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

TOBRAMYCIN

Tobrex, Tobral, Tobramaxin, Thilo-Micine
Tobrex 2x, Tobrex Depot, Tobrex LP , Tobrex LA, Tobrexan, Tobravisc
Tobradex, Tobrasone, Thilomicin-Dex
Ocubrax

FI/W/002/pdWS/001

Part II

Rapporteur:	Finland (FI)
Finalisation procedure (Day 120):	02.06.2012
Date of finalisation of PAR:	23.08.2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal products:	Tobrex, Tobral, Tobramaxin, Thilo-Micine Tobrex 2x, Tobrex Depot, Tobrex LP , Tobrex LA, Tobrexan, Tobravisc, Tobradex, Tobrasone, Thilomicin-Dex, Ocubrax (see section VI)
INN (or common name) of the active substance:	tobramycin
MAHs:	Alcon (see section VI)
Pharmaco-therapeutic group (ATC Code):	S01AA12, S01CC
Pharmaceutical forms and strengths:	eye ointment, eye drops suspension, eye drops solution, eye drops, prolonged-release

I. EXECUTIVE SUMMARY

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Tobramycin was introduced to clinical practice in the 1970s, and it primarily used to treat infections caused by gram-negative bacteria.

Tobramycin is available as solution for injection/infusion, nebuliser solution and several topical formulations to treat ophthalmic infections. This assessment covers the paediatric use of the ophthalmic preparations; Tobi® nebuliser solution is covered in a separate report. No data has been submitted for the parenteral injection/infusion solution.

Tobramycin containing ophthalmic preparations are labelled as follows:

Tobramycin: Treatment of external infections of the eye and its adnexa, caused by bacteria susceptible to tobramycin.

Tobramycin and dexamethasone: Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial infection exists or a risk of bacterial ocular infection exists.

Tobramycin and diclofenac: Prevention and treatment of inflammation of the anterior segment of the eye in cataract surgery, for which a NSAID is indicated, and where concomitant bacterial ocular infection exists or the risk of infection may be high.

The MAH submitted 9 completed paediatric studies for tobramycin containing ophthalmic preparations, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

SmPC and PL changes are proposed to sections 4.1, 4.2, 4.4 (Tobradex only) and 5.1.

Summary of outcome

☐ No change

☒ Change

☐ New study data:

☐ New safety information:

☒ Paediatric information clarified: sections 4.1, 4.2, 4.4 (Tobradex only) and 5.1

☐ New indication:

II. RECOMMENDATION

The MAH is requested to submit a Type IB variation within 60 days to implement the following changes to the Summary of Product Characteristics. Package leaflet should be in line with the SPC.

It is understood that the texts are different in different Member States, and that the purpose of the current procedure is not the harmonisation of the full text of the SPC. However, whenever and wherever possible the Applicant is advised to strive for harmonised text.

Tobrex / Tobrex 2X eye drops and Tobrex ointment

4.1 Therapeutic indications
Treatment of external infections of the eye and its adnexa, caused by bacteria susceptible to tobramycin in adults and children aged 1 year and older.

4.2 Posology and method of administration
Paediatric population
Tobrex/Tobrex 2X eye drops and Tobrex ointment may be used in children 1 year of age and older at the same dose as in adults. Currently available data is described in Section 5.1. The safety and efficacy in children younger than 1 year of age have not been established, and no data are available.

5.1 Pharmacodynamic properties
Paediatric Population
Over 600 paediatric patients were enrolled in 10 clinical studies with tobramycin eye drops or eye ointment for the treatment of bacterial conjunctivitis, blepharitis, or blepharoconjunctivitis. These patients ranged in age from 1 year to 18 years. Overall, the safety profile in paediatric patients was comparable to that of adult patients. For children younger than age 1, no recommendation on a posology can be made due to a lack of data.

Tobradex suspension and ointment

4.1 Therapeutic indications
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older.

4.2 Posology and method of administration
Paediatric population
Tobradex suspension and ointment may be used in children 2 years of age and older at the same dose as in adults. Currently available data is described in Section 5.1. The safety and efficacy in children younger than 2 years of age have not been established, and no data are available.

4.4 Special warnings and precautions for use
… It is advisable that the intraocular pressure be checked frequently. This is especially important in paediatric patients receiving dexamethasone-containing products, as the risk of steroid-induced ocular hypertension may be greater in children below 6 years of age and may occur earlier than a steroid response in adults. The frequency and duration of treatment should be carefully considered, and the IOP should be monitored from the outset of treatment, recognizing the risk for earlier and greater steroid-induced IOP increases in the paediatric patients.

