

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Gentamicin
(gentamicin sulphate)**

DE/W/003/pdWS/001

Marketing Authorisation Holders:

Alcon Laboratories (UK) Ltd.
EUSA Pharma (Europe) Ltd.
Merck KGaA
Sanofi-Aventis
Solvay Pharmaceuticals GmbH
URSAPHARM Arzneimittel GmbH & Co. KG

Rapporteur:	DE
Start of the procedure:	09.03.2009
Date of this report:	18.10.2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	
INN (or common name) of the active substance(s):	gentamicin sulphate
MAH:	
Currently approved Indication(s) as provide by the MAHs	<p>Treatment of serious infections due to susceptible strains of gram-negative bacteria.</p> <p>Treatment of infections of the external structures of the eye and its appendages caused by Pseudomonas and other multi-resistant bacteria. These infections comprise bacterial conjunctivitis, keratitis and bacterial kerato-conjunctivitis, ulcers and abscesses of the cornea, blepharitis and blepharo-conjunctivitis, infected chalazions and hordeola, acute meibomianitis, and dacryocystitis.</p> <p>Treatment of infectious complications: foreign bodies in the cornea or the conjunctiva, traumas caused by a physical or chemical agent, in eye surgery (especially in open-eyeball operations and corneal transplants).</p> <p>Topical treatment of anterior segment infections of the eye with an inflammatory component caused by microorganisms sensitive to gentamicin. Bacterial and allergic blepharoconjunctivitis, conjunctivitis, keratitis, scleritis and episcleritis.</p> <p>Topical treatment of bacterial infections of the auditory canal caused by microorganisms sensitive to gentamicin, as in otitis externa, and other inflammatory disorders where an antibiotic/corticosteroid is indicated.</p> <p>Infections of the anterior segment of the eye caused by microorganisms sensitive to gentamicin: corneal ulcers and corneal bacterial abscesses. Conjunctivitis, Keratitis. Staphylococia. Blepharitis. Dacryocystitis. Preoperative sterilization of the conjunctiva.</p> <p>For supportive treatment in post-traumatic and hematogenic purulent inflammation of bone and bone marrow after surgical restoration of the focal</p>

	point of the infection; the effectiveness is against gentamicin-susceptible micro organisms. Further, the sponge can be used by the so-called spongiosa plastic surgery and during cementless arthroplasty for the infection protection of the bone bed, especially for small, narrow spaces such as the marrow cavity of long bones. For the local treatment of defect- and other residual cavities in soft tissue surgery such as the sacral cavity after the rectal amputation.
Pharmaco-therapeutic group (ATC Code):	J01GB03
Pharmaceutical form(s) and strength(s):	3 mg/ml eye drops, solution 1 mg/ml + 3 mg/ml + 0,5 mg/ml eye drops, solution 5 mg/ml eye drops 5 mg/g eye ointment 1/40/80/120 mg solution for injection 32,5 mg and 130 mg sponge solution for injection (80 mg/2ml, 120 mg/2ml, 160 mg/2ml for adults and 20 mg/2 ml for children) 5 mg/ml for intrathecal administration cream and ointment 0,3% ear/eye drops 0,3% infusion (0.08%, 0.12%, 0.16%)
Rapporteur's contact person: Name of the Assessor:	Durkhani Mangal Tel: +49 228 207 3605 Email: Durkhani.Mangal@bfarm.de Dr. Victor Sack Tel: + 49 228 207 3442 Fax: + 49 228 207 3392 Email: sack@bfarm.de

I. INTRODUCTION

Six MAHs submitted a total of 21 completed paediatric studies for Gentamicin, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

Short critical expert overviews have also been provided by some of the MAHs.

The MAHs stated that the submitted paediatric studies do not influence the benefit risk for Gentamicin and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Background

Gentamicin is an aminoglycoside and has been a mainstay in the treatment of diseases due to susceptible Gram-negative aerobic microorganisms for almost 40 years. Gentamicin sulphate is available in several strengths and forms for a variety of modes of administration including solution for intramuscular, parenteral, or intrathecal administration, ear drops, ophthalmic solution and ointment, and topical cream and ointment.

Like other aminoglycosides, gentamicin is used empirically for serious infections mainly in combination with cell-wall active antimicrobials in hospitalised patients. Widely accepted indications include sepsis, infective endocarditis, neutropenia and fever, burn wound infections and ulcers, intraabdominal infections, nosocomial pneumonia, pyelonephritis, osteomyelitis, septic arthritis, and meningitis. Most indications are approved for adults, children and neonates.

Pharmacodynamic, pharmacokinetic and toxicological properties of gentamicin are well known. Gentamicin (as other aminoglycosides) is poorly absorbed from the gastrointestinal tract but is rapidly absorbed after intramuscular injection. Average peak plasma concentrations of about 4 micrograms per ml are obtained in patients with normal renal function, 30 to 60 minutes after intramuscular administration of 1mg/kg, which is similar to concentrations achieved after intravenous infusion. Several doses are required before plasma equilibrium concentrations occur with important individual variation. Plasma-protein binding of gentamicin is low. Gentamicin diffuses mainly into extracellular fluids. The volume of distribution is 0.3 l/kg. The plasma elimination half-life in normal patients is 2 to 3 hours. Gentamicin is not metabolized and is excreted virtually unchanged in the urine by glomerular filtration.

Limitations of gentamicin are some well-known side effects (e.g. ototoxic and nephrotoxic potential), the requirement of combination for most indications, and the limited efficacy in Gram-positives, anaerobes and atypical pathogens. These limitations are handled by monitoring of both the occurrence of known side effects and serum levels of gentamicin, and appropriate combination with beta-laktam-antibiotics or glycopeptides. Both safety and efficacy have been improved by once daily dosing (ODD) of gentamicin. Applying ODD, efficacy – which depends on the peak serum concentration due to the great postantibiotic effect of gentamicin – increases while safety improves.

Gentamicin is also used topically for the treatment of superficial eye and outer ear infections caused by susceptible organisms, such as conjunctivitis, keratitis, blepharitis, dacryocystitis, as well as otitis externa. Although most cases of mild bacterial eye and outer ear infections improve without anti-infective therapy, topical application of anti-infectives may shorten the infectious process. In addition, topical application of anti-infectives may reduce recurrence rate and morbidity associated with such infections.

Gentamicin also is used topically in conjunction with topical corticosteroids in some cases of bacterial ocular infections. Concomitant therapy with a corticosteroid may be used for steroid-responsive ocular inflammatory conditions for which a corticosteroid is indicated and where a superficial ocular bacterial infection or risk of ocular bacterial infection exists.

II.2 Information on the pharmaceutical formulation used in the clinical studies

Gentamicin (sulphate) is available in the forms of solution for injection, solution, for infusion, solution for intrathecal administration, ear/eye drops, eye cream and ointment. In some countries, solution for injection labelled as “paediatric” is available but is no different in its composition from solutions of the same concentration that are not so labelled.

II.3 Non-clinical aspects

N/A

II.4 Clinical aspects

1. Introduction

The MAH Alcon Laboratories submitted report(s) for:

1. McGlone A, Cranswick N. Evidence behind the WHO Guidelines: Hospital care for children: What is the evidence of safety of gentamicin in children? *Journal of Tropical Pediatrics*. October 2008; 54 (5): 291-293.
2. Darmstadt G L; Miller-Bell M; Batra Maneesh; L; Law K. Extended-interval dosing of gentamicin for treatment of neonatal sepsis in developed and developing countries. *Journal of health, population, and nutrition*. Jun 2008; 26 (2):163-182.
3. Fernandez Rubio E, Cuesta Rodríguez T, Cortés Valdés C. Preoperative eye-drop antibiotherapy in cataract surgery. *Arch Soc Esp Oftalmol*. 2004 May;79(5): 213-219.
4. Pinna A, Zanetti E, Sotgiu M, Sechi LA, Fadda G, Carta F. Identification and antibiotic susceptibility of coagulase negative staphylococci isolated in corneal/external infections. *Br J Ophthalmol* 1999; 83: 771-773.
5. Gonzalez Santacruz M; Tarazona J L; Ferrandis P; Tapia C; Jimenez B. Comparison of two gentamicin dosing schedules in the newborn. *Anales de Pediatría* Jun 2008;68 (6):581-588.

6. Timewell RM, Rosenthal AL, Smith JP, Cagle GD. Safety and efficacy of tobramycin and gentamicin sulfate in the treatment of external ocular infections of children. *J Pediatr Ophthalmol Strabismus*. 1983;20(1):22-26
7. Erjongmanee S, Kasetsuwan N, Phusitphoykai N, Puangsricharern V, Pariyakanok L. Clinical evaluation of ophthalmic lomefloxacin 0.3% in comparison with fortified cefazolin and gentamicin ophthalmic solutions in the treatment of presumed bacterial keratitis. *J Med Assoc Thai*. 2004 Sep;87 Suppl 2:S83-90.
8. Trope GE, Lawrence JR, Hind VM, Everden A. Systemic absorption of topical and subconjunctival gentamicin. *Br J Ophthalmol*. 1979;63(10):692-693. ER5594 Gentamicin Statement 5
9. Fransen L, D'Costa L, Ronald AR, Nsanze H, Brunham R, Piot P. Single-dose kanamycin therapy of gonococcal ophthalmia neonatorum. *Lancet*, December 1, 1984:1234-1236.

The MAH EUSA Pharma submitted report(s) for:

1. Kos, M., Jazwinska-Tarnawska, E., Hurkacz, M., Orzechowska-Juzwenko, K., Pilecki, W., Klempous, J. (2003) The influence of locally implanted high doses of gentamicin on hearing and renal function of newborns treated for acute hematogenous osteomyelitis. *International Journal of Clinical Pharmacology and Therapeutics*, 41 (7), str. 281-286
2. Schafer *et al*, Is the Primary Suture Indicated in Infected Wounds in Pediatric Surgery, *Langenbecks Arch Chir Supp II. Kongreßbericht*, 1997

The MAH Merck KGaA submitted report(s) for:

1. Clinical Comparison of Efficacy and Tolerability. *Chemotherapy* 1988; 34: 158-163
Kienitz M. Gentamicin in the treatment of acute and chronic pyelonephritis in children. *Med Klinik* 1970; 65 (12): 552-557
2. Skopnik H. Pharmacokinetic and antibacterial activity of daily gentamicin. *Archives Dis Childhood* 1992; 67: 57-61
3. Lohr JA. Comparison of three topical antimicrobials for acute bacterial conjunctivitis. *Pediatr Infect Dis J* 1988; 7: 626-629.
4. Verma M. Neonatal conjunctivitis: a profile. *Indian Pediatrics* 1994; 31: 1357
5. Heimann G. Renal toxicity of aminoglycosides in the neonatal period.. *Pediatr Pharmacol* 1983; 3: 251-257.
6. Elhanan K. Gentamicin once-daily versus thrice-daily in children. *J Antimicrob Chemother* 1995; 35: 327-332.

7. Nahata MC. Lack of nephrotoxicity in pediatric patients receiving concurrent vancomycin and aminoglycoside therapy. *Chemotherapy* 1987; 33: 302-304.
8. Skopnik H. Once daily aminoglycoside dosing in full term neonates. *Pediatr Infect Dis J* 1995; 14: 71-72.

The MAH Sanofi-Aventis submitted no study reports. Of the listed literature references none appear to be relevant to the article 45 procedure.

The MAH Solvay Pharmaceuticals submitted a report for:

Trevor Duke, Harry Poka, Frank Dale, Audrey Michael, Joyce Mgone, Tilda Wal
Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. *The Lancet* vol 359 February 9,2002

The MAH URSAPHARM submitted a report for:

Timewell RM, Rosenthal AL, Smith JP, Cagle GD. Safety and efficacy of tobramycin and gentamicin sulfate in the treatment of external ocular infections of children. *J Pediatr Ophthalmol Strabismus*. 1983;20(1):22-26

This study has also been submitted by the MAH Alcon.

2. Clinical study(ies)

McGlone A, Cranswick N. Evidence behind the WHO Guidelines: Hospital care for children: What is the evidence of safety of gentamicin in children? *Journal of Tropical Pediatrics*. October 2008; 54 (5): 291-293.

➤ Description

This clinical review addresses the question: What is the evidence for the safety of gentamicin use in children? Gentamicin is associated with dose-related (trough serum concentrations > 2 µg ml⁻¹) nephro- and ototoxicity. Nephrotoxicity is usually reversible on termination of gentamicin treatment, but ototoxicity can lead to permanent sensori-neural deafness and vestibular disturbance.

This review of the literature concludes that based on the evidence available, short-term gentamicin administration at the recommended doses is an appropriate antibiotic, even without serum gentamicin level monitoring.

