercorticoid symptoms are virtually reversible.

Treat electrolyte imbalance, if necessary. In cases of chronic toxicity, slow withdrawal of corticosteroids is advised.

DOSAGE AND ADMINISTRATION

Eye: In acute conditions, 1 or 2 drops every 1 to 2 hours may be instilled (generally for 2 or 3 days). Subsequently, 1 or 2 drops, 3 or 4 times daily.

Ear: Tilting head to one side, instill 2 or 3 drops in the ear canal 3 or 4 times daily. Squeeze bottle carefully. To avoid possibility of reinfection later, do not touch ear with dropper. Alternatively, a saturated gauze wick may be inserted by the physician into the external auditory meatus.

The need for Sandoz Opticort ear drops should be reassessed, with respect to ototoxicity, 5-7 days after start of treatment and therafter, on a regular basis.

COMPOSITION

Each mL of sterile solution contains: framycetin sulfate 5 mg, gramicidin 0.05 mg, dexamethasone (as sodium metasulphobenzoate) 0.5 mg.

Inactive ingredients: phenylethyl alcohol 0.5% as preservative, sodium citrate, citric acid, polysorbate 80, ethyl alcohol, sodium chloride, sodium hydroxide and/or hydrochloric acid, and water.

STORAGE AND STABILITY

Store between 15 and 25°C. Protect from light. Discard 28 days after initial use.

AVAILABILITY OF DOSAGE FORMS

Sandoz Opticort is available in amber glass ophthalmic bottles of 8 mL (8 mL fill), boxes of 1.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name:	Gramicidin
Chemical name:	Valine-Gramicidin A
Structural formula:	Gramicidin is a linear peptide containing 15 amino acids, with an N-terminal formyl group and a C-terminal aminoethanol group:

HCO-Val-Gly-Ala-$_D$-Leu-Ala-$_D$-Val-Val-$_D$-Val-Trp-$_D$-Leu-Trp-$_D$-Leu-Trp-$_D$-Leu-Trp-NHCH $_2$CH$_2$OH

Physiochemical properties:

Description:	Crystalline gramicidin is a fine white or off-white powder
Solubility:	very soluble in methanol, soluble in ethanol and almost insoluble in water and nonpolar organic solvents.
Melting Point:	229 - 230°C

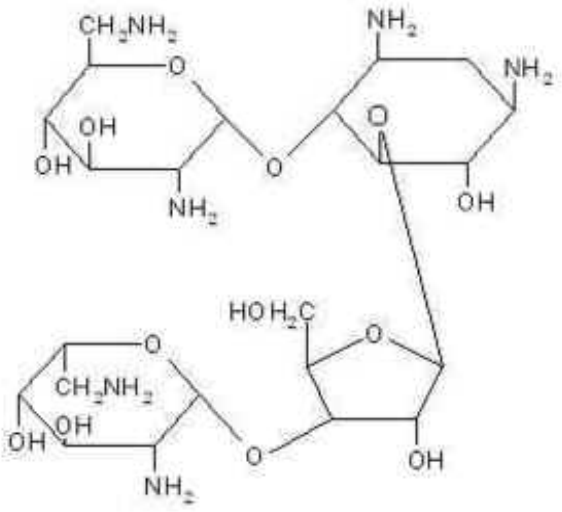
DRUG SUBSTANCE

Proper name: Framycetin Sulfate

Chemical name: Sulfate of 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-O-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin B)

Molecular formula and molecular mass: $C_{23}\ H_{46}\ N_6O_{13} \cdot H_2\ SO_4$; 615 g / mol (base)

Structural formula:



$\cdot H_2\ SO_4$

Physiochemical properties:

Description: A white or yellowish-white powder, hygroscopic.