5.1 Pharmacodynamic properties
Paediatric Population
The safety and efficacy of Tobradex eye drops and eye ointment in children have been established by broad clinical experience, but only limited data are available. In a clinical study of Tobradex suspension for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of Tobradex every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

Ocubrax

4.1 Therapeutic indications
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults.

4.2 Posology and method of administration
Paediatric population
The safety and efficacy of Ocubrax in children aged have not been established.
No data are available.

III. INTRODUCTION

The MAH submitted 9 completed paediatric studies for tobramycin ophthalmic preparations, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short expert overview has also been provided.

In addition, the following documentation has been included as per the procedural guidance:
– A line listing
– An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product (complete SPC texts)

The MAH concluded that tobramycin is safe and effective in paediatric patients of all age groups when used as described above in the proposed SPC text. No specific provision for reduced dosing (as compared to the adult dosing) is required.

The MAH proposed that the following (most commonly used) texts are used in the Alcon products with respect to paediatric use:

4.1 Therapeutic indications

Tobrex Solution, Tobrex 2X Solution, and Tobrex Ointment: Treatment of external infections of the eye and its adnexa, caused by bacteria susceptible to tobramycin. The product can be used in both adults and children, as its efficacy and safety have been established in clinical trials.

Tobradex Suspension and Tobradex Ointment: Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial infection exists or a risk of bacterial ocular infection exists. Safety and effectiveness of Tobradex has not been established in paediatric patients below 2 years of age.

Ocubrax: Prevention and treatment of inflammation of the anterior segment of the eye in cataract surgery, for which a NSAID is indicated, and where concomitant bacterial ocular infection exists or the risk of infection may be high.

4.2 Posology and method of administration

Tobrex, eye drops, solution: In case of mild and moderate infections, 1 - 2 drops of the product should ne instilled in the conjunctival sac with regular intervals 4 hours between the individual instillations for 7 days. For severe infections, 2 drops should be instilled every hour. After the condition has improved, the dosage may be reduced.

Tobrex 2X Solution: Instill one drop of the product into the conjunctival sac two times daily (morning and evening) for one week. For severe infections: on the first day, instill one drop in each eye four times a day while awake.Thereafter instill one drop in each eye twice a day (morning and evening) until completion of total treatment period.

Use in children and adolescents: Tobrex (Tobrex 2X) eye drops may be used in paediatric patients (1 year of age and older) at the same dose as in adults. However, limited information is available in paediatric patients younger than 1 year.

Tobrex Ointment: Adults and children older than 1 year: Apply at least 1 cm of the ointment into the inside of the lower eye lid and repeat this every three to four hours. The length of the treatment is dependent on the origin of the infection and may vary between 5 to 15 days.

Tobradex Suspension: One or two drops instilled into the conjunctival sac of affected eye(s) 4-5 times per day. During the initial 24 to 48 hours, the dose may be increased to one or two drops every two hours. Frequency should be decreased gradually as warranted by the improvement in clinical signs. In severe disease, one or two drops instilled every hour until inflammation is controlled, and gradually decrease frequency to one or two drops every two hours during 3 days; thereafter, one to two drops every 4 hours during 5 to 8 days, and finally one to two drops every day during the 5 to 8 last days, if considered necessary. The treatment should not be prematurely suspended or discontinued. Usually the treatment lasts one to two weeks. Safety and effectiveness of Tobradex has not been established in paediatric patients below 2 years of age.

Tobradex Ointment: Apply a 1.5 cm ribbon in the affected eye(s) 3 or 4 times daily. Blink several times to evenly spread the ribbon of ointment after placing it in the conjunctival sac. In cases of deep inflammation Tobradex ointment may be administered as an adjunct treatment during nighttime. Safety and effectiveness of Tobradex has not been established in paediatric patients below 2 years of age.

Ocubrax Eye Drops, Solution: Generally 1 or 2 drops into the affected eye(s) 4 times daily. By preference, the treatment should be started 24 hours before the cataract procedure. In controlled clinical trials for cataract surgery, the combination has shown to be effective for periods not longer than 21 days. The number of daily applications and length of treatment can be modified in accordance with physician's criteria.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

According to the summary table submitted by the MAH marketed products were used in the studies.