Rapporteur's comment

The Rapporteur considers this review a useful survey of the available literature which appears to indicate that no apparent departures from the known safety profile of gentamicin have been observed.

Darmstadt G L; Miller-Bell M; Batra Maneesh; L; Law K. Extended-interval dosing of gentamicin for treatment of neonatal sepsis in developed and developing countries. Journal of health, population, and nutrition. Jun 2008; 26 (2):163-182.

➤ Description

Traditionally, gentamicin has been administered 2-3 times daily. However, recent evidence suggests that extended-interval (i.e. ≥ 24 hours) dosing may be applicable to neonates. This review examines the available data from randomized and non-randomized studies of extended-interval dosing (i.e. ODD – once daily dosing) of gentamicin in neonates from both developed and developing countries. Available data on the use of gentamicin among neonates suggest that extended dosing intervals and higher doses (>4 mg/kg) confer a favourable pharmacokinetic profile, the potential for enhanced clinical efficacy and decreased toxicity at reduced cost. In conclusion, the following simplified weight-based dosing regimen for the treatment of serious neonatal infections in developing countries is recommended: 13.5 mg (absolute dose) every 24 hours for neonates of $\geq 2,500$ g, 10 mg every 24 hours for neonates of 2,000-2,399 g, and 10 mg every 48 hours for neonates of $\sim 2,000$ g.

Advantages of once-daily and extended-interval gentamicin dosing regimens compared to multiple-daily dosing regimens are listed as follows:

- Higher peak serum levels and higher peak level: MIC (Minimum inhibitory concentration) ratio
- Prolonged post-antibiotic effect (i.e. prolonged efficacy)
- Greater initial bacterial killing
- Reduced risk for emergence of resistant strains of bacteria
- Sub-toxic drug trough levels maintained for longer periods
- Reduced risk for ototoxicity and nephrotoxicity
- More cost-effective
- Reduced costs for supplies, preparation, and administration of drug
- Reduced costs for therapeutic drug monitoring
- Reduced costs for managing complications due to drug toxicity

Rapporteur's comment

The Rapporteur considers this review an extensive and useful survey of the available literature which suggests extended-interval dosing regimens may offer advantages over the traditional multiple-daily dosing regimens.

Fernandez Rubio E, Cuesta Rodríguez T, Cortés Valdés C. Preoperative eye-drop antibiotherapy in cataract surgery. Arch Soc Esp Ophthalmol. 2004 May;79(5): 213-219.

➤ **Description**

The study is in Spanish. The English summary is as follows:

Objective: To ascertain the effectiveness of various antibiotic eye-drops in eradicating the preoperative conjunctival bacteria of patients undergoing cataract surgery and to differentiate the failure of these treatments due to the lack of «in vitro» sensibility from other possible causes.

Methods: Retrospective study of the preoperative conjunctival flora of 4876 consecutive patients; «in vitro» sensibility was analysed by grouping bacteria into eight categories; the susceptibility percentages of the total conjunctival flora to five antibacterial agents were compared. The effectiveness of the eyedrop treatment with a single sensitive tested antibiotic (Aureomicin, Chloramphenicol, Gentamicin, Norfloxacin or Rifamicin) was evaluated in patients with pathogen bacteria.

Results: The «in vitro» sensibilities of Chloramphenicol (84.4%) and Rifampicin (83.9%) were similar ($p < 0.01$) and statistically higher than those of the other antibiotics. Nevertheless, the Chloramphenicol pathogen bacterium treatment failed in 21.2% of cases, in spite of being «in vitro» sensitive. Gentamicin presented the best effectiveness for eradicating *Staphylococcus Aureus* and Gram (—) rods. Aureomicin had the best effectiveness against *Streptococcus* and Gram (—) diplococci. Rifamicin was the most effective for eradicating the whole predominant Gram (+) flora. The effectiveness of all five antibiotics decreased when there was more than one pathogen.

Conclusions: None of the five antibiotic monotherapies maintains the patients' conjunctive free of pathogen bacteria 48 hours after finishing the treatment; however, there are bacterial patrons whose treatment could be optimised. The existence of polymicrobial flora decreases the effectiveness of the treatment (*Arch Soc Esp Ophthalmol 2004; 79: 213-220*).

Rapporteur's comment

There is no indication that this study includes children. Therefore its relevance to the specific requirements of the article 45 procedure cannot be assessed.

Pinna A, Zanetti E, Sotgiu M, Sechi LA, Fadda G, Carta F. Identification and antibiotic susceptibility of coagulase negative staphylococci isolated in corneal/external infections. Br J Ophthalmol 1999; 83: 771-773.

Aims -To identify and determine antibiotic susceptibility of coagulase negative staphylococci (CoNS) isolated from patients with chronic blepharitis, purulent conjunctivitis, and suppurative keratitis.

Methods - A retrospective review of all culture positive cases of chronic blepharitis, purulent conjunctivitis, and suppurative keratitis between July 1995 and December 1996 was performed. Cases in which CoNS were the sole isolates were analysed. Species identification was performed by using a commercially available standardised biochemical test system. Antibiotic susceptibility to penicillin, gentamicin, tetracycline, erythromycin, ciprofloxacin, and teicoplanin was determined by agar disc diffusion (Kirby-Bauer method). Teicoplanin resistance was confirmed by agar dilution.

Results - 42 *Staphylococcus epidermidis*, four *S warneri*, three *S capitis*, two *S horninis*, one each of *S xylosus*, *S simulans*, *S equorum*, and *S lugdunensis* were identified. 37 CoNS were penicillin resistant, 12 gentamicin resistant, 28 tetracycline resistant, 18 erythromycin resistant, four ciprofloxacin resistant, and one teicoplanin resistant (MIC, 32 µg/ml). In total, 16 strains were resistant to three or more antibiotics.

Conclusion - Species of CoNS apart from *S epidermidis* may be isolated from patients with corneal and external infection. Antibiotic susceptibility of CoNS is unpredictable and multiresistant strains are common. As a result, antibiotic susceptibility testing should be performed in all cases of clinically significant ocular infections caused by CoNS.
(*BTJ Ophthalmol*1999;83:771-773)

Rapporteur's comment

There is no indication that this study includes children. Therefore its relevance to the specific requirements of the article 45 procedure cannot be assessed.

Gonzalez Santacruz M; Tarazona J L; Ferrandis P; Tapia C; Jimenez B. Comparison of two gentamicin dosing schedules in the newborn. Anales de Pediatría Jun 2008;68 (6):581-588.

➤ **Description**

The study is in Spanish. The English summary is as follows:

Introduction

Gentamicin is widely used in full-term neonates as empirical therapy for early-onset suspected or proven sepsis. Several dosing schedules for gentamicin have been recommended for this neonatal population.

Objective

To compare gentamicin serum levels, efficacy and toxicity of two dosing schedules in term and preterm newborns.

Material and methods

The study included 200 newborns who were started on gentamicin therapy. Group A (N = 100) was prescribed a multiple-daily dosing regimen and Group B (N = 100) on a once-daily dosing regimen. Newborns in Group A received gentamicin at 2.5-3.5 mg/kg/dose q12-18 h depending on postnatal age and serum creatinine levels, and newborns in Group B received 4-5 mg/kg/dose q24-48 h depending on postconceptional and postnatal age. All peak and trough serum drug levels, demographic data, and markers of potential nephrotoxicity and ototoxicity were compared.

Results

Peak serum gentamicin levels were significantly higher ($8.2 \pm 0.22 \mu\text{g/ml}$ vs. $5.9 \pm 0.13 \mu\text{g/ml}$; $p \leq 0.001$) and trough levels were significantly lower ($0.9 \pm 0.06 \mu\text{g/ml}$ vs. $1.7 \pm 0.08 \mu\text{g/ml}$; $p \leq 0.001$) in Group B than in Group A. There was no significant difference between the groups either in the clinical failure rate or in the nephrotoxicity or ototoxicity outcomes.

Conclusions

Once-daily dosing regimen of gentamicin in preterm and term newborns is safe and effective, with a reduced risk of serum drug concentrations falling outside the therapeutic range.

Rapporteur's comment

The Rapporteur considers this study as useful in showing that an ODD (once daily dosing) regimen may be safe and effective comparative to the traditional multiple daily dosing regimen in newborns.

Timewell RM, Rosenthal AL, Smith JP, Cagle GD. Safety and efficacy of tobramycin and gentamicin sulfate in the treatment of external ocular infections of children. J Pediatr Ophthalmol Strabismus. 1983;20(1):22-26

The purpose of this randomised double-blind study was to confirm the safety and efficacy of tobramycin in the treatment of acute bacterial ocular infections in a paediatric and juvenile (patients aged 20 years or less) population, and compare these with gentamicin sulfate. Also, the infecting bacterial population was examined in order to determine the spectrum of organisms involved in the infections as this may have some bearing on the recommended treatment regimens.

Subjects and Methods

A total of 90 patients, under 20 years of age, were enrolled in the study to compare the safety and efficacy of tobramycin and gentamicin sulfate solutions and ointments. Eighteen of these patients were excluded from the analysis due to protocol deviations, which left 62 patients suitable for safety evaluation. Only 42 patients were eligible for efficacy evaluation, however, since the remaining 20 were either culture negative or they failed to provide follow-up cultures.

The patients enrolled in this study all had acute superficial ocular inflammations of presumed bacterial origin but those who were subsequently found to be culture negative were continued in the study and evaluated for safety of the medication only. Patients who were allergic to aminoglycosides or had received antimicrobial chemotherapy in the preceding 48 hours were excluded from the trial. Tobramycin and gentamicin were used in the form of 0.3% solutions or ointments (Tobrex, Alcon Laboratories Inc., Fort Worth, Texas 76101 and Garamycin sulfate,

Schering Corp., Kenilworth, NJ 07033) and the two drugs in each dosage form were repackaged by Alcon Laboratories Inc., into identical containers (droptainers and tubes, respectively). Thus, treatment allocation was randomized and the study was conducted on a double-masked basis. No concomitant therapy was administered during the course of the study.

Patients given antibiotic solution instilled two drops in the appropriate eye(s), every two hours, while awake for the first two treatment days and then two drops four times a day for treatment days 3-10. Patients given antibiotic ointment, instilled a one-half inch ribbon of ointment in the affected eye(s) five times a day, while awake, on treatment days 1-3 and then three times a day on days 4-10. Therapy was discontinued approximately 12 hours before the final examination on day 11. Patients who were not old enough to administer their own medication had their parents apply the antibiotic during the parents' waking hours. No other therapeutic measures were used to treat these infections.

Patients were examined on days 1, 3, 7 and 11 and specific symptoms (discomfort or pain, tearing, photophobia and visual acuity) and signs (bulbar and palpebral conjunctival inflammation, exudation, scaling, erythema, limbal inflammation, focal stromal infiltrates and cornea1 epithelia1 disease) were evaluated on the scale: normal, mild, moderate or severe. Similarly, at each visit, the progress of the patient was determined, by overall assessment of the above signs and symptoms, and graded as cured, improved, unimproved or worse.

Bacteriological samples were taken from the conjunctivae and skin lash margins of the patients' diseased eyes, with calcium alginate swabs and plated on blood and chocolate agar, on day 1 and 11. The number of organisms of each species present were then compared with threshold levels to determine whether the cultures were classed as positive or negative. The following cultures were regarded as positive: colony count above 0 for group A streptococci, *Streptococcus pneumoniae*, all Gram-negative rods and *Neisseria* species; above 10 for alpha-haemolytic streptococci, *Staphylococcus aureus*, *Micrococcus* species, and *Branhamella catarrhalis*; above 100 for *Bacillus* species and *Staphylococcus epidermidis*; above 10,000 for *Corynebacterium* species. Cultures from specimens taken on day 11 were compared with those taken on day 1 and were classified as eradicated, controlled (organism count below threshold but not eradicated), reduced, unchanged, or proliferated.