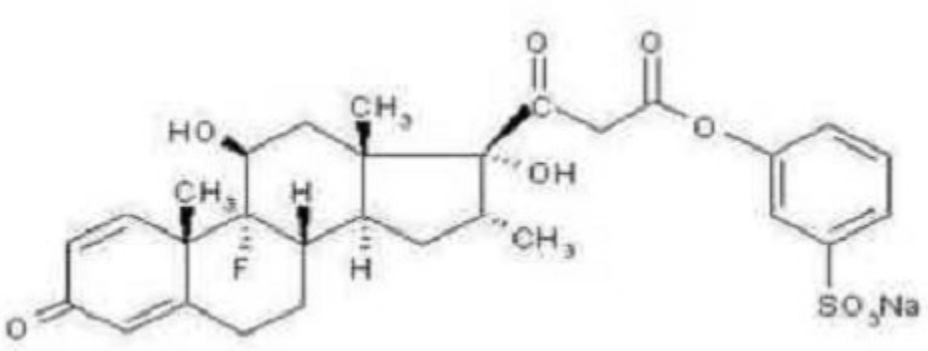
Solubility: Freely soluble in water, very slightly soluble in alcohol, practically insoluble in acetone.

DRUG SUBSTANCE

Proper name: Dexamethasone Metasulphobenzoate

Molecular formula and molecular mass: C_{29} H_{32} F Na O_9 S; 598.6 g / mol

Structural formula:



Physicochemical properties:

Description: White to practically white, microcrystalline powder.

MICROBIOLOGY

Framycetin

Framycetin is effective against many ærobic Gram-negative and some anærobic Gram-positive bacteria. It is not effective against fungi, viruses, or most anærobic bacteria. Mininum Inhibitory Concentration (MIC) values for different bacterial strains obtained from animal or human isolates are listed in **Tables 1** and **2**, respectively.

Table 1: Summary of MIC Values for Different Bacterial Species Obtained From Animal (germ-free mice and dogs) Isolates Using Framycetin as the Antibiotic

Species/No. of strains	MIC (mcg/mL) Mean	MIC (mcg/mL) Range	MIC_{50} (mcg/mL)
Staphylococcus aureus/NR	0.5	-	NR
Escherichia coli/NR	8.0	-	NR
Klebsiella pneumoniæ/NR	2.0	-	NR
Proteus mirabilis/NR	8.0	-	NR
Proteus morganii/NR	8.0	-	NR
Proteus rettgeri/NR	8.0	-	NR
Proteus vulgaris/NR	4.0	-	NR
Bacteroides nodosus/68	-	16 - ≥256	≥256
Bacteroides putredinis/36	-	16 - ≥256	128
Bacteroides buccæ/16	-	2 - ≥256	128
Bacteroides sp./21	-	8 - ≥256	≥256
Fusobacterium necrophorum/10	-	16 - ≥256	128
Fusobacterium sp./19	-	2 - ≥256	128
Peptostreptococcus sp./35	-	≤0.06 - ≥256	64

Abbreviations: MIC, Mean Inhibitory Concentration; No. number; NR, not reported

Table 2:Summary of MIC Values for Different Bacterial Species Obtained from Human Isolates Using Framycetin as the Antibiotic

Species/No. of strains	MIC (mcg/mL) Mean or Range
Escherichia coli/10	0.25 – 12.5
Bacteroides fragilis/55	1 600 - ≥25 600
Bacteroides melaninogenicus/20	<100 – 400
Bacteroides oralis/16	<100 – 400
Fusobacterium sp./22	100 – 3,200
Bifidobacterium adolescentis/11	12.5 - 400
Bifidobacterium longum/11	200 -1,600
Clostridium novyi Type A/16	32 - 512
Clostridium sporogenes/18	32 - 512
Propionicum agnes/38	6.25 - 25

Abbreviations: MIC, Mean Inhibitory Concentration

Strains of various bacteria genera were tested for their susceptibility to neomycin sulfate (framycetin). MIC values were estimated on two agar types, Wilkins Chalgren/glucose medium (WCG) and supplemented blood agar medium (SB). Estimations were made under anaerobic and ærobic conditions (*E. coli*) by the agar dilution method. The results are listed in **Table 3**.

