

# Product Monograph

**Pr NEOSPORIN®**

**Cream**

**Eye and Ear Solution Sterile**

(Polymyxin B and Neomycin Sulfates, and Gramicidin)

**Ointment**

(Polymyxin B and Neomycin Sulfates, and Bacitracin zinc)

**Irrigating Solution**

(Polymyxin B and Neomycin Sulfates)

**Antibacterial**

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### PrNEOSPORIN®

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Eye and Ear Solution, Sterile  
(Polymyxin B and Neomycin Sulfates, and Gramicidin)

Ointment  
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Irrigating Solution  
(Polymyxin B and Neomycin Sulfates)

### Antibacterial

### Clinical Pharmacology

The anti-infective components in the combination are included to provide action against specific organisms susceptible to them. Polymyxin B sulfate and neomycin sulfate together are considered active against the following microorganisms: *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella-Enterobacter* species, *Neisseria* species and *Pseudomonas aeruginosa*. Bacitracin is active against most Gram-positive bacteria, pathogenic *Neisseria spp* and *Haemophilus influenzae*. Gramicidin is active against most species of aerobic and anaerobic Gram-positive bacteria.

## Indications and Clinical Use

### **Cream**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Cream is indicated for: the treatment of infection in dermatologic disorders, particularly where the lesions are moist or weeping; the prophylaxis of bacterial contamination in burns, skin grafts, incisions and other clean lesions; abrasions, minor cuts and wounds, where the cream may prevent infection and permit normal healing.

### **Ointment**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Bacitracin Zinc) Ointment is indicated for all lesions which are infected or likely to become infected by bacteria.

### **Eye and Ear Solution Sterile**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile is indicated for the prophylaxis and treatment of eye and ear infections.

### **Irrigating Solution**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates) Irrigating Solution is to be diluted and used as a continuous irrigant or rinse for short-term use in the urinary bladder of abacteriuric patients to help prevent bacteriuria and gram-negative rod bacteremia associated with the use of indwelling catheters.

## Contraindications

### General

The use of P<sup>r</sup>NEOSPORIN<sup>®</sup> is contraindicated in patients who have demonstrated allergic hypersensitivity to any of the components of the preparation or to cross-sensitizing substances such as aminoglycosides and other related antibiotics.

Due to the known ototoxic and nephrotoxic potential of neomycin sulfate, the use of P<sup>r</sup>NEOSPORIN<sup>®</sup> in large quantities or on large areas for prolonged periods of time is not recommended in circumstances where significant systemic absorption may occur.

A possibility of increased absorption exists in very young children, thus P<sup>r</sup>NEOSPORIN<sup>®</sup> is not recommended for use in neonates and infants (<2 years). In neonates and infants, absorption by immature skin may be enhanced and renal function may be immature.

### Cream

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Cream should not be used in the eyes or in the external ear canal if the eardrum is perforated.

### Ointment

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Bacitracin Zinc) Ointment should not be used in the eyes. It should not be used to treat otitis externa in the presence of a perforated tympanic membrane because of the risk

of ototoxicity.

The presence of preexisting nerve deafness is a contraindication to the use of <sup>P</sup>rNEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Bacitracin Zinc) Ointment or any topical aminoglycoside in circumstances where significant systemic absorption could occur.

### **Eye and Ear Solution Sterile**

For ophthalmic use, <sup>P</sup>rNEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile should not be used during surgical procedures or before surgery in circumstances where the product could gain access to intraocular fluids. Due to the risk of absorption of the preservative (benzalkonium chloride), contact lenses should not be worn when using <sup>P</sup>rNEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile, in the eye.

For otic use, <sup>P</sup>rNEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile is contraindicated in patients in whom perforation of the tympanic membrane is known or suspected and in long-standing cases of chronic otitis media, because of the possibility of ototoxicity caused by neomycin. In otic use, ototoxicity has been reported (see Adverse Reactions section).

## Warnings

### General

Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances including neomycin.