Results

TABLE 1
PATIENT DETAILS

	Treatment Group	
	Tobramycin	Gentamicin
Number patients* (eyes)	29 (46)	13 (20)
% male	31	62
Race: % Caucasian	42	54
% Black	48	38
Other	10	8
Mean age (S.D.)	13.1 (6.7)	10.2 (6.8)

**Efficacy only*

TABLE 2
DIAGNOSES OF INFECTED EYES

	Number of eyes treated (%)	
	Tobramycin	Gentamicin
Total	46	20
Conjunctivitis	20 (43)	13 (65)
Blepharitis	3 (7)	0
Blepharoconjunctivitis	23 (50)	6 (30)
Blepharokeratoconjunctivitis	0	1 (5)

TABLE 3

BACTERIA ISOLATED FROM CONJUNCTIVAL AND LID MARGIN SPECIMENS OF PATIENTS BEFORE TREATMENT

Species	Number of infected* Eyes on Day 1.					
	Tob.	Conjunctiva Gent.	Total (%)	Tob.	Lid Margin Gent.	Total (%)
Strep. pneumoniae	8	2	10 (21)	7	1	8 (11)
a-haemolytic streptococci	1	3	4 (8)	1	4	5 (7)
Staph. aureus	4	4	8 (17)	6	4	10 (14)
Staph. epidermidis	5	2	7 (15)	13	5	18 (25)
Other Micrococci	3	1	4 (8)	5	3	8 (11)
Pseud. aeruginosa	1	0	1 (2)	1	0	1 (1)
Moraxella spp.	1	0	1 (2)	2	1	3 (4)
Haemophilus spp.	4	8	12 (25)	3	5	8 (11)
Other Neisseria	0	1	1 (2)	0	1	1 (1)
Branhamella catarrhalis	0	0	0	2	1	3 (4)
Others	0	0	0	5	3	8 (11)
Total	27	21	48	45	28	73

*Organism counts above threshold levels

TABLE 4

EFFECT OF TOBRAMYCIN AND GENTAMICIN SULFATE
ON THE BACTERIAL CULTURES
FROM CONJUNCTIVAE AND LID MARGINS

	Treatment Group	
	Tobramycin	Gentamicin
Conjunctiva		
Total number of eyes	41	17
Eradication/control	35 (85%)	11 (65%)
Reduction/unchanged	4 (10%)	4 (24%)
Proliferation	2 (5%)	2 (12%)
Lid margin		
Total number of eyes	39	15
Eradication/control	28 (72%)	12 (80%)
Reduction/unchanged	6 (15%)	3 (20%)
Proliferation	5 (13%)	0

TABLE 5

CLINICAL EFFICACY OF TOBRAMYCIN
AND GENTAMICIN SULFATE

Follow-up Impression of Eyes	Treatment Group	
	Tobramycin	Gentamicin
Cured/improved	45 (98%)	19 (95%)
Unimproved	1 (2%)	1 (5%)
Total	46	20

TABLE 6

INCIDENCE OF ADVERSE REACTIONS WITH
TOBRAMYCIN AND GENTAMICIN SULFATE

Patients (eyes)	Treatment Group	
	Tobramycin	Gentamicin
Total number	34 (54)	28 (42)
Adverse reactions	0	2 (3)

In conclusion, this study has shown that the most frequently encountered bacterial eye infection in a young population may be different from that seen in adults and needs separate consideration. Although this study alone was too small to provide any statistically significant results with regard to the relative efficacies of tobramycin and gentamicin, it has shown trends which support the findings of previous, larger investigation. The two antibiotics were found to be as efficacious in the treatment of external ocular infections in a paediatric population as they were in adult population. Also, in agreement with previous reports, patients treated with tobramycin demonstrated a trend towards fewer treatment-related side effects.

Rapporteur's comment

This old study is useful in confirming that gentamicin is as efficacious in the treatment of external ocular infections in a paediatric population as it is in adult population.

Erjongmanee S, Kasetuwan N, Phusitphoykai N, Puangsrucharern V, Pariyakanok L. Clinical evaluation of ophthalmic lomefloxacin 0.3% in comparison with fortified cefazolin and gentamicin ophthalmic solutions in the treatment of presumed bacterial keratitis. J Med Assoc Thai. 2004 Sep;87 Suppl 2:S83-90.

➤ **Description**

An abstract of the study was submitted.

OBJECTIVE: To evaluate the efficacy and safety of 0.3% lomefloxacin single agent solution, by comparing to a combination of fortified ophthalmic solutions of cefazolin sodium 50 mg/ml and gentamicin sulfate 14 mg/ml, in the treatment of acute bacterial keratitis.

DESIGN: Prospective, double-masked, randomized comparative trial.

METHOD: Forty patients with clinical diagnosis of any grade of severity of acute bacterial keratitis were randomized into 2 treatment groups: 20 to fortified cefazolin-gentamicin group, and 20 to lomefloxacin-normal saline group. The dosing of the drugs were scheduled for both treatment groups as follows: 1 drop of each solution was alternately instilled every 5 minutes for the first 30 minutes (as loading dose), then 1 drop with 5-minute interval between 2 bottles instilled hourly for day 1-3, tapering to every 2 hours on day 4-6, and every 4 hours on day 7-14. After day 14, dosing discretion was clinically adjusted, based on the clinical condition and finally discontinued after complete healing. Corneal scraping for cultures was obtained before starting the treatment. Ocular symptoms and signs, time to heal and adverse reactions were evaluated and compared between the 2 groups on day 2, 4, 7, 14, 21 and 28.

RESULTS: No clinically or statistically significant difference were noted between two treatment groups, regarding demographic, symptoms and signs associated with bacterial keratitis. Positive results of bacterial cornea1 cultures were obtained in 27.5%. There was no statistically significant difference in time to complete re-epithelialization in all types of bacterial keratitis (P=0.251). By day 7, the keratitis was healed: 44% in lomefloxacin group, and 33% in fortified antibiotic group. Both study medications were well-tolerated, with no incidence of reported adverse event.

CONCLUSION: In this study, even though there is no statistically significant difference of symptoms and signs between the two study groups at any study visit, we found clinical improvement in all patients in lomefloxacin group. So, lomefloxacin may be used as an alternative to standard treatment in acute bacterial keratitis.

Rapporteur's comment

There is no indication that this study includes children. Therefore its relevance to the specific requirements of the article 45 procedure cannot be assessed.

Trope GE, Lawrence JR, Hind VM, Everden A. Systemic absorption of topical and subconjunctival gentamicin. Br J Ophthalmol. 1979;63(10):692-693. ER5594 Gentamicin Statement 5

➤ **Description**

Ten patients received ocular gentamicin therapy topically or subconjunctivally. Systemic absorption was not detected after topical use but was detected after subconjunctival administration. The relative safety of ocular gentamicin therapy is discussed and the literature is reviewed.

Patients and methods

Ten patients were divided into two groups. *Group I* consisted of 4 children and 1 adult who had been admitted for routine squint surgery. They were treated with topical gentamicin drops (Genticin 0.3% drops) instilled 2-hourly into both eyes for a 5-day period until between 20 and 38 mg of the drug had been administered (Table I). Urine was collected over 24 hours after the last dose was administered and analysed for gentamicin by bacteriological (Alcid and Seligman,1973) and radioimmuno assay (RIA) techniques.

Group II consisted of 5 adult post-cataract patients who were given either 10 or 20 mg of gentamicin subconjunctivally. Blood was removed 1, 2, and 4 to 6 hours after subconjunctival injection. After centrifugation the serum concentration of gentamicin was determined by RIA using a kit supplied by Diagnostic Products Corporation, Los Angeles, Ca 70064, USA. This assay uses ¹²⁵I gentamicin and had a coefficient of variation in our hands from 10.0% at 0.5 µg/ml to 6.5% at 10 µg/ml. The detection limit of this assay was 0.05 µg/ml when drug-free serum was used to prepare standards.

Table 1 Total dose of gentamicin applied to both eyes—group I

<i>Patient</i>	<i>Age</i>	<i>Total dose (mg)</i>
1	39	27.00
2	8	20.00
3	8	23.00
4	3	38.00
5	3	20.00

Results

Group I. No significant amounts of gentamicin were detected in the urine from any of the 5 patients on topical drops. This applied to the bacteriological method of antibiotic detection, the lower limit of detection being 0.5 µg/ml. With the radioimmuno assay technique non-specific

gentamicin binding occurred when urine was used as a control, so that this technique was not applicable to the assay of gentamicin in urine.

Group II. Antibiotic was present in detectable concentration in the serum of all 5 patients tested. Table 2 summarises the serum levels of gentamicin attained in these patients.

Table 2 Total dose applied to both eyes with serum concentrations of drug—group II

<i>Patient no.</i>	<i>Dose (mg)</i>	<i>1 hour (µg/ml)</i>	<i>2 hours (µg/ml)</i>	<i>4 to 6 hours (µg/ml)</i>
1	10	0.20	0.20	Nil
2	10	0.20	0.10	Nil
3	10	0.40	0.30	Nil
4	20	0.98	0.76	0.59
5	20	0.58	0.51	0.30

Gentamicin is very poorly absorbed from the gastrointestinal tract, so systemic absorption must take place directly into the circulation from the eye. The total doses of gentamicin used in group I patients represent 43 ½ days of topical therapy had the drug been applied 3 times daily (0.135 to 0.172 mg gentamicin per 0.05-ml drop of Genticin) (personal communication, Nicholas Laboratories). Our inability to detect significant systemic absorption from this group of patients suggests that even in patients with moderate renal impairment long-term low-dose use of gentamicin eyedrops is relatively safe. We were unable to find any reported cases of topical gentamicin eyedrops causing disease of the vestibular apparatus.

Systemic absorption from subconjunctival injection has been confirmed in the patients of group II. We were able to detect significant blood levels 2 hours after injection in all our patients. Although the levels we recorded are higher than those detected by Mathalone and Harden (1972), they are somewhat lower than those reported by Furgiuele (1970). This latter worker detected high plasma levels 4 hours after the initial injection of 10 mg of gentamicin, while we were unable to detect any drug at this time. Data from Case 4 showed gentamicin had a half life ($T_{1/2}$) after subconjunctival administration of 4.2 hours and a total body clearance of 83 ml/min. These figures are comparable to published figures after intramuscular and intravenous injection (Sawchuk et al., 1977) and confirm the reliability of the method we used.

To produce significant ototoxicity gentamicin should reach serum levels of 4 to 5 µg/ml for a period of 7 to 10 days (Mawer et al., 1974). Thus from the results reported in this paper it is clear that gentamicin is a safe antibiotic to use both topically and subconjunctivally. Large subconjunctival doses are unlikely to produce ototoxicity, as the biggest dose of plasma gentamicin we could detect was 0.98 µg/ml after subconjunctival injection of 20 mg.

Conclusion

Gentamicin would be unlikely to produce potentially toxic plasma levels after topical or repeated subconjunctival administration in doses commonly used in ophthalmological practice. This fact is confirmed by the lack of data in the literature connection ototoxicity with ocularly administered gentamicin. Further studies are indicated to determine how systemic absorption of the drug is affected in the acutely inflamed eye.

Rapporteur's comment

This old study appears to confirm that no apparent departures from the known safety profile of ocularly administered gentamicin in children have been observed.

Fransen L, D'Costa L, Ronald AR, Nsanze H, Brunham R, Piot P. Single-dose kanamycin therapy of gonococcal ophthalmia neonatorum. Lancet, December 1, 1984:1234-1236.

Summary

117 infants with gonococcal ophthalmia neonatorum, including 27 with infections due to penicillinase-producing *Neisseria gonorrhoeae*, were treated as outpatients with five different regimens of single dose intramuscular kanamycin (75 mg or 150 mg) with saline eye washes, gentamicin eye ointment, or chloramphenicol eye drops. There were no treatment failures among 68 patients treated with 75 mg or 150 mg kanamycin and gentamicin eye ointment (for 3 days). However, the minimum and maximum cumulative probabilities of cure of single-dose kanamycin with saline eye washes (for 3 days) were only 60% and 89%. 1 patient of 15 treated with 150 mg kanamycin plus chloramphenicol eye drops did not respond to treatment. Postgonococcal conjunctivitis developed in 14 (12%) infants, of whom 13 had positive cultures for *Chlamydia trachomatis*. Nasopharyngeal infection with *N. gonorrhoeae* was eradicated in 9 of 11 infants colonised.

Patients and Methods

The eyes of all infants with neonatal conjunctivitis seen in 1983 at the Nairobi Special Treatment Clinic were examined by one clinician, and the severity of conjunctivitis was scored by Sandstrom's method on the more inflamed eye. An ophthalmia neonatorum case was defined as an infant younger than 30 days with abnormal ocular discharge from one or both eyes, and with at least one polymorphonuclear leucocyte per oil immersion field (1000 x) on a gram-stained smear of the discharge. Conjunctival swabs were cultured for *N. gonorrhoeae* on modified Thayer-Martin agar, for *Chlamydia trachomatis* on cycloheximide-treated McCoy cells, for herpes simplex virus on fibroblast cells, and for facultative bacteria on blood agar. Additional specimens were obtained from the oropharynx and rectum for *N. gonorrhoeae* and *C. trachomatis* culture. All mothers and 74 fathers underwent genital and ocular examination, and cervical and urethral swabs were collected for *N. gonorrhoeae* and *C. trachomatis* culture. Three treatment trials were conducted sequentially. In the first trial, 53 infants with gram-negative diplococci on a conjunctival smear were assigned randomly to a single intramuscular dose of 75 mg kanamycin combined with topical gentamicin eye ointment (1%) half-hourly for the first 10 h and then four times daily for 3 days (regimen A), or to a single 75 mg dose of kanamycin with saline eye washes applied in the same way and for the same time as the gentamicin ointment (regimen B). In a second study, 38 infants with gonococcal conjunctivitis were randomly assigned to a single intramuscular dose of 150 mg kanamycin in combination with gentamicin

eye ointment for 3 days (regimen C) or saline eye washes for 3 days (regimen D). In the third study, 26 patients with gonococcal conjunctivitis were treated with a single intramuscular dose of 150 mg kanamycin in combination with either topical gentamicin ointment (regimen C) or chloramphenicol eye drops (regimen E), administered in the way described above. Topical treatment was administered by the mothers, who were instructed by a nurse.