IV.2 Non-clinical aspects

No non-clinical studies were submitted.

IV.3 Clinical aspects

IV.3.1 Introduction

The submission is mainly bibliographic.

The MAH submitted two clinical study reports for:

– C-91-92. Clinical Evaluation of Tobradex Ophthalmic Suspension Versus Tobramycin Ophthalmic Solution (Tobrex).

– C-91-29. Efficacy and Safety of Ciprofloxacin Ophthalmic Ointment versus Tobrex® Ophthalmic Ointment for Treating Bacterial Conjunctivitis in Children.

The MAH submitted seven published study reports for:

– Bremond-Gignac D, Mariani-Kurkdjian P, Beresniak A et al. Efficacy and Safety of Azithromycin 1.5% Eye Drops for Purulent Bacterial Conjunctivitis in Pediatric Patients. Pediatr Infect Dis J 2010;29:222-6.

– Abelson M, Protzko E, Shapiro A,, Garces-Soldana A, Bowman L, 1% azithromycin in DuraSite Clinical Study Group. A randomized trial assessing the clinical effi cacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis. Clin Ophthalmol 2007:1(2)177-82.

– Fioretti GM, Campanari C. Bacterial Conjunctivitis in Paediatric Age Patients: Local Antibiotic Therapy with Tobramycin Eyedrop Bacterial Conjunctivitis in Paediatric Age Patients: Local Antibiotic Therapy with Tobramycin Eyedrop. Ped Med Chir (Med Surg Ped) 1989,11:421-3.

– Jackson WB, Low DE, Dattani D, Whitsitt PF, Leeder RG, MacDougall R. Treatment of acute bacterial conjunctivitis: 1% fusidic acid viscous drops vs. 0.3% tobranlycin drops. Can J Ophthalmal 2002;37:228-37.

– Gross RO, Hoffman RO, Lindsay RN. A Comparison of Ciprofloxacin and Tobramycin in Bacterial Conjunctivitis in Children. Clin Pediatr 1997:435-444

– Kernt K,Martinez M, Bertin D et al. A clinical comparison of two formulations of tobramycin 0.3% eyedrops in the treatment of acute bacterial conjunctivitis. Eur J Ophthalmol 2005;15:541-9.

– 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 Ped Ophthalmol Strab 1983;20(1), 22-6.

IV.3.2 Clinical studies

Bremond-Gignac D, Mariani-Kurkdjian P, Beresniak A et al. Efficacy and Safety of Azithromycin 1.5% Eye Drops for Purulent Bacterial Conjunctivitis in Pediatric Patients. Pediatr Infect Dis J 2010;29:222-6.

Background. Purulent bacterial conjunctivitis affects all ages with high frequency in newborns and children. In a subset of 150 children included in a large study having enrolled 1043 patients, our aim was to analyze in children, the efficacy and safety of azithromycin 1.5% eye-drops in the treatment of this disease.

Methods. This multicenter, randomized, investigator-masked, parallel group study, included 150 children and adolescents to study safety and compare azithromycin 1.5% eye drops twice daily for 3 days and tobramycin 0.3% 1 drop every 2 hours for 2 days then 4 times daily for 5 days. Out of 150 patients included, 58 had positive cultures and were studied for efficacy. Signs and symptoms were evaluated and cultures obtained at baseline, Days 3 and 9. Primary efficacy variable was the clinical cure (score 0 for bulbar conjunctival injection and purulent discharge) at the test of cure visit (day 9).

Results. Both treatments were effective with a clinical and microbiologic cure of more than 80% of children on day 9. Azithromycin therapy provided a greater bacteriologic cure on day 3 than did tobramycin (P < 0.001) and eradicated bacteria that were defined as resistant, using classical antibiogram. No adverse effects were noted on the ocular surface.

Conclusions: Azithromycin 1.5% eye drops leads to a rapid clinical and microbiological cure.

Assessor's comments: The study included 77 pediatric patients receiving Tobrex. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

Abelson M, Protzko E, Shapiro A,, Garces-Soldana A, Bowman L, 1% azithromycin in DuraSite Clinical Study Group. A randomized trial assessing the clinical effi cacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis. Clin Ophthalmol 2007:1(2)177-82.