The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling and itching; it may be manifested simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

Following significant systemic absorption: aminoglycosides such as neomycin can cause irreversible ototoxicity; neomycin sulfate, polymyxin B sulfate, and bacitracin zinc have nephrotoxic potential; polymyxin B sulfate has neurotoxic potential.

The concurrent use of other aminoglycoside antibiotics is not recommended in circumstances where significant systemic absorption of neomycin sulfate following topical application could occur.

## **Irrigating Solution**

Prophylactic bladder care with P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates) Irrigating Solution should not be given where there is a possibility of systemic absorption.

P<sup>r</sup>NEOSPORIN<sup>®</sup> Irrigating Solution is intended for continuous prophylactic irrigation of the lumen of the intact urinary bladder of patients with indwelling catheters. Patients should be under constant supervision by a physician. Irrigation should be avoided in patients with defects in the bladder mucosa or bladder wall, such as vesical rupture, or in association with operative procedures on the bladder wall, because of the risk of toxicity due to systemic absorption following diffusion into absorptive tissues and spaces.

P<sup>r</sup>NEOSPORIN<sup>®</sup> Irrigating Solution should not be used for irrigation other than for the urinary bladder. Systemic absorption after topical administration of neomycin to open wounds, burns and granulating surfaces is significant and serum concentrations comparable to and often higher than those attained following oral and parenteral therapy have been reported.

Absorption of neomycin from the denuded bladder surface has been reported. However, the likelihood of toxicity following topical irrigation of the intact urinary bladder with P<sup>r</sup>NEOSPORIN<sup>®</sup> Irrigating Solution is low since no appreciable amounts of these antibiotics enter the systemic circulation by this route if irrigation does not exceed 10 days (see Precautions section).

When absorbed, neomycin and polymyxin B are nephrotoxic antibiotics, and the nephrotoxic potentials are additive. In addition, both antibiotics, when absorbed, are neurotoxins: neomycin can destroy fibers of the acoustic nerve causing

permanent bilateral deafness; neomycin and polymyxin B are additive in their neuromuscular blocking effects, not only in terms of potency and duration but also in terms of characteristics of the blocks produced.

## **Precautions**

### **General**

The use of P<sup>r</sup>NEOSPORIN<sup>®</sup> should not be continued for more than 7 days without medical supervision. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed (see Warnings section).

Articles in current medical literature indicate an increase in the incidence of allergies to neomycin in patient with stasis ulcers or eczema. The possibility of an allergic reaction to neomycin should be borne in mind.

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible.

After a maximal course, treatment should **not** be repeated for at least 3 months.

### ***Eye and Ear Solution***

P<sup>r</sup>NEOSPORIN<sup>®</sup> Eye and Ear Solution Sterile should not be given

subconjunctivally or intraocularly, nor should it be used for the irrigation of fistulous tracts in or about the eye or its socket. Treatment should be continued until at least 48 hours after the eye has apparently recovered.

### ***Irrigating Solution***

Care should be taken to prevent reflux of P<sup>r</sup>NEOSPORIN<sup>®</sup> Irrigating Solution up to the ureters, since the concentration of neomycin may cause renal toxicity.

Ototoxicity, nephrotoxicity, and neuromuscular blockade may occur if the components of the preparation are systemically absorbed (see Warnings).

Absorption of neomycin from the denuded bladder surface has been reported.

Patients with impaired renal function, dehydrated patients, elderly patients, and patients receiving high doses of prolonged treatment are especially at risk for the development of toxicity.

The safety and effectiveness of the preparation for use in the care of patients with recent lower urinary tract surgery have not been established.

Urine specimens should be collected during prophylactic bladder care for urinalysis, culture, and susceptibility testing. Positive cultures suggest the presence of organisms which are resistant to the bladder rinse antibiotics.

### **Use in the Elderly**

P<sup>r</sup>NEOSPORIN<sup>®</sup> is suitable for use in elderly patients. Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of neomycin sulfate may occur (see Dosage and Administration section).

## **Use in Children**

P<sup>r</sup>NEOSPORIN<sup>®</sup> is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus P<sup>r</sup>NEOSPORIN<sup>®</sup> is not recommended for use in neonates and infants (<2 years) (see Contraindications and Dosage and Administration sections).