The infants and their mothers returned for follow-up examination 3, 7, and 30 days after the initial visit. At each follow-up visit the baby's eyes were assessed by the same criteria as at the initial visit, and the mother was given a gynaecological examination. All cultures were repeated in infants and mothers at least at days 3 and 30.

Minimum inhibitory concentrations of kanamycin, penicillin, gentamicin, chloramphenicol, and tetracycline were examined on 52 conjunctival *N. gonorrhoeae* isolates by an agar-dilution method on Mueller-Hinton agar base supplemented with 1% 'IsoVitaleX' (Baltimore Biological Laboratories, Cockeysville) and 5% lysed horse blood (Gibco Ltd, Paisley). The cumulative probability of cure (CPC) was calculated after 3 and 30 days, as the number of cases cured divided by the number of cases treated. Since the treatment outcome is not known for patients lost to follow-up, two CPCs were calculated for each treatment group; CPC max assumes that all defaulters were cured and CPC min assumes that all defaulters represent treatment failures. The statistical significance of differences in CPC between treatment regimens was tested by Fisher's exact test and by calculating the Taylor series confidence intervals or the ratio of the CPCs of the different treatment regimens. Sample means and sample proportions were compared by chi-square or Fisher's exact test and Student's *t* test.

TABLE I—FEATURES OF 117 INFANTS

	Treatment group				
	A	B	C	D	E
n	38	15	30	19	15
Age (days)	12.3±5.8	13.3±7.5	9.5±4.2	11.3±5.9	9.9±5.1
Duration of illness (days)	7.5±1.2	7.4±0.9	7.6±6.6	5.9±4.4	5.6±2.5
Birthweight (kg)	3.4±1.9	3.0±0.4	2.9±0.5	3.4±0.9	2.9±0.5
Conjunctivitis score	6.2±1.4	6.2±0.9	5.8±1.5	5.8±0.7	5.8±1.1
No with <i>N gonorrhoeae</i> isolated from pharynx	3	2	2	3	1
No (%) of PPNG strains	10 (26)	3 (20)	6 (20)	4 (21)	4 (27)

Results

The different treatment groups were comparable with regard to age, severity of conjunctivitis, duration of illness, birthweight, and the proportion of infections caused by PPNG strains (table I). The results of treatment with the different regimens are shown in table II. There were no bacteriological failures at day 3 or day 30 in the groups of infants who received 75 or 150 mg single-dose kanamycin in combination with gentamicin eye ointment (A and C). The CPC max (defaulters considered healed) and CPC min (defaulters considered treatment failures) of regimens A and C at 30 days were between 86 - 6% and 100%. In 8 patients in treatment groups (A and C) postgonococcal conjunctivitis had developed by 3 days after initiation of therapy with kanamycin-gentamicin. *C. trachomatis* was isolated in all cases at the initial visit and at the first follow-up visit.

TABLE II—RESULTS OF TREATMENT AT DAYS 3 AND 30

—	Day 3			Day 30		
	No evaluated	<i>N gonorrhoeae</i> isolated from eye	Mean CS	No evaluated	<i>N gonorrhoeae</i> isolated from eye	Mean CS
A	33	0	1·1	29	0	0·4
B	13	2	0·6	9	1	0·2
C	29	0	1·3	23	0	0·5
D	19	1	0·7	14	0	0·5
E	13	1	1·0	12	0	0·2

Infants from whom *N gonorrhoeae* was reisolated or with a concomitant chlamydia infection are not included in the conjunctivitis score of the patients seen at the next follow-up visit.

CS=conjunctivitis score.

Among the 15 infants treated with 75 mg kanamycin and saline eye washes (group B), 2 had persistent gonococcal conjunctivitis at day 3, and there were 2 bacteriological and clinical relapses at 10 days and at 30 days. In 1 of the babies with a persistent infection, pneumonia, sepsis, and a bilateral corneal ulcer developed. The CPC max and CPC min at 30 days for regimen B were 73% and 60%, respectively—significantly lower than those of regimen A ($p=0\cdot03$ for CPC min). Among the 19 infants given kanamycin 150 mg and saline eye washes (group D), 1 had a persistent gonococcal conjunctivitis at day 3, and 1 relapsed clinically and bacteriologically at day 7. The CPC max and CPC min of this regimen were both 89·5% (not significantly different from those of regimen C). None of the *N. gonorrhoeae* strains isolated from treatment failures produced penicillinase.

In 2 group-D infants cured of conjunctivitis *N. gonorrhoeae* was isolated from the oropharynx, but not from the eye, 3 days after therapy. Chlamydial postgonococcal ophthalmia neonatorum developed in all 5 infants who had had a positive *C. trachomatis* culture before treatment.

There was 1 persistent gonococcal infection at 3 days among the 15 patients treated with kanamycin 150 mg and chloramphenicol eye drops (group E), giving CPC max and

CPC min at 30 days of 93% and 80%. Postgonococcal conjunctivitis developed in 1 infant at day 3.

The 7 patients who were not cured on any treatment regimen did not differ significantly from successfully treated cases in age, body weight, duration of symptoms, presence of cough or diarrhoea, and severity score at the initial visit. 2 of the 7 had *N. gonorrhoeae* isolated from the oropharynx, compared with 9 of 107 patients who responded successfully to treatment (not significant). Infants who were not cured with the kanamycin-saline regimens were cured when given kanamycin 150 mg combined with gentamicin, including the infants with *N. gonorrhoeae* isolated from the pharynx.

The in-vitro susceptibility of 52 gonococcal strains isolated from the eyes is shown in table III. Penicillinase production was detected in 23% of strains, while 9·3% of the penicillinase-negative isolates had a minimum inhibitory concentration of penicillin of 2 mg/1 or more. All strains were

moderately sensitive to kanamycin and gentamicin. Over half of the isolates had a minimum inhibitory concentration of tetracycline of 2-4 mg/1.

TABLE III--IN-VITRO SUSCEPTIBILITY OF 52 NEISSERIA GONORRHOEAE STRAINS ISOLATED FROM EYES OF INFANTS WITH OPHTHALMIA NEONATORUM

	Minimum inhibitory concentration (mg/l)		
	Range	50	90
Chloramphenicol	0.25 - 2	1	2
Gentamicin	2 - 4	4	4
Kanamycin	8 - 16	16	16
Penicillin	0.015 - 8	0.5	8
Tetracycline	0.25 - 4	2	4

Discussion

This study shows that a single dose of 75 or 150 mg kanamycin in association with 1% gentamicin eye ointment for 3 days is an effective treatment for ophthalmia neonatorum due to penicillin-sensitive and penicillinaseproducing *N. gonorrhoeae*.

In our study, topical gentamicin eye ointment increased the cure rate of single-dose kanamycin, compared with the same dose of kanamycin given with saline eye washes only. The need for topical antibiotic treatment in ophthalmia neonatorum is controversial.15,17,18 Topical therapy with penicillin was originally thought to be adequate. However, antibiotic eye drops temporarily alleviate the signs of ophthalmia without eradicating the infection.

A single parenteral dose of 75 mg kanamycin without topical antibiotics had an unacceptable failure rate in this study. Expected peak serum levels of kanamycin after a single intramuscular injection of 75 mg or 150 mg of the drug are 90-150 µg/ml in term infants for 4-7 h, and drug levels at the conjunctiva and cornea are unknown. Thus, the 75-150 mg dose we used may be under the minimum dose required to cure infections with *N. gonorrhoeae* strains with a minimum inhibitory concentration of kanamycin of 8-16 mg/1, which may explain why systemic therapy combined with topical antibiotic treatment yielded a better cure rate.

Rapporteur's comment

This old study appears to confirm that no apparent departures from the known safety profile of ocularly administered gentamicin in infants have been observed.

Kos, M., Jazwinska-Tarnawska, E., Hurkacz, M., Orzechowska-Juzwenko, K., Pilecki, W., Klempous, J. (2003) The influence of locally implanted high doses of gentamicin on hearing and renal function of newborns treated for acute hematogenous osteomyelitis. *International Journal of Clinical Pharmacology and Therapeutics*, 41 (7), str. 281-286

Abstract

Osteomyelitis and arthritis still present a serious diagnostic and therapeutic problem. Difficulties arise in particular in the treatment of acute hematogenous osteomyelitis (AHO) in newborns where mega-doses of gentamicin are administered locally for about 3 weeks. Gentamicin possesses strong oto- and nephrotoxicity and the occurrence of these adverse effects depends on the duration of treatment and the serum drug concentration.

Objective:

Aim of the study was to evaluate the influence of local gentamicin application on auditory and kidney functions.

Material and methods:

Twenty newborns (14 boys and 6 girls) with AHO were treated by local implantation of miniseptopon or gentamicin sponge. Serum urea, creatinine, antibiotic concentrations and NAG activity/g creatinine ratio in urine were estimated before and 1, 4, 8, 16 days after the operation and compared to values in the control group. Brainstem-evoked auditory potentials (BAEP) were examined before, during the first 3 weeks, and 6 - 11 months after gentamicin implantation.

Results:

Mean gentamicin serum concentrations were: 0.67 ± 0.98 mg/l on the 1st day, 0.16 ± 0.37 mg/l on the 4th day, 0.03 ± 0.09 mg/l on the 8th day, 0.01 ± 0.03 mg/l on the 16th day after operation and did not exceed the upper limit therapeutic range. N-acetyl- β -D-glucosaminidase (NAG)/g creatinine in urine ratios were satisfactory: 77.91 ± 36.22 UI/g before the operation, 146.51 ± 82.27 UI/g on the 4th, 162 ± 111 UI/g on the 8th, 168 ± 59.83 UI/g on the 16th day after operation and were statistically significantly ($p < 0.05$) higher than values in the control group. Serum urea and creatinine levels were in the normal range in all groups. Initial BAEP were well in the normal range in 15 of 16 children before treatment and in 14 of 16 children after treatment.

Conclusions:

Locally applied gentamicin as miniseptopon or sponge in newborns produces gentamicin concentrations close to the minimal therapeutic serum concentration which are present over a prolonged period. The raised NAG values in urine and normal serum urea and creatinine levels during treatment with gentamicin without concomitant clinical symptoms of renal failure suggest subclinical destruction of the renal tubules. Lack of change in BAEPs shows that there is no impairment of auditory function.

Rapporteur's comment

This study appears to confirm that no apparent departures from the known safety profile of locally applied gentamicin sponge in treatment of acute haematogenous osteomyelitis in newborns have been observed. However, it should be noted that after local gentamicin application the urine NAG/g creatinine ratio increases, indicating that renal proximal tubular damage. Further studies of the influence of local gentamicin therapy on renal function in neonates with acute haematogenous osteomyelitis should be conducted, as they may enable the dose of gentamicin therapy to be individualised, thereby improving the safety and efficacy of the therapy.

Schafer et al, Is the Primary Suture Indicated in Infected Wounds in Pediatric Surgery, Langenbecks Arch Chir Supp II. Congress Report, 1997

Summary. Since 1994, 25 children have been treated for abscesses of the soft tissue. After the incision, a complete debridement was done, followed by an implantation of a collagen sponge containing gentamicin and primary wound closure. Only two relapses were seen, which had to be re-opened.

Material and Method

Since 1994, 25 children and infants with abscess-forming infections have been treated with primary sutures. After thorough wound debridement and lavage, the gentamicin-collagen-sponge was implanted and subsequently sutured. In the case of large wound cavities, an overflow drainage was implanted for five days.