Objective: The study was designed to evaluate the effi cacy of an ophthalmic formulation of 1% azithromycin in DuraSite® (AzaSite™, InSite Vision, Alameda CA, USA) and demonstrate equivalence with 0.3% tobramycin ophthalmic solution, USP, for the treatment of bacterial conjunctivitis as defi ned by the resolution of clinical signs and the eradication of pathogens.

Design: Prospective, randomized, active-controlled, double-masked, phase 3 trial conducted at 47 US sites between 6 August 2004 and 6 October 2005. Participants: Subjects aged 1 year or older with diagnosis of acute bacterial conjunctivitis.

Methods: Bacteriologically confi rmed participants received either 1% azithromycin in Dura-Site (n = 159) or tobramycin (n = 157). Masked study medications were dosed 4 times a day for 5 days. Participants in the 1% azithromycin in DuraSite group were dosed twice a day with active drug on days 1 and 2 and once daily on days 3 through 5. The other doses were vehicle. Clinical signs and bacterial cultures were evaluated at visit 3 (day 6 + 1).

Results: Clinical resolution was observed in 79.9% of participants in the 1% azithromycin in DuraSite group, as compared with 78.3% of those in the tobramycin group (95% CI: –7.4–10.5). Bacterial eradication was 88.1% in the 1% azithromycin in DuraSite group vs 94.3% in the tobramycin group (95% CI: –12.4–0.0). Analyses of resistance confi rmed that 1% azithromycin in DuraSite eradicated Staphylococci and Streptococci strains that are commonly resistant to azithromycin, erythromycin, and fl uoroquinolones.

Conclusions: The effi cacy of 1% azithromycin in DuraSite and tobramycin are equivalent; however, this formulation of azithromycin also permits effective dosing intervals of twice a day on days 1 and 2 followed by once daily on the last 3 days of therapy, for a total of 65% fewer doses. *In vitro*, the killing spectrum of 1% azithromycin in DuraSite appears to be enhanced relative to 1% azithromycin without DuraSite.

Assessor's comments: The study included 77 pediatric patients receiving Tobrex. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

Fioretti GM, Campanari C. Bacterial Conjunctivitis in Paediatric Age Patients: Local Antibiotic Therapy with Tobramycin Eyedrop Bacterial Conjunctivitis in Paediatric Age Patients: Local Antibiotic Therapy with Tobramycin Eyedrop. Ped Med Chir (Med Surg Ped) 1989,11:421-3.

A total of 122 children, aged 1 to 12, with suspected bacterial conjunctivitis, were treated with Tobramycin 0.3 % eye drops. The follow-up assessment was on Day 3 (+2), Day 7 (+2) and a third assessment was performed around Day 15, for longer treatments. All patients showed a significant remission of the signs and symptoms already at the first assessments. No local or systemic side effect was noticed. Locally, the product was well-tolerated.

Assessor's comments: The study included 122 pediatric patients receiving Tobral. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

Jackson WB, Low DE, Dattani D, Whitsitt PF, Leeder RG, MacDougall R. Treatment of acute bacterial conjunctivitis: 1% fusidic acid viscous drops vs. 0.3% tobranlycin drops. Can J Ophthalmal 2002;37:228-37.

Background: A frequent cause of conjunctivitis is an acute bacterial infection, presenting with mucopurulent discharge and conjunctival hyperemia. The authors compared the clinical and microbiologic efficacy, safety and acceptability of 1% fusidic acid viscous drops (Fucithalmic) with 0.3% tobramycin ophthalmic solution (Tobrex) in the treatment of suspected bacterial conjunctivitis.

Methods: Patients were recruited at 20 sites in Ontario, Saskatchewan and Alberta from October 1995 to December 1998. Patients who presented to their primary care physician with suspected bacterial conjunctivitis, as identified by conjunctival hyperemia and purulent or mucopurulent discharge, were eligible for the study. Patients were randomly assigned to receive 7 days of treatment with either 1% fusidic acid (one drop applied twice daily) or 0.3% tobramycin (one to two drops applied four to six times daily). The investigators were blinded as to treatment status. Bacteriologic samples were taken from the inferior conjunctival cul-de-sac on day 0 and at the end of treatment. Signs and symptoms of conjunctivitis were assessed at baseline and after 3 and 7 days of treatment. The acceptability of treatment was assessed by having the patient or the parent or guardian complete a questionnaire on degree of compliance and ease of use after 3 and 7 days of treatment.