## **Use in Pregnancy**

There is little information to demonstrate the possible effect of topically applied neomycin in pregnancy. However, neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity, thus use of P<sup>r</sup>NEOSPORIN<sup>®</sup> is not recommended in pregnancy.

## **Nursing Mothers**

There is little information to demonstrate the possible effect of topically applied neomycin in lactation. Thus, use of P<sup>r</sup>NEOSPORIN<sup>®</sup> is not recommended in nursing mothers.

## **Patients with Special Diseases and Conditions**

In renal impairment the plasma clearance of neomycin is reduced (see Dosage and Administration).

## **Drug Interactions**

Following significant systemic absorption, both neomycin sulfate and polymyxin B sulfate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents. However, the neuromuscular blocking activity

of neomycin sulfate and polymyxin B sulfate is unlikely to present a hazard during use of P<sup>r</sup>NEOSPORIN<sup>®</sup>.

## **Adverse Reactions**

Adverse reactions have occurred with topical use of antibiotic combination containing neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In 1 clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in two of 2175 (0.09%) individuals in the general population. In another study the incidence was found to be approximately 1%.

Ototoxicity and nephrotoxicity have been reported (see Warnings section).

Stinging and burning have been reported rarely when this product has gained access to the middle ear.

The incidence of allergic hypersensitivity reactions to neomycin sulphate in the general population are low. There is, however, an increased incidence of hypersensitivity to neomycin sulfate in certain selected groups of patients in dermatological practice, particularly those with venous stasis eczema and ulceration, and chronic otitis externa.

Allergic hypersensitivity to neomycin following topical use may manifest itself as an eczematous exacerbation with reddening, scaling, swelling and itching of the affected skin, or as a failure of the lesion to heal.

Allergic hypersensitivity reactions following the topical administration of bacitracin zinc and polymyxin B sulfate are rare events.

Anaphylactic reactions following the topical application of bacitracin zinc have been reported, but are rare events.

Reactions occurring most often from the presence of the anti-infective ingredient in ophthalmic use are localized hypersensitivity, including itching, swelling and conjunctival erythema. Local irritation on instillation has also been reported.

Irritation of the urinary bladder mucosa has been reported with use of P<sup>r</sup>NEOSPORIN<sup>®</sup> Irrigating Solution.

## **Symptoms and Treatment of Overdosage**

### **Symptoms**

No specific symptoms or signs have been associated with excessive use of P<sup>r</sup>NEOSPORIN<sup>®</sup>. However, consideration should be given to significant systemic absorption (see Contraindications, Warnings, and Precautions sections).

Following accidental ingestion, minimal absorption is expected.

### **Treatment**

Use of the product should be stopped and the patient's general status, hearing acuity, renal and neuromuscular functions should be monitored.

Blood levels of neomycin sulfate, polymyxin B, and bacitracin zinc should be determined. Hemodialysis may reduce the serum level of neomycin sulfate.

## Dosage and Administration

Treatment should not be continued for more than 7 days without medical supervision.

### Use in Adults

#### *Cream*

Following any necessary removal of debris, such as pus, crusts, etc., from the affected area, apply a small quantity 2 to 5 times daily, as required. Rub in gently if condition permits.

#### *Ointment*

Following any necessary removal of debris, such as pus, crusts, etc., from the affected area, apply a thin film 2 to 5 times daily over the affected area. Cover with dressing or leave exposed. **Do not use in the eyes.**

#### *Eye and Ear Solution*

One or 2 drops in the affected eye or ear, 2 to 4 times a day, or more frequently as required.

#### *Irrigating Solution*

For use with three-way catheters or with other catheter systems permitting continuous bladder irrigation. Under sterile conditions, add 1 mL of solution to a 1000 mL bottle of isotonic saline solution. Connect this solution to the inflow lumen of the three-way catheter, which has been inserted with aseptic precautions. The outflow lumen is connected via a sterile disposable plastic hose to a sterile disposable collection bag. The in-flow rate, for most patients, should be adjusted to a slow drip to deliver about 1,000 mL every 24 hours. If the

patient's urine output exceeds 2 litres per day, it is recommended that the in-flow rate should be adjusted to deliver 2,000 mL of the solution in a 24-hour period.