Table 3:Summary of MIC Values Under Different Agar Medium and Inoculum Density Condition Using Framycetin as the Antibiotic

Bacterial Species/Genus	Strains	MIC_{50} (mcg/mL)[a]			
		Low Density[b]		High Density[c]	
		SB[d]	WCG[d]	SB[d]	WCG[d]
Bacteroides	15[e,f]	>128	>128	>128	>128
Bifidobacterium	12[e]		16		128
Clostridium	11[e], 5[f]	>128	128		>128
Enterococcus	10[e], 2[f]	>128	128	>128	>128
Escherichia	13[e]		16		64
Escherichia - ærobic	13[e]		>128		>128
Escherichia - anærobic	9[e]		8		>128
Fusobacterium	5[e], 3[f]	16	32	>128	128
Lactobacillus	15[e], 2[f]	>128	32	>128	64
Peptostreptococcus/ Peptococcus	16[e], 14[f]	>128	32	>128	128

[a] MIC_{50} values are for the multiple strains included in the assay
[b] Low density inocula had cell concentrations of approximately 1 x 10^8 cells/mL
[c] High density inocula had cell concentrations of approximately 1 x 10^{10} cells/mL
[d] SB = Supplemented blood medium; WCG = Wilkins-Chalgren/glucose medium
[e] Number of tested strains of which MIC values for WCG were used to calculate the summary values
[f] Number of tested strains of which MIC values for SB were used to calculate the summary values

Gramicidin
Studies show that gramicidin is particularly effective against Gram-positive bacteria. It increases the permeability of the bacterial cell membrane to inorganic cations by forming a network of channels through the normal lipid bilayer of the membrane.

PHARMACOLOGY

Framycetin
Ototoxicity of framycetin is partially mediated through destruction of the hair cell of the organ of Corti. Framycetin is considered to be more ototoxic and nephrotoxic than streptomycin and possesses similar antibacterial activity.

Dexamethasone
Dexamethasone is a corticosteroid and is a potent anti-inflammatory and antineoplastic agent, as well as an antiemetic. Dexamethasone may slow or delay healing. Corticosteroids diffuse across cell membranes, complex with cytoplasmic receptors, and enter the cell nucleus, where the complex binds to DNA, stimulates mRNA transcription, and subsequently, protein synthesis. Effects include decreased cellular and fibrinous exudation and tissue infiltration, inhibition of fibroblastic activity and collagen formation, retarded epithelial regeneration and postinflammatory neovascularization, and reduction of excessive capillary permeability.

TOXICOLOGY

GRAMICIDIN

The results of acute toxicity after oral, intravenous, subcutaneous or intraperitoneal administration of gramicidin to mice are summarized in **Table 4**.

Table 4:Acute Toxicity of Gramicidin

Species	Route of Administration	LD_{50} Unless otherwise specified (mg/kg bw unless otherwise specified)
Mouse	PO	>3 g/kg bw
Mouse	IP	100
Mouse	SC	>1 500
Mouse	IV	LDLo = 1 200 mcg/kg bw
Mouse	IV	1 500 mcg/kg

Abbreviations: bw, body weight; IP., intraperitoneal; IV, intravenous; PO, oral; SC, subcutaneous

FRAMYCETIN

Acute Toxicity

The results of acute toxicity after intravenous or intraperitoneal administration of neomycin to mice are summarized in **Table 5**.

Table 5:Acute Toxicity of Neomycin

Species/Sex	Route of Administration	Substance	Purity	LD_{50} (mg/kg bw)
Mouse/M and F	IV	Neomycin in HCH	NR	74–115
Mouse/M and F	IP	Neomycin B sulfate	NR	277–389
Mouse/M and F	IP	Neomycin B sulfate	1 000 mcg/mg	533

Abbreviations: bw, body weight; F, female; IP, intraperitoneal; IV, intravenous; M, male; NR, not reported; HCH : hexachlorocyclohexane

A repeated dose study of framycetin was conducted in guinea pigs in order to study the ototoxicity of framycetin. Animals were administered 50, 100, or 200 mg/kg body weight/day for a period of 8 to 11 days by subcutaneous injection (dosing was interrupted twice for 2-day periods). Selected animals underwent a recovery period of 2 to 29 days postdosing. Body weights (a marker of toxicity) were recorded daily until the day of last dose or on the day of sacrifice (i.e. postrecovery). Several animals died after the start of treatment; no further details on toxicity were reported.