Results

Among the 25 children, there were 11 abscesses mainly in the head and neck region, two Tenckhoff catheter-related tunnel infections, two infected neck fistulas, three infected and persisting urachal fistula, two third-degree, infected soft tissue injuries, and five cases of osteitis (Fig. 1). The average age was 4.5 years. A pathogen was shown in 52% of the cases of which 32% were Staph. Aureus (Fig. 2). A pre-operative antibiotics already existed in 60% of the cases which was only continued in 20% as a post-operative i.v. antibiotics. In each case, a pre operative antibiotics with a second generation cephalosporin was performed. In two children, the wound had to be opened, through premature suture removal, and regularly flushed. In both cases the subsequent secondary healing of the wound was without complication. In 92% of the cases there was primary wound healing. Average inpatient care duration was 6 days. A second population of 52 patients from the same time period had conventional, open, surgical treatment and were hospitalized for 10 days. In two other children, recidivist intervention had to be undertaken because an atypical mycobacteriosis with accompanying specific lymphadenitis colli was present.

Discussion

To this day, the principle of “ubi pus, ibi evacua” has proven itself. The treatment suggested here does not question this guideline but rather seeks to modify it. Unrestricted perfusion conditions in pediatric systems with rapid wound healing are a precondition for this change in treatment. This was supported through experience in septic abdominal pediatric surgery such as e.g. in the case of appendicitis perforata and its low wound infections. Studies and case reports with local antibiotics by means of gentamicin in the presence of osteitis, in the presence of hand infections, in the face, and in the case of infected wounds describe primary closure as a treatment possibility. Here we used both septopal chains and a bio-reabsorbable gentamicin-collagen sponge. The target of the prospective examination was to develop a treatment appropriate for children with limited postoperative pain. This was generated through manipulations such as removing the tamponades, changing them, and regularly flushing them with iodine-containing antiseptics. A bio-reabsorbable gentamicin-collagen-sponge was implanted as an adjuvant treatment measure. Here, a painful removal is no longer required and a defined local antibiotics exists in relation to active substance concentration and duration when compared to the septopal chain. The very good results of the treatment presented, as well as the simple change in strategy to conventional treatment through premature suture removal when this treatment fails, should be an impetus to reconsider septic soft tissue surgery during childhood years. Systemic antibiotics treatment is only required in exceptional cases where the patients have clear immune deficiencies or where distinctive, phlegmonous infection is present.

Perioperatively, prophylactic antibiotic treatment should be undertaken with a wide spectrum antibiotic that is effective against staphylococci.

Number N

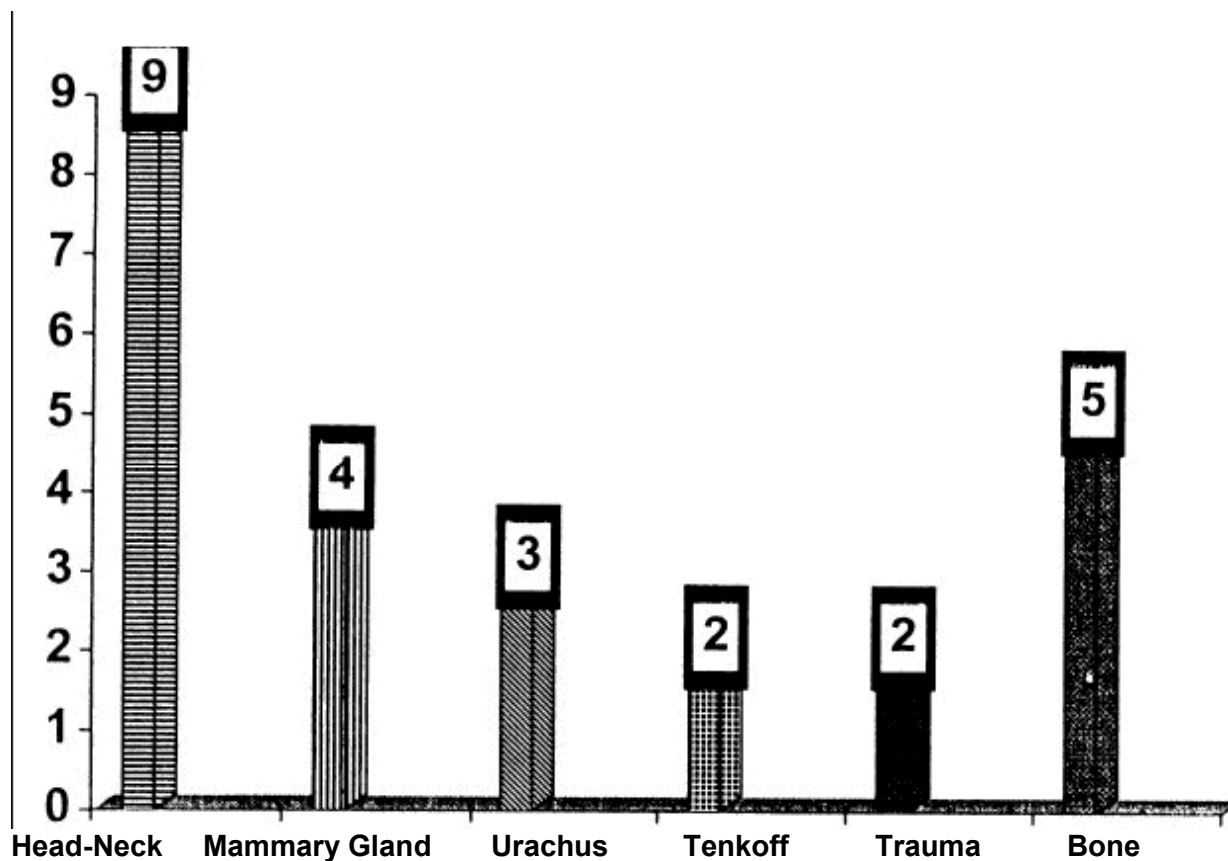


Fig. 1. Abscess localization in 25 children

Number N

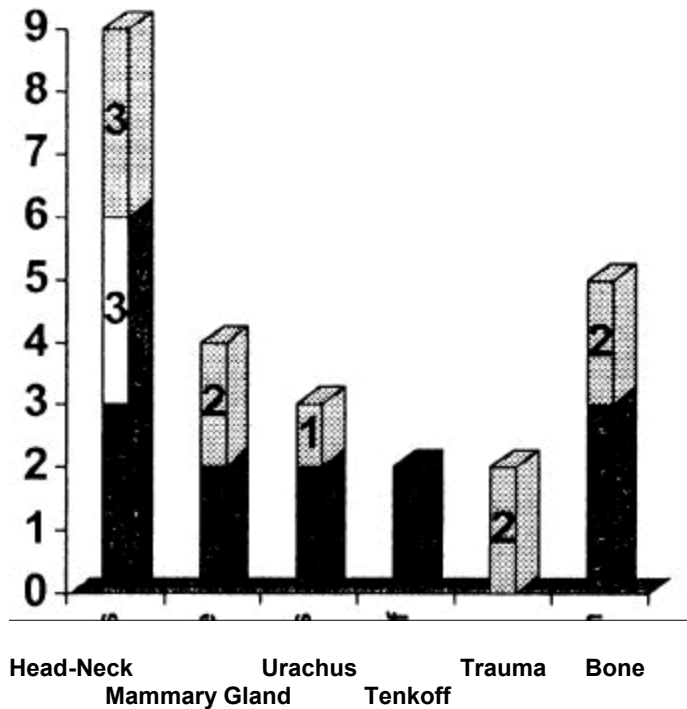


Fig. 2. Bacterial Spectrum in 25 Children

Conclusion

After substantial wound debridement and adjuvant implantation of a gentamicin-collagen sponge, primary wound closing is advantageous in the case of soft tissue infections during childhood years for the following reasons:

1. No post-operative traumatizing follow-up treatment is required.
2. The cosmetic result is significantly better.
3. There is no risk of suppression of the thyroid gland through antiseptics containing iodine.
4. The hospital stay is shortened.

Rapporteur's comment

This report appears to confirm that no apparent departures from the known safety profile of implantation of gentamicin-collagen sponge in treatment of abscesses of soft tissue after debridement in children and infants have been observed.

A summary of the following studies follows:

Clinical Comparison of Efficacy and Tolerability. Chemotherapy 1988; 34: 158-163
Kienitz M. Gentamicin in the treatment of acute and chronic pyelonephritis in children. Med Klinik 1970; 65 (12): 552-557

Skopnik H. Pharmacokinetic and antibacterial activity of daily gentamicin. Archives Dis Childhood 1992; 67: 57-61

Lohr JA. Comparison of three topical antimicrobials for acute bacterial conjunctivitis. Pediatr Infect Dis J 1988; 7: 626-629.

Verma M. Neonatal conjunctivitis: a profile. Indian Pediatrics 1994; 31: 1357

Heimann G. Renal toxicity of aminoglycosides in the neonatal period.. Pediatr Pharmacol 1983; 3: 251-257.

Elhanan K. Gentamicin once-daily versus thrice-daily in children. J Antimicrob Chemother 1995; 35: 327-332.

Nahata MC. Lack of nephrotoxicity in pediatric patients receiving concurrent vancomycin and aminoglycoside therapy. Chemotherapy 1987; 33: 302-304.

Skopnik H. Once daily aminoglycoside dosing in full term neonates. Pediatr Infect Dis J 1995; 14: 71-72.

Table 1: Use of gentamicin in children

Author	N° of children	Indication	Duration	Dosage	Design	Target parameters	Results
Not yet submitted							
Wiese	49, gentamicin and azlocillin (25) vs ceftriaxone and gentamicin (24)	Neonatal sepsis	5-7 days	3-5mg/d	randomized	Sepsis score; Total duration of necessary treatment	Similar efficacy in both groups
Kienitz	24	Acute and chronic pyelonephritis	10-12 days	1.2mg /kg	open	Elimination of bacteriuria	Good clinical efficacy, no safety problems
Skopnik	20, od (10) vs bid (10)	Pharmacokinetic	4 days	4mg/kg/d	Randomized, prospective	Pharmacokinetic parameters bactericidal activity	No differences in bactericidal activity

Already submitted							
Lohr	337 < 21 yrs, refobacin (110) vs TP (117) vs SS (110)	Bacterial conjunctivitis	Up to 10 days	1 drop/ every 3 hrs /eye/day	Controlled	Cure rate improvement rate	Similar results in all groups
Verma		Neonatal conjunctivitis	Review article				
Heimann	<81	Septicemia	Varying	5mg/kg/ daily + penicillin	Controlled	AAP excretion rate	Lower renal accumulation in newborns
Elhanan	50, od (26) vs tid (24)	Pharmacokinetic trial	5-10 days	4.5 mg/kg/d	Open randomized	Clinical cure serum levels	Similar outcome
Nahata	90 plus vancomycin	Nephrotoxicity	3-38 days	2.514mg/kg	Retrospective	Clinical status urine analysis	No evidence of renal toxicity
Skopnik	302, gentami-cin or tobramycin od (C79) vs bid (223)	Pharmacokinetic	3-5 days	2-2.5mg /kg bid; 3.5-4mg /kg od	Prospective	Pharmacokinetic parameters	Better PK profile under once daily administration

Rapporteur's comment

Main indications for the use of gentamicin in children were severe infections and sepsis for the parenteral use and conjunctivitis for the topical use. In these indications, gentamicin was shown to be effective and well tolerated, particularly concerning nephro- and ototoxicity.

Trevor Duke, Harry Poka, Frank Dale, Audrey Michael, Joyce Mgone, Tilda Wal
Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe
pneumonia in children in Papua New Guinea: a randomised trial. The Lancet vol 359
February 9,2002

Summary

Background

Pneumonia is the most frequent cause of child mortality in less developed countries. We aimed to establish whether the combination of benzylpenicillin and gentamicin or chloramphenicol would be better as first-line treatment in children with severe pneumonia in Papua New Guinea.

Methods

We did an open randomised trial in which we enrolled children aged 1 month to 5 years of age who fulfilled the WHO criteria for very severe pneumonia and who presented to hospitals in two provinces. Children were randomly assigned to receive chloramphenicol (25 mg/kg 6 hourly) or benzylpenicillin (50 mg/kg 6 hourly) plus gentamicin (7.5 mg/kg daily) by intramuscular injection. The primary outcome measure was a good or an adverse outcome.

Findings

1116 children were enrolled; 559 children were treated with chloramphenicol and 557 with benzylpenicillin and gentamicin. At presentation the median haemoglobin oxygen saturation was 71% (IQR 57-77) for those allocated chloramphenicol and 69% (55-77) for those allocated penicillin and gentamicin. 147 (26%) children treated with chloramphenicol and 123 (22%) treated with penicillin and gentamicin had adverse outcomes ($p=0.03$). 36 children treated with chloramphenicol and 29 treated with penicillin and gentamicin died. More children treated with chloramphenicol than penicillin and gentamicin represented with severe pneumonia within 1 month of hospital discharge ($p=0.03$).

Interpretation

For children with severe pneumonia in less developed countries the probability of a good outcome is similar if treated with chloramphenicol or with the combination of benzylpenicillin and gentamicin.