### **Use in Children**

<sup>Pr</sup>NEOSPORIN<sup>®</sup> is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus <sup>Pr</sup>NEOSPORIN<sup>®</sup> is not recommended for use in neonates and infants (<2 years) (see Contraindications and Precautions sections).

### **Use in the Elderly**

<sup>Pr</sup>NEOSPORIN<sup>®</sup> is suitable for use in elderly patients. Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of neomycin sulfate may occur (see Warnings, and Precautions sections).

### **Use in Renal Impairment**

Dosage should be reduced in patients with reduced renal function (see Precautions section).

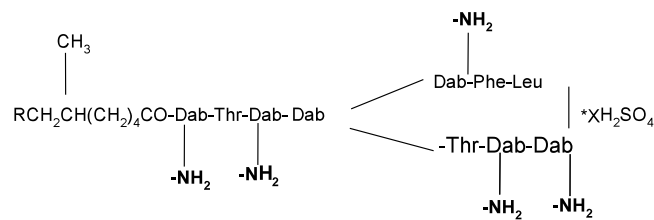
## Pharmaceutical Information

### Drug Substance

<sup>Pi</sup>NEOSPORIN<sup>®</sup> formulations are antibacterial preparations for topical use. Only <sup>Pi</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile is a sterile preparation appropriate for use in the eye.

### *Polymyxin B Sulfate*

Polymyxin B sulfate is the sulfate salt of polymyxin B<sub>1</sub> and B<sub>2</sub>, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. The structural formulae are:



Polymyxin B<sub>1</sub>:

R=CH<sub>3</sub>

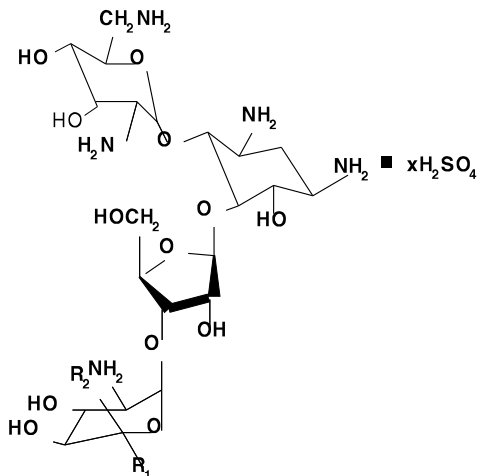
Polymyxin B<sub>2</sub>:

R=H

DAB = α,γ-diaminobutyric acid

## Neomycin Sulfate

Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae* Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600µg of neomycin standard per mg, calculated on an anhydrous basis. The structural formulae are:



Neomycin B:  $R_1=H$ ,  $R_2=CH_2NH_2$

Neomycin C:  $R_1=CH_2NH_2$ ,  $R_2=H$

## Gramicidin

Gramicidin (also called Gramicidin D) is a mixture of three pairs of antibiotic substances (Gramicidin A, B, and C) produced by the growth of *Bacillus brevis* Dubos (Fam. Bacillaceae). It has a potency of not less than 900µg of standard gramicidin per mg.

## Composition

### Cream

Each g contains: polymyxin B sulfate 10,000 units, neomycin sulfate (equivalent to 3.5mg neomycin base) 5mg, and gramicidin 250µg in a white vanishing cream base, pH approximately 5.0. Non-medicinal ingredients: emulsifying wax,

methylparaben, mineral oil, petrolatum, propylene glycol and poloxamer.

### ***Ointment***

Each g contains: polymyxin B sulfate 5,000 units, bacitracin zinc 400 units, and neomycin sulfate 5mg in a low melting point petrolatum base.

### ***Eye and Ear Solution***

Each mL of sterile solution contains: polymyxin B sulfate 10,000 units, neomycin sulfate 2.5mg, and gramicidin 25µg. Non-medicinal ingredients: propylene glycol, alcohol, poloxamer and benzalkonium chloride.