The potential for nephrotoxicity of neomycin B was examined in mice (10/group, sex not reported) administered 0, 30, 100, 300, 600, or 1 000 mg/kg body weight for 14 days subcutaneously. At the two highest dose levels, all animals died by the end of the 2-week treatment. Neomycin B was considered to be nephrotoxic based on lesion indices.

Neomycin was demonstrated to be ototoxic in a repeated dose study in guinea pigs. Animals received 25, 50, 100, or 150 mg neomycin/kg body weight/day intramuscularly for 30 to 60 weeks. One animal in the high-dose group died after 22 days of the study. In a separate study, guinea pigs (50/sex/dose group) received 0, 1, 5, or 10 mg neomycin B sulfate/kg body weight/day orally for 90 days; additional positive control animals (20/sex/group) received 10 or 100 mg/kg body weight/day subcutaneously for 90 and 34 days, respectively. Clinical signs and body weights were noted and gross necropsy and histopathology were performed. Ototoxicity was reported in the high-dose positive control group but not in the low-dose positive control or orally treated groups; no other signs of toxicity were reported and the NOEL was 10 mg/kg body weight/day.

A study examining the effects of the intramuscular administration of 24, 48, or 96 mg neomycin/kg body weight/day in 12 dogs reported the deaths of all animals in the high dose group within 1-3 weeks of treatment. Increased blood urea nitrogen, impaired renal function, and epithelial necrosis in the proximal convoluted tubules were reported, as well as moderate alterations in bone marrow and marked liver congestion. Effects in the mid-dose group were less marked. In animals of the low-dose group sacrificed following a 1-month recovery period, slight renal damage was characterized by increased granularity and occasional desquamation of epithelial cells. In contrast, no renal damage was reported in a 6-week repeated dose study in dogs (number/sex/group not reported) at a dose level of 100 mg neomycin/kg body weight/day, based on urinalyses and gross and histopathological examination of the kidneys, nor were other signs of toxicity reported.

A repeated dose study in cats (number/sex/dose level not reported) involved subcutaneous administration of 80 mg/kg body weight/day of a clinical neomycin formulation containing predominantly neomycin B or neomycin B sulfate for 5 or 15 days. The clinical formulation was also administered subcutaneously to cats at doses of 20, 40, or 100 mg/kg body weight/day for 90, 60, and 30 days, respectively, with a group also receiving unpurified neomycin (70% pure) *via* the oral route (2 daily doses of 500 mg/kg body weight for 30 days; equivalent to 1 g/animal/day). Vestibular function, hearing ability, cochlear function, and kidneys (histopathology) were examined. Vestibular function was altered in cats dosed with 100 mg/kg body weight/day for 30 days; decreased cochlear function and degeneration of hair cells occurred in all treated animals (the effects were most severe in animals receiving the clinical formulation). Dose-dependent damage to the renal tubular epithelium was observed in animals receiving the clinical preparation or crude neomycin.

Local Toxicity

The cross-sensitivity of 9 neomycin-sensitized guinea pigs to kanamycin, streptomycin, dihydrostreptomycin, and bacitracin was examined using the patch test; 1/9 and 8/9 animals showed positive results to kanamycin and streptomycin, respectively.

Reproductive Toxicity
Framycetin (10 mg/kg body weight/day) administered to male rats for 8 days (route of administration not reported) was associated with altered mitosis (nuclear degeneration, failure for spermatocytes to reach metaphase, altered dehydrogenase activities in testis cells) in spermatogenesis.

Genotoxicity
Tests such as *in vitro* chromosome aberration assay, sister chromatid exchange and *in vivo* cytogenetic assay were conducted, using different concentrations, on human lymphocytes as well as mouse bone marrow cells. The results of the available genotoxicity studies on neomycin are summarized in **Table 6**.