Results: Conjunctival swabs were obtained from 484 patients (410 over 9 years of age and 74 aged 2 to 9 years) to determine baseline bacteriology. Of the 484, 319 (65.9%) (63% of the older patients and 80% of those aged 2 to 9 years) had positive results of culture for bacteria. Ninety-four patients (19%) (63 [15%] of the older patients and 31 [42%] of those aged 2 to 9 years) had per-protocol pathogens as defined by quantitative bacteriology criteria. There was a direct correlation between the presence of mucopurulent discharge and the presence of per-protocol pathogens. There were no significant differences in clinical or bacteriologic efficacy between the treatment groups. Treatment compliance was similar between the treatment groups for the older patients; however, for those aged 2 to 9 years.

Assessor's comments: The study included 40 pediatric patients receiving Tobrex. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

Gross RO, Hoffman RO, Lindsay RN. A Comparison of Ciprofloxacin and Tobramycin in Bacterial Conjunctivitis in Children. Clin Pediatr 1997:435-444

Summary: A study was conducted to determine the safety and efficacy of topically applied ciprofloxacin ophthalmic solution in a pediatric population experiencing acute bacterial conjunctivitis. Topically applied ciprofloxacin (3mg/mL) is known to be a safe and effective treatment for adults suffering from bacterial conjunctivitis; however, the safety and effectiveness of this broad-spectrum fluoroquinolone in pediatric patients is not well established. Ciprofloxacin was evaluated in a double-blind, randomized, controlled study of 257 patients ranging from 0 (i.e., less than 1 year) to 12 years of age from 33 geographically diverse medical.centers. The children received either 0.3% ciprofloxacin ophthalmic solution (Ciloxan™, Alcon Laboratories, Fort Worth, TX) or tobramycin ophthalmic solution (Tobrex™, Alcon Laboratories, Fort Worth, TX). Both test medications were administered topically every 2 hours on days 1 and 2 followed by every 4 hours on days 3 through 7. Eyes were cultured prior to enrollment and again on day 7. Treatment efficacy as determined by microbiological culture data and physicians' judgment of overall resolution was similar for the ciprofloxacin and tobramycin groups. Microbiological eradication was observed in 90.1% of the ciprofloxacin group and 84.3% of the tobramycin group (P= 0.29). Physicians judged 87.0% of the ciprofloxacin patients and 89.9% of the tobramycin patients clinically cured on day 7 (P>0.5) There were no serio~s adverse medical events attributable to either treatment. This study showed that topically applied ciprofloxacin ophthalmic solution is safe and effective in a pediatric population experiencing acute bacterial conjunctivitis.

Assessor's comments: The study included 129 pediatric patients receiving Tobrex. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

Kernt K,Martinez M, Bertin D et al. A clinical comparison of two formulations of tobramycin 0.3% eyedrops in the treatment of acute bacterial conjunctivitis. Eur J Ophthalmol 2005;15:541-9.

Purpose. To compare the safety and efficacy of a new enhanced viscosity ophthalmic formulation of tobramycin, given twice daily (BID), with the existing four times daily (OID) treatment regimen in patients with acute bacterial conjunctivitis.
Methods. This was a 12-day, multicenter, observer-masked, randomized, parallel group study. Patients received one drop of tobramycin 0.3% (3 mg/ml) enhanced viscosity ophthalmic solution BID or tobramycin 0.3% (3 mg/ml) ophthalmic solution OID in the affected eyes for 7 days. The primary efficacy variable was the percentage of patients with sustained cure/presumed bacterial eradication based on clinical judgment at the test-of-cure visit (Day 12). Pre therapy bacterial isolates were obtained and tested for susceptibility to tobramycin
by determination of minimum inhibitory concentrations (MIC).
Results. A total of 276 patients were enrolled in the study and 203 of these were culture positive and attended all follow-up examinations. In this group, 98% of those treated with tobramycin enhanced viscosity ophthalmic solution and 99% of those treated with tobramycin 0.3% ophthalmic solution were categorized as having sustained cure/presumed eradication at the test-of-cure visit (p=O. 603 7). Reported adverse events were not serious, mild to moderate in severity, and generally did not prevent continuation in the study. Several pre-treatment pathogens demonstrated tobramycin resistance (MIC > 4 mg/ml). However, therapy with both treatments was effective in the majority of the cases.
Conclusions. Tobramycin enhanced viscosity ophthalmic solution is well tolerated and has equivalent efficacy to the established treatment regimen with a simplified posology. The formulation provides an alternative therapy for acute bacterial conjunctivitis that should improve patient compliance and satisfaction.