Rapporteur's comment

This study offers a comparison to systemic administration of chloramphenicol which is generally considered an outdated therapy, at least in the European context. The study is thus deemed not suitable for the requirements of the article 45 procedure.

III. RAPPORTEUR'S PRELIMINARY OVERALL CONCLUSION AND RECOMMENDATION

➤ Preliminary overall conclusion

Overall, no new clinically relevant efficacy data that would warrant an SPC change were provided in the studies submitted.

Most publications are old (only 5 studies relevant to the article 45 procedure were published after 2000). One of these studies referred to a comparison to an outdated systemic administration of chloramphenicol.

No apparent departures from the known safety profile of gentamicin were observed in the studies provided.

Overall, no SPC changes are deemed necessary on the basis of the studies provided in response to article 45 of the Paediatric Regulation.

However, the precise wording of all European national SPCs was not provided by the MAHs and it is unclear whether there are specific recommendations for dosage in paediatric patients in all European countries where gentamicin is approved. Furthermore, according to the CMD(h) best practice guide on article 45-Paediatric regulation (September 2008), *“the aim of Article 45 procedure is to make the information on the use of medicines in the paediatric population available for all healthcare professionals and patients (or parents). After finalisation of the assessment of the data recommendations for the text to be included in the SmPC and PL will be published on the CMD(h) website. This information should be included in all SmPC's/PLs of products with the same active substance and pharmaceutical form within 90 days of publication of Public assessment report.”*

This particularly applies to the ODD (once daily dosing) regimen as distinct to the traditional multiple daily dosing regimen. In case of any divergence of dosage recommendations in European national SPCs, the MAHs are requested to review the available studies and all other available information which should form a basis for a proposed harmonised SPC text regarding paediatric dosage recommendation in each of the indications for both systemic and local administration.

➤ Recommendation

Not fulfilled:

Based on the data submitted, the MAHs should provide additional data in support of a harmonised text concerning paediatric patients, as part of this procedure P45 DE/W/003/pdWS/001 (see section VI “Additional clarifications requested by the Rapporteur and MSs”).

IV. ADDITIONAL CLARIFICATIONS REQUESTED BY THE RAPPORTEUR

The MAHs are requested to:

- Provide a list of the current wording (in English) relevant for paediatric patients in the SPCs from all MS in which gentamicin is an approved medical compound (including section 4.1).
- In case of divergences between Member States, the MAHs should provide a proposal for a harmonised SPC text in sections 4.2, 4.4 and 5.2 (if considered applicable) regarding paediatric use. The proposal should be justified by supporting data from the MAHs' databases and relevant published data.

The timetable as proposed by the Rapporteur is as follows:

a 30 day response timetable with clock stop will apply.

V. CHMP MEMBERS' COMMENTS ON THE PRELIMINARY ASSESSMENT REPORT

ES: The Spanish Agency agrees with the rapporteur's overall conclusion and request for supplementary information. In addition, the Spanish Agency has the following comments for you to consider:

Regarding the dosage recommendations for the paediatric population it is agreed that there is a need to harmonize this issue. For the purpose of this harmonization we consider the following relevant:

- Children older than 1 year old: the 24 hour dosing interval may be considered too prolong due to the fast clearance of gentamicin (Duke T. et al. 2002). A 12-hour interval may rather be more adequate in this paediatric subset.

Preterm neonates and neonates: 3.5-4 mg/24 hour regimen would be acceptable for the treatment of severe infections provided that close monitorization of drug levels is performed, giving the high pharmacokinetic variability.

<u>Rapporteur's comment</u>

Comments from ES are recommended for consideration.

HU: The NIP agrees with the overall conclusion of the Rapporteur.

We have additional comments.

Points for clarification:

There are a lot of publications about the ototoxic effect of aminoglycoside ear drops. We think it must be considered.

References:

1. Bath AP, Walsh RM, Bance ML, Rutka JA. Ototoxicity of topical gentamicin preparations. Laryngoscope 109:1088-1093, 1999
2. Hui Y, Park A, Crysedale W, Forte V. Ototoxicity from ototopical aminoglycosides. J. Otolaryngology, #26, 1997, 53-56
3. Lelevier WC. Topical gentamicin-induced positional vertigo. Otolaryngol HNS 1994:110:598-602
4. Longridge NS. Topical gentamicin vestibular toxicity. J Otolaryngol 1994:23:444-445
5. Manolidis S and others. Comparative efficacy of aminoglycoside versus fluoroquinolone topical antibiotic drops. Supplement to Otolaryngology Head and Neck surgery, 2004, 130, S83-
6. Rutka J. How serious a problem is topical aminoglycoside ototoxicity. ENT journal supplement 1, 2006, 19-21.
7. Walby P, Stewart R, Kerr AG. Aminoglycoside ear drop ototoxicity: a topical dilemma ? Clin Otolaryngol 1998:23:289-290
8. Wong DLH, Rutka JA. Do aminoglycoside otic preparations cause ototoxicity in the presence of tympanic membrane perforations ? Oto HNS 116, #3, 404-410, 1997
9. Wright CG, Meyerhof WL. Halama AR. Ototoxicity of neomycin and polymyxin B following middle ear application in the chinchilla and baboon. Am J. Otol 1987;8:495-9.

Rapporteur's comment

Comments from HU are recommended for consideration.

FR: Please be informed that France fully agrees with the rapporteur's conclusions and has no further comments.

NO: The Norwegian Medicines Agency fully endorse the Rappoerteu's day 70 report for the DE/W/003/pdWS/001 Gentamicin Article 45 procedure.

SE: Sweden has no comments.

UK: The UK fully endorses the Rapporteur's recommendations for the above mentioned procedure.

VI. ADDITIONAL CLARIFICATIONS REQUESTED BY THE RAPPORTEUR AND MSS

The MAHs are requested to:

1. Provide a list of the current wording (in English) relevant for paediatric patients in the SPCs from all MS in which gentamicin is an approved medical compound (including section 4.1).
2. In case of divergences between Member States, the MAHs should provide a proposal for a harmonised SPC text in sections 4.2, 4.4 and 5.2 (if considered applicable) regarding paediatric use. The proposal should be justified by supporting data from the MAHs' databases and relevant published data.
3. Consider the following:

Regarding the dosage recommendations for the paediatric population it is agreed that there is a need to harmonize this issue. For the purpose of this harmonization we consider the following relevant:

- Children older than 1 year old: the 24 hour dosing interval may be considered too prolong due to the fast clearance of gentamicin (Duke T. et al. 2002). A 12-hour interval may rather be more adequate in this paediatric subset.

Preterm neonates and neonates: 3.5-4 mg/24 hour regimen would be acceptable for the treatment of severe infections provided that close monitorization of drug levels is performed, giving the high pharmacokinetic variability.

4. Consider the following:

There are a lot of publications about the ototoxic effect of aminoglycoside ear drops. We think it must be considered.

References:

1. Bath AP, Walsh RM, Bance ML, Rutka JA. Ototoxicity of topical gentamicin preparations. *Laryngoscope* 109:1088-1093, 1999
2. Hui Y, Park A, Crysedale W, Forte V. Ototoxicity from ototopical aminoglycosides. *J. Otolaryngology*, #26, 1997, 53-56
3. Lelevier WC. Topical gentamicin-induced positional vertigo. *Otolaryngol HNS* 1994:110:598-602
4. Longridge NS. Topical gentamicin vestibular toxicity. *J Otolaryngol* 1994:23:444-445
5. Manolidis S and others. Comparative efficacy of aminoglycoside versus fluoroquinolone topical antibiotic drops. *Supplement to Otolaryngology Head and Neck surgery*, 2004, 130, S83-

6. Rutka J. How serious a problem is topical aminoglycoside ototoxicity. ENT journal supplement 1, 2006, 19-21.
7. Walby P, Stewart R, Kerr AG. Aminoglycoside ear drop ototoxicity: a topical dilemma ? Clin Otolaryngol 1998;23:289-290
8. Wong DLH, Rutka JA. Do aminoglycoside otic preparations cause ototoxicity in the presence of tympanic membrane perforations ? Oto HNS 116, #3, 404-410, 1997
9. Wright CG, Meyerhof WL. Halama AR. Ototoxicity of neomycin and polymyxin B following middle ear application in the chinchilla and baboon. Am J. Otol 1987;8:495-9.

VII. MAHS'S RESPONSES

Alcon Laboratories, Inc.

The MAH submitted a list of current wording of sections 4.1, 4.3, 4.4, and 5.2 of the SPCs for its eye drop or eye/ear drop products containing gentamicin as marketed in Belgium, Portugal, and Spain.

Rapporteur's comment

None of the wording can be considered specifically applicable to paediatric patients.

The MAH also submitted a proposal for a harmonised SPC text in sections 4.1, 4.2, 4.4 and 5.2 and provided references:

GENTAMICIN EYE DROPS/EYE OINTMENT

SPC Section	Proposed Text
4.1	<p>Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 – 16 years)</p> <p><i>Indication as per current national approval</i></p> <p>Add in statement: Consideration should be given to official guidance on the appropriate use of antibacterial agents.</p>

SPC Section	Proposed Text
4.2	<p>Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 – 16 years)</p> <p><i>Posology as per national approval.</i></p>
4.3	Hypersensitivity to the active substance or to any of the excipients.
4.4	<p>As with all antibacterial preparations prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.</p> <p>Sensitivity to topically administered aminoglycosides may occur in some patients. If hypersensitivity develops during use of this medicine, treatment should be discontinued and other medications should be used. (1, 2)</p> <p>Cross-hypersensitivity with other aminoglycosides can occur, and the possibility that patients who become sensitized to topical ocular gentamicin may also be sensitive to other topical and/or systemic aminoglycosides should be considered. (2,3)</p> <p>Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic gentamicin therapy. Although these effects have not been reported following topical ocular use of gentamicin, caution is advised when used concomitantly with systemic aminoglycosides. (2,3)</p>
5.2	Oral doses of gentamicin administered up to 5mg/kg in adults and 2.5 mg/kg in infants and children up to 2 years of age are safe and well-tolerated. In comparison, ophthalmic gentamicin is equivalent to a maximum of 0.08 mg/kg/day in a 50 kg patient (Note this is maximum ocular dosage, the appropriate comparative value will be provided per SPC dependent upon quantity of gentamycin present in product)

GENTAMICIN EAR DROPS

SPC Section	Proposed Text
4.1	<p><i>Indication as per current national approval</i></p> <p>Add in statement: Consideration should be given to official guidance on the appropriate use of antibacterial agents.</p>

SPC Section	Proposed Text
4.2	<p><u>Use in adults including the elderly</u> <i>Posology as per national approval.</i></p> <p><u>Paediatric patients</u> This medicinal product is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.</p>
4.3	<p>Hypersensitivity to the active substance or to any of the excipients. Perforation of the ear drum</p>
4.4	<p><u>Otic use:</u> The condition of the ear drum must always be checked before this medicinal product is prescribed. Irreversible toxic effects may result from direct contact of the gentamicin with the middle and inner ear. This medicinal product must not be used if the integrity of the ear drum cannot be guaranteed.</p> <p>As with other antibiotic preparations, prolonged use may result in overgrowth of non-susceptible organisms.</p> <p>Sensitivity to topically administered aminoglycosides may occur in some patients. If hypersensitivity develops during use of this medicine, treatment should be discontinued and other medications should be used. (1,2)</p> <p>Cross-hypersensitivity with other aminoglycosides can occur, and the possibility that patients who become sensitized to topical otic gentamicin may also be sensitive to other topical and/or systemic aminoglycosides should be considered. (2,3)</p> <p>Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic gentamicin therapy. Although these effects have not been reported following topical otic use of gentamicin, caution is advised when used concomitantly with systemic aminoglycosides. (2,3,4)</p>
5.2	<p>Oral doses of gentamicin administered up to 5 mg/kg in adults and 2.5 mg/kg in infants and children up to 2 years of age are safe and well-tolerated</p>

Footnote, please note the references are included for purposes of this response only and will not be included in the SPC

References:

1. Bartlett JD, editor. Ophthalmic Drug Facts. 20th ed. St. Louis, Missouri: Wolters Kluwer Health, Inc.; 2009. p. 123-126.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 35th ed. London: Pharmaceutical Press; 2007. p. 251-5
3. McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, Inc. 2009. p.65-7
4. Haynes DS. Topical antibiotics: strategies for avoiding ototoxicity. 2004; 83:12-4

Rapporteur's comment

Only the proposal for the wording of section 5.2 can be considered particularly applicable to paediatric patients.

