PRODUCT MONOGRAPH

SANDOZ PENTASONE
(Gentamicin Sulfate and Betamethasone Sodium Phsophate Ophthalmic/Otic Solution)

Topical Corticosteroid - Antibiotic

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PRODUCT MONOGRAPH

Pr SANDOZ PENTASONE™

(Gentamicin Sulfate and Betamethasone Sodium Phosphate Ophthalmic/Otic Solution)

Therapeutic Classification

Topical Corticosteroid - Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

The anti-inflammatory and anti-allergic activity of betamethasone sodium phosphate is combined with the broad spectrum bactericidal activity of gentamicin sulfate. Betamethasone sodium phosphate inhibits the inflammatory response of the eye and ear to irritating agents of a mechanical, chemical or immunological nature, while gentamicin sulfate is active *in vitro* against a wide range of pathogenic gram-negative and gram-positive bacteria.

INDICATIONS

Ophthalmic: **SANDOZ PENTASONE** is indicated for ocular inflammation when concurrent use of an antimicrobial is judged necessary: e.g., *staphylococcal blepharoconjunctivitis*. **SANDOZ PENTASONE** is indicated for the treatment of non-purulent bacterial infections of the anterior

segment of the eye due to microorganisms sensitive to the antibiotic and when the anti-inflammatory action of betamethasone sodium phosphate is indicated, as in allergic vernal and phlyctenular conjunctivitis; non-purulent blepharitis; interstitial sclerosing post-operative keratitis; superficial chemical and thermal burns of the cornea.

In stubborn cases of anterior segment eye disease or in deep-seated ocular diseases, systemic therapy may be required. However, in these diseases SANDOZ PENTASONE solution may be used as adjunctive therapy.

Otic: **SANDOZ PENTASONE** may also be used for the treatment of lesions in the external ear canal, such as acute otitis externa, eczematoid-dermatitis, seborrheic dermatitis and contact dermatitis secondarily infected with susceptible microorganisms.

CONTRAINDICATIONS

SANDOZ PENTASONE is contraindicated in those individuals who have shown hypersensitivity to any of its components and to other aminoglycosides or to other corticosteroids.

Ophthalmic: Ophthalmic use is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva, mycobacterial infections of the eye, trachoma, fungal diseases of ocular structures.

Use of corticosteroid/antibiotic combinations is contraindicated after removal of a corneal foreign body or in the presence of acute local viral lesions, e.g. herpes, and in patients with absent or perforated tympanic membranes. As with all ophthalmic products containing benzalkonium chloride,

patients are advised not to wear soft contact lenses during treatment with **Sandoz PENTASONE** ophthalmic/otic solution.

Otic: Patients with a non-intact eardrum (broken, perforated or absent eardrum or with presence of surgical ear tubes) should not use **SANDOZ PENTASONE.**

WARNINGS

General: If prompt clinical response is not obtained with the use of **SANDOZ PENTASONE** Ophthalmic/Otic Solution, further evaluation is advised.

Ophthalmic Use: **SANDOZ PENTASONE** is for topical use only. It should never be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

Prolonged ophthalmic use may result in increased intraocular pressure in some individuals with a family history of open-angle glaucoma, with a high degree of myopia or with diabetes. If 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.

Otic: When **SANDOZ PENTASONE** is used locally in the ear, potential eighth cranial nerve toxicity should be considered. Animal studies have shown that gentamicin applied topically to the external ear canal may be absorbed since the drug has been detected in the serum and urine after this route of administration.

PRECAUTIONS

General: During long-term use of preparations containing corticosteroids, such as **SANDOZ PENTASONE,** the possibility of overgrowth of nonsusceptible microorganisms such as fungi must be considered, especially in the presence of a persistent corneal ulceration that fails to respond to conventional therapy. By reducing inflammation, steroids may mask the symptoms of serious disease or enhance existing infection due to microorganisms resistant to gentamicin. Should this occur, or if irritation or hypersensitivity to **SANDOZ PENTASONE** develops, discontinue use of this preparation and institute appropriate therapy.