Assessor's comments: The study included 2 pediatric patients receiving Tobrex and 4 pediatric patients receiving Tobrex 2X. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

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 Ped Ophthalmol Strab 1983;20(1), 22-6.

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, 18 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.

Efficacy: A total of 64 of the 66 infected eyes (98% tobramycin group, 95% gentamicin group) WID:e classed as cured or improved by the investigator at the end of the treatment period (Table 5). Ofthe two patients graded by the physician as unimproved after treatment, one received tobramycin solution and the other gentamicin solution. These results show that both antibiotics were effective in clinically treating the diseases and there was no significant difference between the two.

Safety: A total of 62 patients (96 eyes) wcre suitable for evaluation of the safety of the two antibiotics in this study (Table 6). Only two adverse reactions (3 eyes) were reported and these both occurred in patients treated with gentamicin sulfate. One patient complained of increased irritation and discomfort and showed signs of mild chemical irritation after using gentamicin ointment, in one eye, as directed for six days. The other patient exhibited erythema,lid swelling, chemosis and a folliculopapillary reaction after uBing gentamicin solu· tion, in both eyes, as directed for four days. This difference in safety between the two antibiotics was not statistically significant.

Conclusions. This study showed 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 investigations. The two antibiotics were found to be as efficacious in the treatment of external ocular infections in a pediatric population as they Were in adult populations. Also, in agreement with previous reports, patients treated with tobramycin demonstrated a trend towards fewer treatment-related side effects. Tobramycin is a valuable addition to the ophthalmologist's repertoire for treatment of bacterial superficial ocular infections.

Assessor's comments: The study included 46 pediatric patients receiving Tobrex. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

C-91-92. Clinical Evaluation of Tobradex Ophthalmic Suspension Versus Tobramycin Ophthalmic Solution (Tobrex).

Objective. To determine the clinical and microbiological efficacy and safety of Tobradex ophthalmic suspension versus Tobrex ophthalmic solution.

Methods. 2 days double-masked Tobradex Eyedrops vs Tobrex Eyedrops followed· by 5 days open label Tobradex Eyedrops, randomized, controlled

Patients. Two hundred fifteen (215) patients with external ocular inflammation:of bacterial origin were randomized to treatment (107 on Tobradex Eyedrops and 108 on Tobrex Eyedrops) and 215 were evaluable for intent-to-treat, 213 for safety analysis (two patients were enrolled twice with at least 5 months in between). Ninety-two (92) patients were , evaluable for efficacy analysis (42 on Tobradex Eyedrops and 50 on Tobrex Eyedrops). Patients were excluded from the efficacy analysis for various. reasons, such as negative culture, ,lost to follow-up, Day 2 out of range, no culture(s) collected, only open label medication received and exclusion criteria. The age ranged from 1 to .94 years and 98.1 % were caucasian. There were 103 males in the study (47.9 %) and 112females (52.1 %). Study Design Tobradex Eyedrops consists of tobramycin ophthalmic solution 0.3% and dexamethasone ophthalmic suspension 0.1 %. In this study Tobrex-Eyedrops (antibiotic only) was evaluated for microbial and clinical safety and efficacy against Tobradex Eyedrops. The evaluation was conducted in patients with a history of external ocular bacterial infection, e.g., blepharoconjunctivitis, conjunctivitis or keratoconjunctivitis. Patients were treated 4-6 times daily for two days with either Tobradex Eyedrops or Tobrex Eyedrops.

Efficacy. Tobradex Eyedrops is statistically equivalent to Tobrex Eyedrops in eradicating organisms. No statistically significant treatment differences were detected for physician's impression or the signs of ocular inflammation.

Safety. Tobradex Eyedrops was compared against Tobrex Eyedrops for two days in a double-masked phase followed by Tobradex Eyedrops for 5 (± 1) days in an open label phase in 213 (2 patients were enrolled twice) patients with bacterial inflammation. Adverse events related to Tobradex Eyedrops and/or Tobrex Eyedrops were nonserious, mild to moderate, usually occurred with each instillation, resolved generally without treatment, and usually did not interrupt continuation in the study. No serious events related or unrelated to Tobradex Eyedrops and/or Tobrex Eyedrops were reported during the study, and no patient was discontinued due to a serious treatmentrelated event. No clinically significant difference in visual acuity was observed in patients receiving Tobradex Eyedrops and/or Tobrex Eyedrops. Tobradex Eyedrops and/or Tobrex Eyedrops were safe and well tolerated for multiple dose regimen use in patients with bacterial inflammation.