Table 6: Results of Genotoxicity Studies on Neomycin

Test System	Test Object	Concentration	Results
In vitro chromosome aberration assay	Human lymphocytes	20, 40, and 80 mcg/mL	Positive [a,b]
Sister chromatid exchange	Human lymphocytes	20, 40, and 80 mcg/mL	Negative [b]
In vivo cytogenetic assay	Mouse bone marrow cells	50 mg/kg bw	Positive [b,c]

Abbreviations: bw, body weight
[a] At doses that significantly inhibit the progression of the cell cycle.
[b] No positive control group was incorporated in the study design.
[c] Test was not conducted pursuant to current standards, i.e. results from 12 fixation times are combined in 6 groups and number and sex of animals were not reported. Mitotic frequency was decreased, leading to the conclusion that neomycin reached the bone marrow.

Dexamethasone
The results of the lethal dose value for dexamethasone after subcutaneous or intraperitoneal administration to mice, rats and rabbits are summarized in **Table 7**.

Table 7: LD_{50} Values for Dexamethasone

Species	Route of Administration	LD_{50} (mg/kg bw unless otherwise specified)
Mouse	SC	4 440
Mouse	IP	410
Rat	SC	14
Rat	IP	54
Rabbit	SC	7 200 mcg/kg bw

Abbreviations: bw, body weight; IP, intraperitoneal; SC, subcutaneous

Reproductive Toxicity

The teratogenic potential of dexamethasone was studied in CD-1 and C57BL/6N mouse and F344 rat embryonic secondary palatal explants. The embryonic secondary palatal explants were obtained on gestational day 14, cultured for 4 days, and incubated with 1 x 10^{-11} to 1 x 10^{-3} M dexamethasone for up to 4 days. The cultures were assessed microscopically to determine the extent of teratogenicity, as measured by palate clefting. Dexamethasone treatment was associated with clefting in a dose-dependent fashion.

Dexamethasone (0.2 or 0.8 mg/kg body weight) administered to pregnant rats on gestational days 17 to 19 was associated with decreased pup body weight and brain region weight, as well as alterations in brain region cell development that were marked by growth sparing in favour of maintenance of cell numbers with concomitant decreased cell size, decreased brain cell acquisition until weaning, and changes indicating replacement of neurons with glial tissue. Offspring were subsequently challenged with hypoxia on postnatal days 1 and 8. At postnatal day 1, decreased protein synthesis (measured by [^{3}H]-leucine incorporation) was observed in the midbrain+brain stem and forebrain areas in the low-dose dexamethasone group, but was less pronounced than in controls; conversely, protein synthesis was increased in the high-dose dexamethesone group. By postnatal day 8, low-dose animals also exhibited increased protein synthesis in the brain, while the magnitude of the increase in high-dose animals was attenuated. Reduced DNA synthesis (incorporation of [^{3}H]-thymidine) was observed in controls but not in the high-dose dexamethasone group at postnatal day 1, with negligible effects on postnatal day 8. In contrast to the effects on protein synthesis, dexamethasone-treated groups did not exhibit increased DNA synthesis with hypoxia.

Dexamethasone was administered subcutaneously to pregnant rats on gestational days 9 to 14 at dose levels of 0, 0.2, or 0.4 mg/kg body weight. Animals were sacrificed on gestational days 15 to 20 and clinical chemistry, maternal body weight gain, food and water intakes, urine output, urinary electrolytes, and glucose levels were examined; fetal weight, organ weights, and amniotic fluid volume were determined throughout the course of the study. Treatment-related effects included decreased food intake and increased water intake. Other treatment-related effects included anorexia at the high dose, maternal toxicity (decreased weight gain, altered white blood cell, hemoglobin, alanine aminotransferase, and aspartate aminotransferase levels), decreased fetal liver weight on gestational days 18 and 20, and decreased amniotic fluid volume (perhaps related to cleft palate and wavy ribs noted in dexamethasone groups) at the high dose. Temporal effects included increased urine output and decreased electrolyte excretion in late pregnancy and increased glucose levels during mid to late dexamethasone treatment.