The MAH has also provided the following proposal for the wording of section 4.3 and section 4.4 in response to comments from HU:

Alcon acknowledges that gentamicin is ototoxic. Accordingly, Alcon proposes that Section 4.3 (Contraindications) and 4.4 (Special warnings and precautions for use) of the SmPCs should state the following:

Section 4.3

Otic:

Perforation of the ear drum

Section 4.4

Otic use:

The condition of the ear drum must always be checked before this medicinal product is prescribed.

Irreversible toxic effects may result from direct contact of the gentamicin with the middle and inner ear. This medicinal product must not be used if the integrity of the ear drum cannot be guaranteed.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic gentamicin therapy. Although these effects have not been reported following topical otic use of gentamicin, caution is advised when used concomitantly with systemic aminoglycosides.

Rapporteur's comment

The MAH's proposal for the wording in sections 4.3 and 4.4 is recommended for products for topical otic use, but is not specifically applicable to paediatric patients.

Merck KGaA

Concerning the question of once daily dosing versus twice daily dosing for children older than 1 year, the MAH submitted the following response and provided references:

Refobacin is used for severe infections caused by gentamicin-susceptible pathogens, including infections of the kidneys and urinary tract, genital infections (except gonorrhoea), hospital-acquired pneumonia, endocarditis, intraabdominal infections, hospital-acquired sepsis, meningitis from gram-negative pathogens, osteomyelitis and suppurative arthritis, and infections or imminent infection in immunosuppressed patients.

High peak serum concentrations or concentrations that significantly exceed the MIC of the isolated relevant pathogens (4-8 x MIC) correlated with a significantly better clinical outcome (*Binder et al 1998, Moore et al 1984, Moore et al 1987*).

Interestingly, gentamicin continues to suppress bacterial growth even after antibiotic concentrations have fallen below the MIC for the pathogens (*Darmstadt et al 2009*). As this “post-antibiotic effect” is concentration-dependent, a prolonged effect is assumed for higher peak concentrations with once daily dosing (*Bass al 1999*).

These insights and indications of reduced toxicity prompted changes in dosage guidelines in recent years, i.e., prolongation of the dosing interval to the point of once daily dosing (e.g. *Bates and Nahata 1994, Blaser 1996, Darmstadt 2008, Gilbert 1997, Hof and Lode 1995*).

A meta-analysis (*Blaser 1996*) of 24 randomized clinical trials involving a total of 3181 patients evaluated the efficacy and safety of gentamicin, amikacin or netilmicin once daily compared to conventional dosing. This meta-analysis disclosed significant advantages in favour of once-daily dosing compared with multiple daily dosing both as regards clinical efficacy (89% versus 84.7%, $p < 0.001$) and bacteriological efficacy (88.6% versus 83.4%), $p < 0.01$. Also the safety was better under once daily dosing with nephrotoxicity to have occurred in 4.5% of patients who had received the aminoglycosides once daily, as compared with 5.5% for conventional dosing.

Other meta-analyses (e.g. *Ali and Goetz 1997, Bailey et al 1997, Hatala et al 1996*) confirm these results.

Studies on clinical efficacy of once-daily dosing as compared with multiple daily doses have also been performed in the pediatric population. Elhanan and Siplovich Raz (*1995*) treated 26 children with gram-negative bacterial infections with 4.5 mg/kg of body weight of gentamicin once daily; another 24 children received the same dose divided into three portions. Ampicillin or metronidazole were authorized co-medications in children with suspected gram-positive pathogens or anaerobes. Once-daily dosing achieved clinical recovery in 23 (88.8 %) of the children. The recovery rate in the group receiving gentamicin in divided doses was 91%. Bacteriological response (eradication) was achieved in all 10 evaluable children (100%) after once-daily dosing and in 12/13 children (92%) in the control group.

Bass et al (*1998*) conducted a prospective, controlled, randomized trial in 50 paediatric patients (age between 6 months and 18 years) that required gentamicin for the treatment of severe infections. They did not monitor only clinical efficacy and safety, but evaluated pharmacokinetic parameters of gentamicin (peak, 4-hour, 8-hour and trough levels) as well. 33 children were treated once daily and 17 children three times daily. 24-hour dosing resulted in higher peak levels compared to 8-hour dosing (20.4 ± 4.4 versus 7.2 ± 6.2 mg/l, $p < 0.0001$) and lower trough levels (0.29 ± 0.02 versus 0.69 ± 0.13 , $p < 0.0001$). The rate of elimination constant and the distribution volume did not differ significantly.

The authors conclude that once-daily dosing of gentamicin in children is a safe method that provides equivalent pharmacokinetics but enhanced bacterial effects, based on higher peak levels, compared with traditional dosing and avoids toxicity.

Therefore, the MAH proposes to keep the recommendation of once daily dosing for children older than 1 year.

Rapporteur's comment

The MAH's argumentation for a once-daily dosing of gentamicin in children is well-supported by the literature and clinical practice and is recommended for adoption.

Recently published studies(*) evaluating pharmacokinetic parameters of gentamicin in neonates not only support once-daily dosing, but provide good evidence that even longer dosing intervals (48 or 60 hours), with the initial dose of gentamicin being larger, result in therapeutic peak plasma concentrations and acceptable trough concentrations. Furthermore, higher initial doses and a prolonged dose interval should decrease the likelihood of true bacterial resistance and adaptive resistance.

Therefore, it is proposed that neonates should not be administered more than one dose a day (see Rapporteur's overall conclusion concerning section 4.2 of the SPC).

(*) Hoff DS, Wilcox RA, Tollefson LM, Lipnik PG, Commers AR, Liu M.
Pharmacokinetic Outcomes of a Simplified, Weight-Based, Extended-Interval Gentamicin Dosing Protocol in Critically Ill Neonates *Pharmacotherapy*. 2009 Nov;29(11):1297-305

(*) Begg EJ, Vella-Brincat JW, Robertshawe B, McMurtrie MJ, Kirkpatrick CM, Darlow B.
Eight years' experience of an extended-interval dosing protocol for gentamicin in neonates *J. Antimicrob. Chemother.* 2009 63: 1034-1042

(*) Hossain MM, Chowdhury NA, Shirin M, Saha SK, Miller-Bell M, Edwards D, Aranda J, Coffey P, Darmstadt GL
Simplified Dosing of Gentamicin for Treatment of Sepsis in Bangladeshi Neonates *J Health Popul Nutr* 2009 Oct; 27(5):640-645

The MAH submitted a list of current wording of sections 4.1, 4.2, 4.4, and 5.2 of the SPCs for its eye ointment, and eye drops products containing gentamicin as marketed in Austria and Germany.

Annex 1: Overview of specific wording relevant for paediatric patients - ophthalmic drops and ophthalmic ointment

Current approved text for Gentamicin - ophthalmic drops - Austria (Nov-2007) relevant for paediatric patients	Current approved text for Gentamicin - ophthalmic ointment - Austria (Jun-2008) relevant for paediatric patients	Current approved text for Gentamicin - ophthalmic drops and ophthalmic ointment - Germany (May-2008) relevant for paediatric patients	MAH comments
4. CLINICAL PARTICULARS	4. CLINICAL PARTICULARS	4. CLINICAL PARTICULARS	
4.1 Therapeutic indications	4.1 Therapeutic indications	4.1 Therapeutic indications	This section contains no specific relevant information on paediatric patients
4.2 Posology and method of administration	4.2 Posology and method of administration	4.2 Posology and method of administration	This section contains no specific relevant information on paediatric patients
4.4 Special warnings and precautions for use	4.4 Special warnings and precautions for use	4.4 Special warnings and precautions for use	This section contains no specific relevant information on paediatric patients
5.2 Pharmacokinetic properties	5.2 Pharmacokinetic properties	5.2 Pharmacokinetic properties	This section contains no specific relevant information on paediatric patients

Rapporteur's comment

The wording of the sections of the SPC for eye drops and eye ointment contains no specific relevant information on paediatric patients.

The MAH also submitted a list of current wording of sections 4.1, 4.2, 4.4, and 5.2 of the SPCs for its solution for injection products containing gentamicin as marketed in Austria and Germany.

Annex 2: Overview of specific wording relevant for paediatric patients - solution for injection

Current approved text for Gentamicin - solution for injection - Austria (Oct-2007) relevant for paediatric patients	Current approved text for Gentamicin - solution for injection - Germany (Jul-2008) relevant for paediatric patients	MAH comments
4. CLINICAL PARTICULARS	4. <u>Clinical particulars</u>	
4.1 Therapeutic indications	4.1 <u>Therapeutic indications</u>	This section contains no specific relevant information on paediatric patients
4.2 Posology and method of administration	4.2 <u>Posology and method of administration</u>	Section 4.2 will be amended with information on paediatric patients. For a new text proposal refer to Annex 3 .
	<p>The initial dose recommended, independent of renal function, is 1.5-2.0 mg/kg body weight. Adults, children and adolescents with normal renal function receive as a maintenance dose 3-6 mg/kg/day and infants after the first month of life 4.5-7.5 mg/kg/day. Due to the longer half-life, newborn infants are given the required daily doses (4-7 mg/kg) always as 1 up to 2 single doses.</p>	

Adults and adolescents:

- Uncomplicated infections with sensitive germs:
2 mg/kg body weight/ day in 2 (or 3) single doses.

In intermediate germs or when clinical improvement is too slow, the daily dose is increased to 3 mg/kg body weight.

- Severe infections:
Up to 5 mg/kg body weight, split into 3-4 single doses.

- Septic infections:
Maximum daily dosage (see table) as short infusion, split into 1-2 administrations/day.

Children:

Dosage in children corresponds to adult dosage, stated as daily dosage in mg/kg body weight. Newborn babies and infants up to 3 weeks are administered the daily dose in 2 single doses.

Blood sampling:

Monitoring of serum concentration of aminoglycosides is recommended in all patients, especially elderly, newborns and patients with impaired renal function to adjust dosage. Blood samples are taken at the end of a dosing interval (trough level) and directly after conclusion of the infusion (peak level). Excessive peak levels (>10-12 µg/ml) and trough levels (>2 µg/ml) should be avoided.

4.4 Special warnings and precautions for use

4.4 Special warnings and precautions for use

Section 4.4 will be amended with information on paediatric patients. For a new text proposal refer to [Annex 3](#).

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended. In patients with instable renal function and in patients with irregular distribution volume (e.g. patients receiving large infusion volumes, newborns and infants) gentamicin levels must be monitored.

5.2 Pharmacokinetic properties

5.2 Pharmacokinetic properties

Section 5.2 will be amended with information on paediatric patients. For a new text proposal refer to [Annex 3](#).

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In newborn infants the distribution volume is greater and decreases from 3rd month on with increasing age.

Distribution

The distribution volume of gentamicin, at 0.25 l/kg, is about equivalent to the volume of extracellular water. In neonates the distribution volume is 60% of the body weight and decreases with increasing age.

Metabolization and elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half-life is about 120 minutes. In newborn infants (especially neonates) and infants the serum half-life is prolonged due to immature renal function. Recovery in urine is 70-90% within 24 hours.

Elimination

Gentamicin is not metabolised in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys by glomerular filtration. In patients with normal renal function the elimination half-life is about 2-3 hours. In newborn infants up to the 3rd week of life the serum half-life is prolonged by about 1/3 due to immature renal function.

The MAH submitted the following proposal for a harmonised SPC text in sections 4.2, 4.4 and 5.2 and provided paediatric literature:

Posology and method of administration

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in infants after the first month of life is 4.5-7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in newborns is 4-7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose always in 1 (preferred) up to 2 single doses.

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function.

...

Monitoring advice:

Serum concentration monitoring of gentamicin is recommended, especially in elderly, in newborns and in patients with impaired renal function. Samples are taken at the end of a dosing interval (trough level). Trough levels should not exceed 2 µg/ml administering gentamicin twice daily and 1 µg/ml for a once daily dose.

...

4.4 Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

5.2 Pharmacokinetic properties

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 L/kg for a premature newborn to 0.25 L/kg for an adolescent. The larger volume of distribution means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered (*Touw et al 2009*).

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half-life is about 2 to 3 hours. Elimination half life and clearance change during neonatal life since gentamicin is mainly eliminated by the kidney and the elimination rate is reduced at birth due to immature renal function. Elimination half life averages approximately 8 hours in neonates at a gestational age of 26 to 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 to 37 weeks.

Correspondingly, clearance values increase from about 0.05 L/h in neonates at a gestational age of 27 to 0.2 L/h in neonates at a gestational age of 40 weeks (*Touw et al 2009; Pacifici 2009*).

Rapporteur's comment

The MAH's proposal for the wording for the SPC is supported, even though the wording of section 4.4 is not specifically applicable to paediatric patients.

Furthermore, it is proposed that neonates should not be administered more than one dose a day.

Sanofi-Aventis

The MAH submitted the following table which summarizes the information regarding the labelling of gentamicin marketed by sanofi-aventis in Europe.