Conclusion. Tobradex Eyedrops is microbiologically and statistically equivalent to Tobrex Eyedrops in eradicating bacteria in patients with external ocularJnflammation of bacterial origin. Both Tobradex Eyedrops and Tobrex Eyedrops are safe for use in patients with a history of external ocular inflammation

Assessor's comments: The study included 19 pediatric patients receiving Tobrex and 13 pediatric patients receiving Tobradex (figures have been checked from the CSR line listing). The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

C-91-29. Efficacy and Safety of Ciprofloxacin Ophthalmic Ointment versus Tobrex® Ophthalmic Ointment for Treating Bacterial Conjunctivitis in Children.

Objective. To evaluate the efficacy and safety of Ciprofloxacin Ophthalmic Ointment versus Tobrex Ophthalmic Ointment in Children Randomized, double-masked, active~controlled, parallel group study

Patients. 203 patients (210 patient numbers randomized)

Methods. Ciprofloxacin was compared to Tobrex for the treatment of acute bacterial conjunctivitis (≤ 7 days) in children between the ages of 1 and 12. For this prospective, randomized, double-masked, parallel study, 9 investigators enrolled a total of 203 patients, using 210 patient numbers (4 patients had both eyes enrolled as-separate patient numbers, 1 patient was enrolled twice and 1 patient was enrolled 3 times). One hundred three (103) patient numbers were randomized to Ciprofloxacin and 107 patient numbers were randomized to Tobrex. The dosing regimen consisted of a Y,z inch ribbon in each affected eye at 9 a.m., 3 p.m. and 9 p.m. Days 1 and 2, followed by a Y,z-inch ribbon at 9 a.m. and 9 p.m. on Days 3 through 7.

Results. For the Intent-To-Treat Group, the mean ages (± S.D.) of the Ciprofloxacin and Tobrex treated patients were 4.5 (± 3.19) years and 4.6 (± 3.21) years, respectively. The median age was 4 years for both treatment groups, with a range of 1-12 years in the Ciprofloxacin group and 0-13 years in the Tobrex group. The majority of the patients (Ciprofloxacin 60.2%; Tobrex 62.6%) were 4 years old or younger. Males (M) and females (F) were equally represented (Ciprofloxacin 56% M/44% F; Tobrex 54% Mf46% (F). Eighty-nine percent (89%) of the Ciprofloxacin patients and 90% of the Tobrex patients were Caucasian. There were no statistically significant differences between treatment groups for demographic and baseline characteristics in any of the datasets.

No statistically significant treatment differences were found between Ciprofloxacin Ophthalmic Ointment (Ciprofloxacin) and Tobrex Ophthalmic Ointment (Tobramycin) for Microbiological Efficacy, Physician's Judgment, or the 3 Cardinal Signs (discharge/exudate, erythema/swelling, bulbar conjunctiva) of bacterial conjunctivitis in acute conjunctivitis patients between the ages of 1 and 12 years who were treated for 7 days.

In the Efficacy group, 86.2% of the Ciprofloxacin patients and 83.3% of the Tobrex patients had microbiological eradication on follow-up. Of all isolated organisms, 51% were Gram-positive and 49% were Gram-negative. The predominant pathogens were Haemophilus influenzae (46.9%) and Streptococcus pneumoniae (36.7%).Ciprofloxacin effectively eradicated 91% of the H. influenzae versus 80% for Tobrex, and 82.6% of S. pneumoniae versus 87.1% for Tobrex. No significant treatment difference was detected for overall microbiological efficacy ($p = 0.63$). For physician's judgment, 95.3% of the Ciprofloxacin patients and 91.3% of the Tobrex patients were clinically cured on Day 7. No statistically significant treatment difference was found for physician's judgment on Day 3 or Day 7 ($p > 0.26$). In addition, Ciprofloxacin and Tobrex were equally effective in resolving the three cardinal signs of acute bacterial conjunctivitis on Day- 7 ($p > 0.42$). Results for the Culture Positive and Intent-To-Treat groups support these findings.