Clinical studies have shown that microorganisms previously sensitive to gentamicin have become resistant during therapy. Although this has occurred infrequently, the possibility should nevertheless be considered. There is evidence that cross-resistance between gentamicin and other aminoglycoside antibiotics may occur since bacteria made resistant to aminoglycoside antibiotics artificially in the laboratory are also resistant to gentamicin. However, gentamicin may be active against clinical isolates of bacteria resistant to other aminoglycosides. Conversely, microorganisms resistant to gentamicin may be sensitive to other aminoglycoside antibiotics.

If irritation occurs with the use of **SANDOZ PENTASONE**, hypersensitivity to a component of the preparation is a possibility and use of the product should be discontinued. Cross-allergenicity among aminoglycosides and corticosteroids has been demonstrated (**see CONTRAINDICATIONS**).

To avoid possible contamination and cross-infection, avoid the use of the same bottle of medication for treatment of otic and ocular infections. The use of this dispenser by more than one person may spread infection. Contamination may occur of the dropper tip touches any surface. Do not allow dispenser tip to touch the surface of the eye.

Ophthalmic: In ophthalmic use, intraocular pressure should be checked frequently (tonometry) (**see WARNINGS**). Slit-lamp examination should be done for dendritic keratitis.

It is not advisable to treat bacterial corneal ulcers, which may be due to *P. aeruginosa*, with a combination antibiotic-anti-inflammatory product as initial therapy. It is prudent to use an anti-infective agent alone initially. For ulcers caused by *Pseudomonas*, Gentamicin Ophthalmic Ointment

USP would be indicated. If the infection responds to the anti-infective treatment, then the addition of an anti-inflammatory agent to minimize the fibrous reaction and scarring of the cornea is suggested.

Eyelid cultures and tests to determine the susceptibility of infecting organisms may be indicated if signs/symptoms persist or recur in spite of recommended course of treatment with this product.

Otic: Sandoz PENTASONE, when administered by otic route should be used for the shortest duration possible to minimize the risk of ototoxicity. The patients 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 PENTASONE** should be reassessed, with respect to ototoxicity, 5-7 days after start of treatment and thereafter, on a regular basis.

Children: Safety and effectiveness in children below the age of 8 years have not been established.

Pregnancy: Safety of topical corticosteroid/antibiotic preparations during pregnancy has not been established, therefore, drugs of this class should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Since it is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in breast milk, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EFFECTS

Ophthalmic: Adverse reactions reported include: increased ocular pressure; ocular hypersensitivity manifested by increased ocular hyperemia, edema and burning/stinging sensation.

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.

Transient eye irritation has been reported with ophthalmic gentamicin sulfate. Ophthalmic preparations may sting briefly upon application.

Otic: 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 gentamicin-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

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.

A single overdosage of gentamicin would not be expected to produce symptoms.

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.

Although a single overdose is not expected to require treatment, gentamicin can be removed from the blood by hemodialysis or peritoneal dialysis. Approximately 80% to 90% is removed from the circulatory system during twelve hours of hemodialysis. Peritoneal dialysis appears to be less effective.

DOSAGE AND ADMINISTRATION

Ophthalmic: Instill 2 drops into the conjunctival sac of the affected eye 3 or 4 times daily. During the acute stage, 2 drops may be administered every 2 hours.

Otic: Thoroughly clean the ear canal of cerumen and debris. Instill 3 or 4 drops into the affected ear 3 times daily or as directed by the physician. The patient should lie with the affected ear turned upward; instill the solution and let the patient remain in this position for several minutes to insure penetration of the medication into the ear canal. If preferred, a cotton wick may be inserted into the canal and then saturated with the solution. The wick should be kept moist by adding further solution every 4 hours. The wick should be replaced once every 24 hours.

Improvement usually occurs within 48 hours, with clearing of the signs and symptoms usually within 2 weeks. In chronic conditions, withdrawal of treatment should be carried out by gradually decreasing the frequency of application.

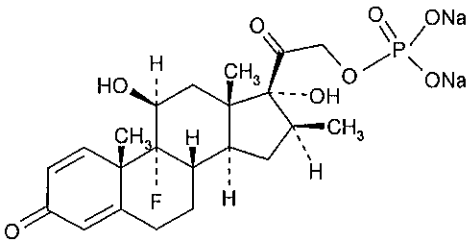
After a favourable response is obtained, reduce dosage gradually and discontinue once a cure is achieved.