### **Irrigating Solution**

Each mL of sterile, aqueous solution contains: polymyxin B sulfate 200,000 units and neomycin sulfate 57mg, equivalent to 40mg neomycin base. Non-medicinal ingredients: methylparaben, sulfuric acid and/or sodium hydroxide, as pH adjusters. Not for injection.

### **Stability and Storage Recommendations**

Store <sup>P</sup>rNEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates) Irrigating Solution at 2° to 8°C.

Store <sup>P</sup>rNEOSPORIN<sup>®</sup> Cream, Ear and Eye Solution Sterile (Neomycin and Polymyxin B Sulfates and Gramicidin), Ointment (Neomycin and Polymyxin B Sulfates and Bacitracin Zinc) formulations between 15° to 25°C.

Protect <sup>P</sup>rNEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile from light.

## **Special Instructions**

Except for P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates) Irrigating Solution — for which dilution is required for administration — dilution of P<sup>r</sup>NEOSPORIN<sup>®</sup> is not recommended; reduction of the antibiotic concentrations may reduce their therapeutic efficacy.

## **Availability of Dosage Forms**

### **Cream**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Cream is available in tubes of 15g.

### **Ointment**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Bacitracin Zinc) Ointment is available in tubes of 15g and 30g.

### **Eye and Ear Solution Sterile**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile is available in plastic dropper bottles of 10mL.

### **Irrigating Solution**

P<sup>r</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates) Irrigating Solution is available in ampoules of 1mL and vials of 20mL.

## **Information for the Consumer**

### **General**

If redness, irritation, swelling or pain persists or increases, discontinue use and notify your physician.

### **Eye and Ear Solution**

Avoid contaminating the dropper with material from the eye, ear, fingers, or other source. This caution is necessary if the sterility of the solution is to be preserved. Due to the risk of absorption of the preservative (benzalkonium chloride), contact lenses should not be worn when using <sup>P</sup>NEOSPORIN<sup>®</sup> (Neomycin and Polymyxin B Sulfates, and Gramicidin) Eye and Ear Solution Sterile, in the eye.

## References

1. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents. *New England Journal of Medicine*; 1977 296: 722-728.
2. Bamford MFM, Jones LF. Deafness and biochemical imbalance after burns treatment with antibiotics in young children. *Arch Dis Child* 1978; 53: 326-9.
3. Binnick AN, Clendenning WF. Bacitracin contact dermatitis. *Contact Dermatitis* 1978; 4: 180-181.
4. Bjorkner B, Moller H. Bacitracin: A cutaneous allergen and histamine liberator. *Acta Dermatovener (Stockholm)* 1973; 53: 487-492.
5. Chindasilpa V, Schauf V, Hamilton LR, Riff LJ. Netilmicin use in pediatric patients. *Dev Pharmacol Ther* 1980; 7: 238-253.
6. Davia JE, et al. Uremia, deafness and paralysis due to irrigating antibiotic solutions. *Archives of Internal Medicine*; 1970 125: 135-139.
7. Dollery C. Bacitracin. Gramicidin. Neomycin. In *Therapeutic Drugs*; Dollery C (Ed), 1991.
8. Edson RS, Keys TF. The Aminoglycosides. *Mayo Clin Proc* 1983; 58: 99-102.
9. Epstein S, Wenzel FJ. Sensitivity to neomycin and bacitracin. Cross-sensitization or coincidence? *AC Dermatovenereol* 1963; 43: 1-9.
10. Finitzo-Hieber T, McCracken GH, Clinton Brown K. Prospective controlled evaluation of auditory function in neonates given netilmicin or amikacin. *J Pediatr* 1985; 106: 129-36.
11. Forstrom L, Pirila V, Pirila L. Cross-sensitivity within the neomycin group of antibiotics. *Acta Dermato-Venereologica* 1979; 59: 67-69.
12. Greenblatt DJ, et al. Drug disposition in old age. *New England Journal of Medicine*; 1982 306: 1081-1088.
13. Hemmer M. Anesthésie générale et antibiotiques. (General anaesthesia and antibiotics). *Médecine et Hygiène*; 1973 31: 1630-1631.
14. Hoeprich PD. The Polymyxins. *Med Clin North Am* 1970; 54: 1257-65.
15. James O. Pharmacological differences in old age. *Medicine International*; 1983 36: 1704-1706.
16. Jawetz, E. Polymyxin, Colistin and Bacitracin. *Pediatric Clinics of North America* 1961; 8/4: 1057-65.
17. Kruyswijk MRJ, Van Driel LMJ, Polak BCP, Go-Sennema AA. Contact allergy following administration of eye drops and eye ointments. *Documenta*