Table 1 – sanofi-aventis Gentamicin labelling text related to paediatrics in EU

Country	Section 4.1: Therapeutic indications	Section 4.2: Posology and method of administration	Section 4.4: Special warnings and precautions for use	Section 5.2: Pharmacokinetic properties
Finland	No paediatric mention	<u>Children and neonates</u> : For premature infants and full term neonates up to 1 week of age 3 mg/kg every 12 hours. For ages between 1 week and 3 months initial dose is 2 mg/kg every 8 hours or 3 mg/kg every 12 hours.	<u>Children</u> during the neonatal period should be treated with Gensumycin only in severe and life threatening infections.	No paediatric mention
Hungary	No paediatric mention	The dose of infants up to 1 year of age is 5-7.5 mg/kg daily. The dose of newborns less than one week old is 5 mg/kg daily, divided into three parts, every 8 hour The usual dose of children is 3-6 mg/kg daily, divided into three equal parts, every 8 hour..	No paediatric mention	No paediatric mention
Ireland	Gentamicin is indicated for the treatment of serious systemic infections including those of the central nervous system due to organisms sensitive to this anti-infective. Such infections include urinary tract infections, chest infections, bacteraemia, septicaemia, <u>severe neonatal infections</u> and other systemic infections due to sensitive organisms.	<u>Children</u> 2 weeks to 12 years: the usual total daily dose is 6mg/kg in three divided doses. Under two weeks of age: the usual daily dose is 6mg/kg in two divided doses.	No paediatric mention	No paediatric mention
Norway	No paediatric mention	<u>Children</u> Neonates under 1 week: 5 mg/kg/day in 2 equal doses (every 12	No paediatric mention	No paediatric mention

Country	Section 4.1: Therapeutic indications	Section 4.2: Posology and method of administration	Section 4.4: Special warnings and precautions for use	Section 5.2: Pharmacokinetic properties
		hours) Neonates 1 – 4 weeks: 6 mg/kg/day in 2 or 3 equal doses (every 12 or 8 hours) Children over 4 weeks: : 6 mg/kg/day in 2 or 3 equal doses (
Sweden	No paediatric mention	<u>Dosage for children and neonates:</u> Premature children and neonates up to one week of age are given an initial dose corresponding to 3 mg/kg body weight every 12 hours. From 1 week up to 3 months of age the initial dose given is 2 mg/kg body weight every 8 hours or 3 mg/kg body weight every 12 hours.	<u>Children in the neonatal period</u> should be treated with Gensumycin only when severe or life-threatening infections.	No paediatric mention
United Kingdom	No paediatric mention	<u>Children:</u> Premature infants or full term neonates up to 2 weeks or age : 3mg/kg 12 hourly. 2 weeks to 12 years: 2mg/kg 8 hourly.	Ototoxicity has been recorded following the use of gentamicin. <u>Groups at special risk include patients with impaired renal function, infants and possibly the elderly.</u> Consequently, renal, auditory and vestibular functions should be monitored in these patients and serum levels determined so as to avoid peak concentrations above 10mg/l and troughs above 2mg/l. As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery. In some patients with impaired renal function there has been a transient rise in blood-urea-nitrogen which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosage according to the degree of	No paediatric mention

Country	Section 4.1: Therapeutic indications	Section 4.2: Posology and method of administration	Section 4.4: Special warnings and precautions for use	Section 5.2: Pharmacokinetic properties
			renal function.	

The MAH declared to be in no position to propose a harmonised SPC text.

Rapporteur's comment

It is to be noted that only twice-daily dosing is called for in the SPCs of the products marketed by Sanofi-Aventis in Europe.

Ursapharm Arzneimittel GmbH & Co. KG

The MAH markets only products for ocular use as eye ointment or eye drops. The SPCs of these products do not contain any information related to gentamicin that is specifically applicable to paediatric patients.

Rapporteur's comment

Information provided by the MAH does not warrant any regulatory action.

VIII. RAPPORTEUR'S FINAL OVERALL CONCLUSION AND RECOMMENDATION (DATED 07.12.2009)

The following changes are recommended for inclusion in the SPCs of products for systemic use. Once-daily dosing as a preferred option is particularly supported.

4.2 Posology and method of administration

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in infants after the first month of life is 4.5-7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in newborns is 4-7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function.

...

Monitoring advice:

Serum concentration monitoring of gentamicin is recommended, especially in elderly, in newborns and in patients with impaired renal function. Samples are taken at the end of a dosing interval (trough level). Trough levels should not exceed 2 µg/ml administering gentamicin twice daily and 1 µg/ml for a once daily dose.

...

4.4 Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

5.2 Pharmacokinetic properties

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 L/kg for a premature newborn to 0.25 L/kg for an adolescent. The larger volume of distribution means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered (*Touw et al 2009*).

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half-life is about 2 to 3 hours. Elimination half life and clearance change during neonatal life since gentamicin is mainly eliminated by the kidney and the elimination rate is reduced at birth due to immature renal function. Elimination half life averages approximately 8 hours in neonates at a gestational age of 26 to 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 to 37 weeks.

Correspondingly, clearance values increase from about 0.05 L/h in neonates at a gestational age of 27 to 0.2 L/h in neonates at a gestational age of 40 weeks (*Touw et al 2009; Pacifici 2009*).

The following changes are recommended for inclusion in the SPCs of products for topical otic use.

4.3 Contraindications

Perforation of the ear drum

4.4 Special warning and precautions for use

The condition of the ear drum must always be checked before this medicinal product is prescribed.

Irreversible toxic effects may result from direct contact of gentamicin with the middle and inner ear. This medicinal product must not be used if the integrity of the ear drum cannot be guaranteed.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic gentamicin therapy. Although these effects have not been reported following topical otic use of gentamicin, caution is advised when used concomitantly with systemic aminoglycosides.

No changes in the SPC text of other medicinal products for topical use other than otic are deemed necessary.

IX. CHMP MEMBERS' COMMENTS ON THE FINAL ASSESSMENT REPORT (DATED: 07.12.2009)

SE: The MPA agrees with the overall conclusion of the Rapporteur. However, the MPA has some additional points for consideration by the Rapporteur and other member states before adopting final recommendations for the SmPC.

Specific comments:

Section 4.1

As the proposed dose ranges is quite wide and that the dosages in small children will most likely be directed by local guidelines we would like to ensure that the following standard sentence is implemented:

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

Section 4.2

The MPA suggests that, if possible, specific dosage information is given for preterm and term neonates, respectively, as the currently proposed range of daily dose seems high for preterm neonates.

Gonzalez Santacruz M; et al. Comparison of two gentamicin dosing schedules in the newborn. Anales de Pediatria Jun 2008;68 (6):581-588.

Section 5.2

As the reference Touw et al 2009 is a review article it is assumed that accordance with the original references has been checked. References should not be included in section 5.2.

The following minor amendments are proposed:

-//-

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 L/kg for a premature newborn to 0.25 L/kg for an adolescent. The larger volume of distribution *per kg bodyweight* means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered (*Touw et al 2009*).

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half-life is about 2 to 3 hours. ~~Elimination half life and clearance change during neonatal life since gentamicin is mainly eliminated by the kidney and the~~ *In neonates* elimination rate is reduced at birth due to immature renal function. Elimination half life averages approximately 8 hours in neonates at a gestational age of 26 to 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 to 37 weeks.

Correspondingly, clearance values increase from about 0.05 L/h in neonates at a gestational age of 27 to 0.2 L/h in neonates at a gestational age of 40 weeks (*Touw et al 2009; Pacifici 2009*).

-//-

Rapporteur's comment

SE's proposals regarding sections 4.1 and 5.2 are supported and recommended for implementation.

As to the proposal concerning section 4.2, the Rapporteur is of the opinion that the available data are insufficient to support specific dosage recommendations for preterm neonates. The article by *Gonzalez Santacruz M; et al.* is available to the Rapporteur only in the form of an abstract, as the main parts of the publication are in Spanish, and does not provide enough justification for any firm dosage recommendations for preterm neonates. Therefore, we propose to remain with the wording suggested by the originator (Merck).

X. RAPPORTEUR'S 1. UPDATED FINAL OVERALL CONCLUSION AND RECOMMENDATION (DATED 05.01.2010)

The following changes are recommended for inclusion in the SPCs of products for systemic use. Once-daily dosing as a preferred option is particularly supported.

4.1 Therapeutic indications

The following standard sentence should be added to the section:

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.4 Posology and method of administration

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in infants after the first month of life is 4.5-7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in newborns is 4-7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function.

...

Monitoring advice:

Serum concentration monitoring of gentamicin is recommended, especially in elderly, in newborns and in patients with impaired renal function. Samples are taken at the end of a dosing interval (trough level). Trough levels should not exceed 2 µg/ml administering gentamicin twice daily and 1 µg/ml for a once daily dose.

...

4.4 Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

5.2 Pharmacokinetic properties

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 L/kg for a premature newborn to 0.25 L/kg for an adolescent. The larger volume of distribution per kg bodyweight means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered.

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half-life is about 2 to 3 hours. In neonates elimination rate is reduced due to immature renal function. Elimination half life averages approximately 8 hours in neonates at a gestational age of 26 to 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 to 37 weeks.

Correspondingly, clearance values increase from about 0.05 L/h in neonates at a gestational age of 27 to 0.2 L/h in neonates at a gestational age of 40 weeks.

The following changes are recommended for inclusion in the SPCs of products for topical otic use.

4.5 Contraindications

Perforation of the ear drum

4.4 Special warning and precautions for use

The condition of the ear drum must always be checked before this medicinal product is prescribed.

Irreversible toxic effects may result from direct contact of gentamicin with the middle and inner ear. This medicinal product must not be used if the integrity of the ear drum cannot be guaranteed.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic gentamicin therapy. Although these effects have not been reported following topical otic use of gentamicin, caution is advised when used concomitantly with systemic aminoglycosides.

No changes in the SPC text of other medicinal products for topical use other than otic are deemed necessary.

XI. CHMP MEMBERS' COMMENTS ON THE 1. UPDATED FINAL ASSESSMENT REPORT

SE (08.10.2010 by e-mail): We have received a variation application implementing changes from article 45 for gentamicin DE/W/003/pdWS/001.

The problem is that the company has implemented the dosing recommendations for a product intended for intrathecal use and thereby changed the dose to be mg/kg instead of a fixed mg dose. Depending on body weight this could mean up to 50 to 100 times higher dose for children and adults, which could be very serious.

Although this is likely a mistake it shows that the recommendations can be misinterpreted and we believe that assessors handling the variation applications need to be alerted that the changes are only applicable for intravenous and intramuscular use, i.e., should not replace existing dose recommendations for intrathecal administration.

Rapporteur's comment

SE's proposal is supported and recommended for implementation.

XII. RAPPORTEUR'S 2. UPDATED FINAL OVERALL CONCLUSION AND RECOMMENDATION (DATED 18.10.2010)

The following changes are recommended for inclusion in the SPCs of products for intravenous and intramuscular use. Once-daily dosing as a preferred option is particularly supported.

4.1 Therapeutic indications

The following standard sentence should be added to the section:

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in infants after the first month of life is 4.5-7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in newborns is 4-7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function.

...

Monitoring advice:

Serum concentration monitoring of gentamicin is recommended, especially in elderly, in newborns and in patients with impaired renal function. Samples are taken at the end of a dosing interval (trough level). Trough levels should not exceed 2 µg/ml administering gentamicin twice daily and 1 µg/ml for a once daily dose.

...

4.4 Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

5.2 Pharmacokinetic properties

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 L/kg for a premature newborn to 0.25 L/kg for an adolescent. The larger volume of distribution per kg bodyweight means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered.

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half-life is about 2 to 3 hours. In neonates elimination rate is reduced due to immature renal function. Elimination half life averages approximately 8 hours in neonates at a gestational age of 26 to 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 to 37 weeks. Correspondingly, clearance values increase from about 0.05 L/h in neonates at a gestational age of 27 to 0.2 L/h in neonates at a gestational age of 40 weeks.

The following changes are recommended for inclusion in the SPCs of products for topical otic use.

Contraindications

Perforation of the ear drum

4.4 Special warning and precautions for use

The condition of the ear drum must always be checked before this medicinal product is prescribed.

Irreversible toxic effects may result from direct contact of gentamicin with the middle and inner ear. This medicinal product must not be used if the integrity of the ear drum cannot be guaranteed.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic gentamicin therapy. Although these effects have not been reported following topical otic use of gentamicin, caution is advised when used concomitantly with systemic aminoglycosides.

No changes in the SPC text of other medicinal products for topical use other than otic are deemed necessary.

No changes in the SPC text of medicinal products intended for intrathecal use are deemed necessary.