The need for **Sandoz PENTASONE** should be reassessed, with respect to ototoxicity, 5-7 days after start of treatment and thereafter, on a regular basis.

PHARMACEUTICAL INFORMATION

Proper Name: Betamethasone Sodium Phosphate

Structure:



Chemical Name:

(1) Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17-dihydroxy-16-methyl-21-(phosphonooxy)-, disodium salt, (11β,16β)-

(2) 9-Fluoro-11β,17,21-trihydroxy-16β-methyl-pregna-1,4-diene-3,20-dione 21-(disodium phosphate)

Molecular Formula: $C_{22}H_{28}FNa_2O_8P$

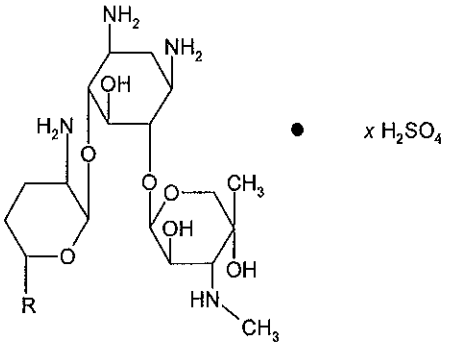
Description: White to almost white powder, odourless; Very hygroscopic; freely soluble in water; Slightly soluble in alcohol; Practically insoluble in ether and methylene chloride.

Melting Point:

pH (1%): 7.5-9.0

Proper Name: Gentamicin Sulfate

Structure: Gentamicin is a mixture of the following three substances:



	Formula	**Molecular Weight**
a) gentamicin C_1 R: -$CH(CH_3)NHCH_3$	$C_{21}H_{43}N_5O_7$	477.61
b) gentamicin C_2 R-$CH(CH_3)NH_2$	$C_{20}H_{41}N_5O_7$	463.59
c) gentamicin C_{1a} R: -CH_2NH_2	$C_{19}H_{39}N_5O_7$	449.56

The relative ratio of C_1:C_{1a}:C_2 is variable in a range of 25-50%: 10-35%: 25-55%.

Chemical Name:

(1) *O*-3-Deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabino-pyranosyl-(1→6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl-(1→4)]-2-Deoxy-D-streptamine

Description: White or beige powder; Freely soluble in water; Soluble in pyridine, dimethylformamide, in acidic media with salt formation; Moderately soluble in methanol, ethanol, acetone; Practically insoluble in benzene and halogenated hydrocarbons.

pH (1:25): 3.5-5.5

Melting point: 218-237°C

Composition

Each mL of sterile solution contains: gentamicin (as sulfate) 3.0 mg and betamethasone (as sodium phosphate) 1.0 mg, benzalkonium chloride 0.01 % (as preservative), disodium edetate, sodium borate, sodium chloride, sodium citrate, sodium phosphate dibasic and monobasic, sodium hydroxide and/or hydrochloric acid to adjust pH, and water for injection.

Stability and Storage Recommendations

Store between 2° and 25°C. Protect from light. Do not freeze. Discard 28 days after first opening.

AVAILABILITY OF DOSAGE FORMS

Sandoz PENTASONE is available in dropper bottles of 7.5 mL, boxes of 1.

PATIENT INFORMATION LEAFLET

Sandoz PENTASONE™
(Betamethasone Sodium Phosphate/Gentamicin Sulfate Ophthalmic/Otic Solution)

INFORMATION FOR THE PATIENT: Please read this information carefully before you start using your medication. If you have any questions about Sandoz PENTASONE™, ask your doctor or pharmacist.

WHAT IS Sandoz PENTASONE™? Sandoz PENTASONE™ is the brand name for betamethasone sodium phosphate/gentamicin sulfate. It is only available by prescription from your doctor.

Your doctor has prescribed Sandoz PENTASONE™ for relief of swelling, redness and itching associated with certain eye conditions, including those associated with allergies or suspected or proven bacterial infection. Sandoz PENTASONE™ may also be used to treat disorders of the outer ear canal, such as those due to allergy or infection.

HOW DOES Sandoz PENTASONE™ WORK?: Sandoz PENTASONE™ is a medication containing betamethasone sodium phosphate which is a cortisone-type medicine that helps to relieve swelling, redness and itching and gentamicin sulfate which is an aminoglycoside antibiotic that helps to prevent or treat infection.