Dexamethasone administered to pregnant rats on days 17 to 19 of gestation was associated with decreased gas exchange surface area and number; gas exchange surface area, average volume of gas exchange saccules, and average volume of gas exchange alveoli at 14 days of age were not altered. Decreased gas exchange surface area was observed at days 16-18 of age in female pups exposed prenatally to dexamethasone, while effects were delayed in male pups (until days 17 to 19).

The effect of maternal exposure of pregnant CD albino rats to dexamethasone on fetal development was investigated. Animals were administered 0, 0.2, or 0.4 mg dexamethasone/kg body weight on gestational days 9 to 14 or 14 to 19, and euthanized on day 20. Dose-dependent toxicity (decreased maternal and fetal body weights) and stunting in all organs, except the cerebellum, was observed and developmental stage-specific malformations occurred in the high dose group (cleft palate in the group treated on days 14 to 19 and wavy ribs in the group treated later in gestation). Organs sensitive to dexamethasone treatment were the thymus, spleen, adrenals, lungs, liver, and kidneys, while the brain, testes, heart, and long bones were less sensitive. Decreased food consumption and increased water intake were observed in some dams. It was reported that these effects were not mediated through the hypophagic effect of dexamethasone.

Administration of dexamethasone to the conjunctiva of young pregnant New Zealand white rabbits was associated with malformations of the abdominal cavity.

The results of the teratogenicity toxicity studies for dexamethasone after oral, parenteral, ocular, inhalation, dermal, intramuscular, subcutaniuos or intrathecal administration to mice, rats, hamsters, rabbits, dog, pigs, monkeys, and horses are summarized in **Table 8**.

Table 8`:Teratogenicity Toxicity Values for Dexamethasone

Toxicity Parameter	Species	Route of Administration	Dosing Regimen	Toxicity Value
TDLo	Mouse	PO	GD 6–15 in F	5 mg/kg bw
TDLo	Mouse	IM	GD 13	50 mg/kg bw
TDLo	Mouse	SC	GD 7–15 in F	3 600 mcg/kg bw
TDLo	Mouse	SC	GD 7–15 in F	28 800 mcg/kg bw
TDLo	Mouse	SC	GD 6–15 in F	10 mg/kg bw
TDLo	Mouse	Parenteral	GD 16 in F	400 mcg/kg bw
TDLo	Mouse	Parenteral	GD 16 in F	6 mg/kg bw
TDLo	Mouse	Ocular	GD 10–13 in F	1,200 mcg/kg bw
TDLo	Mouse	Ocular	GD 10–13 in F	6 mg/kg bw
TDLo	Rat	PO	GD 6–15 in F	2 mg/kg bw
TDLo	Rat	PO	GD 7–17 in F	880 mcg/kg bw
TDLo	Rat	PO	GD 7–17 in F	8 800 mcg/kg bw
TDLo	Rat	PO	GD 15–17 in F	7 500 mcg/kg bw
TDLo	Rat	PO	GD 8–13 in F	6 mg/kg bw
TDLo	Rat	IP	GD 14–15 in F	3 mg/kg bw
TDLo	Rat	Inhalation	21 days in M	26 700 mcg/m^3
TDLo	Rat	SC	3 days in M	3 mg/kg bw
TDLo	Rat	SC	GD 12-18	700 mcg/kg bw
TDLo	Rat	SC	GD 8–16	900 mcg/kg bw