- Ophthalmologica 1979; 48: 251-253.
18. Kunin CM. Nephrotoxicity of antibiotics. JAMA 1967; 202: 132-6.
  19. Lambert HP, O'Grady FW. Aminoglycosides and aminocyclitols. In: Antibiotic and chemotherapy, 6th Edition. Edinburgh: Churchill-Livingstone, 1992, 2-26.
  20. Lambert HP, O'Grady FW. Peptides. In: Antibiotic and Chemotherapy, 6th Edition, Edinburgh: Churchill-Livingstone, 1992,231-44.
  21. Leading Article. Deafness after topical neomycin. BMJ 1969; 4: 181-2.
  22. Leyden JJ, Kligman AM. Contact dermatitis to neomycin sulfate. JAMA 1979; 242: 1276-1278.
  23. Leyden JJ, Sulzberger MB. Topical antibiotics and minor skin trauma. Am Fam Physician 1981; 23: 121-5.
  24. Lloyd DK. Expert Clinical Statement - GlaxoWellcome Drugs Containing Neomycin Sulphate. GlaxoWellcome Internal Document D961101 (Confidential). 1996.
  25. Lortholary O, Tod M, Cohen Y, Petitjean O. Aminoglycosides. Medical Clinics North America 1995 ; 79(4): 761-787.
  26. MacDonald RH, Beck M., Neomycin: a review with particular reference to dermatological usage. Clin Exp Dermatol 1983; 8: 249-258.
  27. Manian FA, Stone WJ, Alford RH. Adverse antibiotic effect associated with renal insufficiency. Review of Infectious Diseases; 1990 12(2): 236-249.
  28. Matze GR, Frye RF. Drug administration in patients with renal insufficiency. Drug safety 1997; 16: 205-31.
  29. McCracken GH. Aminoglycoside toxicity in infants and children. Am J Med 1986; 80(suppl 6B): 172-8.
  30. McEvoy GK, Ed. AHFS 95 Drug Information. American Society of Health System Pharmacists, 1995, p1865-1867.
  31. Moller H. Eczematous contact allergy to oxytetracycline and Polymyxin B. Contact Derm 1976; 5(2): 289-90.
  32. Pittinger CB, et al. Antibiotic-induced paralysis. Anesthesia and Analgesia; 1970 49: 487-501.

33. Prystowsky SD, Allen AM, Smith RW, Nonomura JH, Akers WA. Allergic hypersensitivity to nickel, neomycin, ethylenediamine and benzocaine. *Arch Dermatol* 1979; 115: 959-962.
34. Rudzki E, Kecik T, Portacha L, Rebandel P, Pauk M. Czestosc wyatepowania uczulen na antybiotyki I srodki konserwujace w kroplach ocznych (Incidence of hypersensitivity to antibiotics and conservants in eye drops). *Klinika Oczna* 1995; 97: 66-67.
35. Saryan JA, Dammin TC, Bouras AE. Anaphylaxis to topical bacitracin zinc ointment. *Am J Emerg Med* 1998; 16: 512-3.
36. Toscano WA, Storm DR. Bacitracin. *Pharmac Ther* 1982; 16: 199-210.
37. Vale MA, Connolly A, Epstein AM, Vale MR. Bacitracin-induced anaphylaxis. *Arch Dermatol* 1978; 114: 800.
38. Zaske DE. Aminoglycosides. In: *Applied Pharmacokinetics*, 3rd Edition. Eds: Evans WE, Schentang JJ, Jusko NJ. Vancouver: Applied Therapeutics, 1994; pp 14-1 - 14-47.