IMPORTANT POINTS TO NOTE BEFORE YOU START TAKING Sandoz PENTASONE™: Although Sandoz PENTASONE™ is effective, there are some people who should not take it. Talk to your doctor if you:

- Have had any unusual or allergic reaction (such as wheezing, rash, hives or any other sign of irritation) to this medicine or to its ingredients.
- Have had any unusual or allergic reaction to other cortisone-type medicines or to aminoglycoside antibiotics.
- Have infection following vaccination, varicella (chicken pox), herpes simplex infection or other viral infection of the eye, or fungal infection of the eye or ear.
- Have had any type of object (such as those embedded during eye injury) removed from the cornea of your eye.
- Wear soft contact lenses.
- Have perforated, absent or punctured ear drum.

- Are pregnant, planning to become pregnant or think you may be pregnant. If you become pregnant while taking Sandoz PENTASONE™, stop taking it and tell your doctor right away.

- Are breast-feeding.

Precautions: Do not give Sandoz PENTASONE™ to anyone else or use it for other disorders; your doctor has prescribed this medicine only for you and your current condition. Do not use this product more often or for a longer time than your doctor recommends. Sandoz PENTASONE™ is not for use by injection or by mouth. Keep this medicine out of the reach of children and pets. Check with your doctor if your eye condition does not improve, worsens or seems to be infected, because you may need additional medication or another type of treatment.

Do not use Sandoz PENTASONE™ in children under 8 years of age unless under close medical supervision.

HOW TO USE Sandoz PENTASONE™: Use this medicine only as prescribed for your specific eye or ear condition. If prescribed for an eye problem, do not use it for the ear or, if prescribed for an ear problem, do not use it for the eye. Keep taking your medication for the prescribed amount of time, even if you feel better.

It is extremely important that you keep this medicine as germ-free as possible to avoid contamination:

- Wash your hands before and after using Sandoz PENTASONE™.
- Do not allow the tip of the eye/ear drop applicator tube to touch any surface, including the eye or ear or surrounding areas.
- Always keep the container closed tightly when not in use.
- Do not use any leftover medicine for future eye or ear problems without first checking with your health professional.

USE IN THE EYE

Your doctor or health professional will determine the dosage treatment time for your specific eye disorder.

Either tilt the head back or lie down and gaze upward. With the index finger, pull the lower eyelid away from the irritated eye to form a pouch. Drop the prescribed medicine into the pouch and gently close the treated eye. Do not blink or rub the eye. Keep the eye closed for about one minute so that the medicine comes in contact with the irritated part of the eye. Remove any excess medicine from around the eye with a clean tissue.

USE IN THE EAR

Your doctor or health professional will determine the dosage and treatment time for your specific ear disorder.

Clean the outer ear before use. Either lie down or tilt the head so that the affected ear faces up. Do not insert the dropper into the ear. Instill the prescribed number of drops into the ear. Keep the ear facing up for several minutes to allow the medicine to run to the bottom of the ear canal.

Your physician might instruct you to use a cotton wick. The cotton wick may be inserted into the ear canal and then saturated with the solution. The wick should be kept moist by adding further solution periodically as instructed by your physician. The wick should be replaced every 24 hours.

SIDE EFFECTS OF THIS MEDICINE:
Along with its desired effects, a medicine may cause side effects. Although not all of these side effects may occur, they may need medical attention if they do occur.

Eye Use:
Effects that may be associated with Sandoz PENTASONE™ include: brief stinging upon application; increased ocular pressure. Effects with other steroid-anti-infective combinations include: glaucoma, eye nerve damage; problems with vision; cataract formation; delayed wound healing; widened pupil; drooped eyelid.

Ear Use:
In patients with perforated, absent or punctured ear drums, rarely, use of ear drops containing gentamicin has been associated with ear damage. Signs of ear damage are: hearing loss, ringing in the ears, dizziness or imbalance. If you note any of these symptoms, stop use of Sandoz PENTASONE™ and contact your physician immediately.

Check with your doctor if you experience any other effects that are troublesome.