Toxicity Parameter	Species	Route of Administration	Dosing Regimen	Toxicity Value
TDLo	Rat	SC	GD 8-16	3 600 mcg/kg bw
TDLo	Rat	SC	GD 7-17	11 mg/kg bw
TDLo	Rat	SC	GD 7-17	1 100 mcg/kg bw
TDLo	Rat	Inhalation	21 days premating in M	26 700 mcg/m^3
TDLo	Rat	Dermal	9 weeks in M; 2 weeks premating and GD 1–7 in F	4 200 mcg/kg bw
TDLo	Rat	Dermal	26 weeks in M	1 802 mcg/kg bw
TDLo	Hamster	IM	GD 11 in F	4 mg/kg bw
TDLo	Rabbit	PO	GD 13–16 in F	400 mcg/kg bw
TDLo	Rabbit	PO	GD 13–16 in F	2 mg/kg bw
TDLo	Rabbit	IM	GD 25–26 in F	1 600 mcg/kg bw
TDLo	Rabbit	SC	GD 6–18	130 mcg/kg bw
TDLo	Rabbit	SC	GD 6–18	390 mcg/kg bw
TDLo	Rabbit	Parenteral	GD 25–26 in F	2 mg/kg bw
TDLo	Rabbit	Parenteral	GD 25–27 in F	360 mcg/kg bw
TDLo	Rabbit	Ocular	GD 6–18 in F	554
TDLo	Dog	IT	1 day in M	18 mg/kg bw
TDLo	Monkey	IM	GW 18–23 in F	3 700 mg/kg bw
TDLo	Pig	IM	GW 14 in F	6 667 mcg/kg bw
TDLo	Pig	Parenteral	GW 14 in F	6 670 mcg/kg bw
TDLo	Pig	Parenteral	GW 14 in F	3 750 mcg/kg bw
TDLo	Horse	IM	GW 45 in F	1 905 mcg/kg bw
TDLo	Horse	IM	GW 45–46 in F	800 mcg/kg bw
TDLo	Horse	Parenteral	GW 45–46 in F	889 mcg/kg bw

Abbreviations: bw, body weight; F, female; GD, gestational day; GW, gestational week; IM intramuscular; IP intraperitoneal; IT, intrathecal; M, male; PO, oral; SC., subcutaneous; TCLo, lowest teratogenic concentration; TDLo, lowest teratogenic dose

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr] Sandoz Opticort
5 mg Framycetin sulphate, 0.05 mg Gramicidin and 0.5 mg Dexamethasone
Ophtalmic/Otic solution

Read this carefully before you start taking Sandoz Opticort and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Sandoz Opticort.

What is Sandoz Opticort used for?

It is used in the eye(s) to treat:

- Inflammation due to infection (redness, itching, swelling, burning) in the front parts of the eye:
  - White of the eye (scleritis)
  - Clear layer on top of the white part of the eye (episcleritis)
  - Coloured part of the eye (iridocycitis)
  - Muscles and tissue involved in focusing the eye
- Inflammation due to infection (redness, swelling, burning) of the eyelid (blepharitis)
- Infected itchy, red rash of the eyelid
- Allergic and contagious eye infections
- Face skin reddening leading to red and yellow bumps (rosacea keratitis)

It is used in the ear(s) for:

- Redness and swelling of the ear canal (otitis externa)
- Red, scaly, greasy, itchy and inflamed skin of the outer ear

Sandoz Opticort contains antibacterial ingredients called framycetin and gramicidin, and it should be used exactly as directed by your healthcare professional.

How does Sandoz Opticort work?
Sandoz Opticort is a combination product that contains:

- 2 antibiotics (framycetin and gramicidin) that kill the bacteria that are causing the infection.
- 1 steroid (dexamethasone) that lowers inflammation

What are the ingredients in Sandoz Opticort?
Medicinal ingredients: dexamethasone sodium metasulfobenzoate, framycetin sulphate, gramicidin

Non-medicinal ingredients: phenylethyl alcohol 0.5% as preservative, sodium citrate, citric acid, polysorbate 80, ethyl alcohol, sodium chloride, sodium hydroxide and/or hydrochloric acid to adjust pH and water.

Sandoz Opticort comes in the following dosage forms:
Each milliliter of solution contains 5 mg framycetin sulphate; 0.05 mg gramicidin and 0.5 mg dexamethasone (as dexamethasone sodium metasulfobenzoate).

Sandoz Opticort is available in amber glass ophthalmic bottles of 8 mL (8 mL fill).