DRUG INTERACTIONS: Tell your doctor or health professional if you are taking any prescription or non-prescription medications, especially cortisone-type medicines or antibiotic medicines.

ABILITY TO DRIVE AND OPERATE MACHINERY: If you experience temporary blurring of vision after applying Sandoz PENTASONE™ to the eye, do not drive or operate machinery until vision returns to normal.

SPECIAL WARNINGS: Before beginning treatment with Sandoz PENTASONE™, tell your doctor or health professional of any medical problems you have or have had.

Eye Use: Tell your doctor if you use contact lenses and if you have had cataracts, glaucoma (or a family history of glaucoma), herpes infection of the eye or any other eye infection, tuberculosis of the eye, or if you have diabetes.

Ear Use: Tell your doctor if you have a perforated ear drum.

It is important to tell your doctor or health professional if you are allergic to any substance, including foods or other preservatives or dyes.

WHAT TO DO IF AN OVERDOSE IS TAKEN? Sandoz PENTASONE™ should be used only at the recommended dosage. Contact your doctor or health professional if you have used this product in large amounts or for a longer period of time than prescribed.
If you swallow Sandoz PENTASONE™ accidentally, seek medical assistance.

IF YOU MISS A DOSE: If you forget to use Sandoz PENTASONE™ as directed, apply it as soon as possible, then go back to your regular schedule. If is time for your next dose, skip the missed dose and take your next dose.

INGREDIENTS:

Sandoz PENTASONE™ comes in a 7.5 mL dropper bottle.
Each milliliter of sterile solution contains 3.0 mg of gentamicin sulfate, and 1.0 mg betamethasone sodium phosphate.
Inactive ingredients: sodium chloride, sodium citrate, sodium borate, sodium phosphate dibasic and monobasic, disodium edetate, sodium hydroxide and/or hydrochloric acid, with benzalkonium chloride as preservative.

STORAGE PRECAUTIONS: Store between 2 and 25 °C. Protect from light. Do not freeze.

Discard 28 days after first opening.

If you need more information about Sandoz PENTASONE™, talk to your doctor or pharmacist.

PHARMACOLOGY

Description

Gentamicin sulfate is a water soluble antibiotic derived from *Micromonospora purpurea*, an actinomycete. It is a white to cream colored powder which is readily soluble in water and moderately soluble in methanol, ethanol and acetone. Betamethasone disodiumphosphate is a water soluble coricosteroid with an anti-inflammatory potency approximately 25 times that of hydrocortisone. The mechanism by which it suppresses inflammation is not entirely known, but it is believed that inhibition of accumulation of macrophage cells, suppression of infiltration of polymorphonuclear leucocytes and inhibition of release of mediators of inflammation, may be involved. The rapid anti-inflammatory response to betamethasone is due to its rapid rate of absorption and transport into tissues.

In plasma, betamethasone sodium phosphate has a half-life of approximately 6.5 hours. However, its biological half-life has been estimated to be longer, between 36 to 72 hours. Betamethasone sodium phosphate is taken up rapidly by tissues of the eye as concentration in the cornea, aqueous humor and iris of the rabbit averaged 1.76, 0.48 and 0.77 μg/g of tissue after application of 50 mg tritiated betamethasone sodium phosphate to the cornea. At 4 hours, the concentrations averaged 0.4, 0.016 and 0.18 μg/g of tissue. The drug or its metabolite disappeared from the cornea and the iris with a half-life of approximately 1 hours. The half-life of elimination from the aqueous humor was slightly longer. The absorption of gentamicin into aqueous humor was investigated in rabbits by applying either gentamicin or gentamicin plus betamethasone sodium phosphate solution or ointment to the eyelids of normal eyes or eyes inflamed by mechanical abrasion of the cornea or by a 10% sodium hydroxide treatment. Following topical application of a 0.3% solution (2 drops q 15 min. x 1 hour) to the eye with the abraded cornea, the gentamicin concentration at one-half hour post application was 0.4 μg/mL in the aqueous humor.

Application of a 2 inch strip of 0.3% ointment resulted in an aqueous humor concentration of 1.6 μg/mL, one hour post application. The absorption of gentamicin was not affected by the presence of betamethasone sodium phosphate. The range of antibiotic detected in the aqueous humor in this study is in excess of the minimum inhibitory concentration for most strains of

Staphylococcus aureus and *Pseudomonas aeruginosa.*

Comparable kinetic studies have not been conducted with Gentamicin Sulfate and Betamethasone Sodium Phosphate Ophthalmic/Otic Solution in the ear.