Do not use Sandoz Opticort if:

Eye:
- You are allergic to any of the ingredients in Sandoz Opticort;
- You have herpetic eye disease or other viral diseases of the cornea and conjunctiva;
- You have tuberculosis and fungal diseases of the eye;
- You have trachoma;
- You have untreated eye infections with thick discharges.

Ear:
- You are allergic to any of the ingredients in Sandoz Opticort;
- You have viral or fungal infections;
- You have untreated ear infections of the ear discharges;
- Your eardrum is punctured.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Opticort. Talk about any health conditions or problems you may have, including if you:
- Used corticostroids before.
- Have open wounds or damaged skin since deafness might happen if Sandoz Opticort is used directly on them.

Experience Allergies
- New itching, rash, redness or irritation that happens after using Sandoz Opticort.

Experience Eye Problems
- Blurred vision or other changes in vision (cataracts)
- Increased eye pressure
- If you take Sandoz Opticort for a long period of time, you should have your eye pressure checked regularly
- Perforation of the cornea due to thinning of the cornea

Get Pregnant

- If you become pregnant while taking Sandoz Opticort, talk to your healthcare professional right away.
- Sandoz Opticort should not be used for a long period of time during pregnancy unless the benefits outweigh the risks.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Sandoz Opticort:

Use in the Eye(s):
- Wash your hands.
- Remove the cap on the bottle.
- Tilt your head back. Pull down the lower lid of your eye.
- Squeeze 1 drop at a time into the pocket made by the lower lid.
- To avoid possibility of reinfection later, do not touch eye with dropper.
- Close your eye.
- Wipe away any excess drops with a clean tissue.

- Always put the cap back on the bottle as soon as you have used it.

Use in the Ear(s):
- Wash your hands.
- Remove the cap on the bottle.
- Tilt your head on one side.
- Squeeze 2 or 3 drops into your ear. Squeeze the dropper carefully.
- Lie your head with your affected ear facing upwards for a few minutes.
- To avoid possibility of reinfection later, do not touch ear with dropper. Alternatively, a saturated gauze wick may be inserted by the physician into the external ear canal.
- Wipe away any excess drops with a clean tissue.

- Always put the cap back on the bottle as soon as you have used it.

Misuse or overuse of Sandoz Opticort could lead to the growth of bacteria that will not be killed by framycetin or gramicidin. This means that Sandoz Opticort or other medicines that contain framycetin or gramicidin may not work for you in the future.

Do not share your medicine.

Usual dose:

In the eye(s)
- 1 or 2 drops every 1 to 2 hours (generally for 2 or 3 days).
- Afterwards, 1 or 2 drops 3 or 4 times daily.

In the ear(s)

- 2 or 3 drops in the ear canal 3 or 4 times daily.

Overdose:

If you think you have taken too much Sandoz Opticort, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important to take this medication exactly as prescribed by your doctor. If you miss a dose, administer it as soon as possible and continue with your regular schedule. If it is almost time for your next dose, skip the missed dose and continue with your regular dosing schedule. Do not administer a double dose to make up for a missed one. If you are not sure what to do after missing a dose, contact your doctor or pharmacist for advice.

What are possible side effects from using Sandoz Opticort?

These are not all the possible side effects you may feel when taking Sandoz Opticort. If you experience any side effects not listed here, contact your healthcare professional.

Eye disorders

- Increased eye pressure (glaucoma);
- Perforation of the cornea (the transparent layer forming the front of the eye);
- Eye allergies;
- Burning or stinging of the eye;
- Cloudy vision;
- Blurred or distorted vision (chorioretinopathy).

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN Allergic reaction: • rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; • wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; • swelling of the mouth, face, lips, tongue, or throat.			√
Decreased vision			√
Eye infection		√	
Eye pain			√
Gradual blurring or loss of vision			√
Dizziness/feeling of spinning			√
Hearing loss			√
Ringing in the ears		√	
Unsteadiness/loss of balance			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15 and 25 °C. Protect from light. Discard 28 days after initial use.

Keep out of reach and sight of children.

If you want more information about Sandoz Opticort:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.sandoz.ca ,or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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