MICROBIOLOGY

Gentamicin is active against gram-positive bacteria commonly found in eye and/or ear infections: coagulase-positive and coagulase-negative *Staphylococci*, Group A beta-hemolytic and non-hemolytic *Streptococci* and *Diplococcus pneumoniae.*

Gentamicin is also active against gram-negative bacteria including *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Serratia marcescens*, *Neisseria gonorrhoea*, *Enterobacter aerogenes*, *Providence* species and *Herellea vaginicola.*

The relatively high concentrations achieved locally with application of Gentamicin Sulfate and Betamethasone Sodium Phosphate Ophthalmic/Otic Solution may be bactericidal against bacteria only slightly sensitive *in vitro* at low concentrations.

Pseudomonacidal Activity in Rabbit Eyes

Dramatic improvement occurred in approximately two thirds of rabbit comeas infected with *Pseudomonas aeruginosa* and treated topically or subconjunctivally with gentamicin drops; five days after the start of treatment, only minimal hyperemia remained in the eye treated with gentamicin whereas corneal perforation and widespread loss of corneal and conjunctival tissue occurred in the untreated eyes.

In a clinical survey including 216 cases of infectious otorrhea, microbiological studies have identified the following microorganisms as etiological agents and they are classified by order of frequency:

Staphylococcus aureus	76 (35%)
Pseudomonas species	70 (32%)
Proteus species	14 (6%)
Escherichia coli	9 (4%)
Other gram-negative species alone or in combination	47 (23%)

TOXICOLOGY (OPHTHALMOLOGICAL)

Acute Toxicity: Twenty guinea pigs and albino rats were treated with one drop of 0.1% betamethasone sodium phosphate plus 0.3% gentamicin sulfate. No local or systemic toxic effects were observed and microscopic examination of eyes did not reveal any pathological changes. In rats, the LD_{50}s for gentamicin and betamethasone sodium phosphate were respectively 371 mg/kg and 955 mg/kg.

Subacute Ocular Tolerance: Rabbits were treated with 0.1 mL of the combination of betamethasone sodium phosphate (0.1%) and gentamicin sulfate (0.3%), nine times daily, five days a week for 3 weeks. Only mild intermittent conjunctival hyperemia was evidenced in some instances. A similar study with the ointment formulation caused transient blepharospasm in some animals.

Chronic Ocular Toxicity: Twelve New Zealand rabbits were divided into two equal groups of males and females. One group of equal number received the placebo vehicle formulation while the other group was administered the betamethasone/gentamicin either the ophthalmic solution or ointment formulation, 3 times per day for 12 weeks. Neither the placebo nor the combination caused any pathological changes in body weight, blood count, SGOT, SGPT, blood urea nitrogen, blood sugar, total serum proteins or urine.

No specific otic toxicology studies have been carried out on Gentamicin Sulfate and Betamethasone

Sodium Phosphate Ophthalmic/Otic Solution.

CLINICAL STUDIES

The safety and efficacy of gentamicin sulfate Ophthalmic/Otic preparations have been described.[1-18]

Safety

An open clinical trial was conducted in patients with either staphylococcal marginal keratitis, allergic conjunctivitis complicated by bacterial infection, phlyctenular keratoconjunctivitis, or vernal catarrh.[19] Patients received either one drop of betamethasone/gentamicin solution four times daily or ointment three times daily. The majority of patients had a favourable response with an absence of any abnormal increase in intraocular pressure or serious adverse effects.

Safety and Efficacy

In two double-blind, randomized, placebo-controlled studies, Gentamicin Sulfate and Betamethasone Sodium Phosphate Ophthalmic/Otic Solution was compared to their ingredients for the treatment of chronic staphylococcal blepharoconjunctivitis.[20] Gentamicin Sulfate and Betamethasone Sodium Phosphate Ophthalmic/Otic Solution was significantly superior to placebo and gentamicin, and equivalent to betamethasone in the parameters measured. No adverse reactions were reported.

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