Safety. All 203 patients enrolled in the study were evaluated for safety: 101 were treated with Ciprofloxacin and 102 were treated with Tobrex. There were no serious adverse medical events attributable to treatment with either Ciprofloxacin or Tobrex. Ciprofloxacin Ophthalmic Ointment 0.3% was safe and well tolerated for multiple dose regimen use for up to 7 days in pediatric patients with acute bacterial conjunctivitis.

Conclusions. Ciprofloxacin is clinically and microbiologically equivalent to Tobrex Eyedrops. Ciprofloxacin has eradication and cure rates of 86% and 95%, respectively. Ciprofloxacin provides excellent antibacterial efficacy for the most common pathogens isolated in pediatric conjunctivitis patients (*H. influenzae* and *S. pneumoniae*). Ciprofloxacin is as safe as Tobrex.

Assessor's comments: The study included 80 pediatric patients receiving Tobrex ointment. The safety and efficacy results do not affect the present risk-benefit assessment. Thus, no changes to the current product information are warranted.

IV.3.3 Discussion on clinical aspects

Altogether 595 pediatric patients have participated in the clinical studies submitted; 497 in published reports and 98 in clinical studies conducted by the MAH. The efficacy and safety of Tobrax in pediatric use has also been established in clinical use over several decades. In paediatric patients younger than 1 year the available data is limited.

Only 13 patients have received Tobradex in a clinical study setting. The MAH states that safety and effectiveness of Tobradex has not been established in paediatric patients below 2 years of age. However, the clinical data submitted does not justify pediatric use. Same conclusion has been reached in Mutual Recognition Procedure UK/H/777/01 in 2005, and no new data has been submitted since then.

No pediatric study data was submitted for Ocubrax. Pediatric use and Posology have not been approved.

The MAH also submitted full SPC texts from all European countries. The texts are quite inconsistent from country to country. It is not the purpose of this procedure to assess national SPCs, but it is recommended that the MAH makes efforts to harmonise the SPC texts using an appropriate procedure.

As a consequence of the data submitted and the discussion above, changes were proposed to the Summary of Product Characteristics, sections 4.1, 4.2 and 5.1. In addition, the MAH was asked to address the following List of Questions:

1) Should the MAH wish to retain the 'most commonly used texts' as submitted (see section III) a detailed justification must be provided.

2) The MAH should submit clinical trial data summaries to SPC section 5.1 for Tobrex and Tobradex. For data on Tobrex brevity is advised to summarise the accumulated evidence, i.e. the 9 studies need not be described individually. However, if possible, the data on children under 1 year of age should be specified. For study C 91-92 the number of pediatric subjects in each group should be verified (Tobrex/Tobradex 18/14 as tabulated v. 19/13 in manual count by the assessor).

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

V.1 Overall conclusion

The Applicant addressed the List of Questions adequately. Relevant updates to sections 4.1, 4.2 and 5.1 have been introduced and agreed. For Tobradex suspension and ointment, the Applicant proposed to retain the pediatric indication for children aged 2 years and older. This is considered justified based upon the pediatric experience with the tobramycin and dexamethasone separately, as well as limited data with Tobradex eye drops. For Tobradex, an additional update has been introduced to section 4.4.

This Public Assessment Report has been prepared to facilitate the publication of the end result of the procedure at the Agency website.

V.2 Recommendation

The MAH is requested to submit a Type IB variation within 60 days to implement the following changes to the Summary of Product Characteristics. Package leaflet should be in line with the SPC.

It is understood that the texts are different in different Member States, and that the purpose of the current procedure is not the harmonisation of the full text of the SPC. However, whenever and wherever possible the Applicant is advised to strive for harmonised text.

Tobrex / Tobrex 2X eye drops and Tobrex ointment

4.1 Therapeutic indications
Treatment of external infections of the eye and its adnexa, caused by bacteria susceptible to tobramycin in adults and children aged 1 year and older.

4.2 Posology and method of administration
Paediatric population
Tobrex/Tobrex 2X eye drops and Tobrex ointment may be used in children 1 year of age and older at the same dose as in adults. Currently available data is described in Section 5.1. The safety and efficacy in children younger than 1 year of age have not been established, and no data are available.

5.1 Pharmacodynamic properties
Paediatric Population
Over 600 paediatric patients were enrolled in 10 clinical studies with tobramycin eye drops or eye ointment for the treatment of bacterial conjunctivitis, blepharitis, or blepharoconjunctivitis. These patients ranged in age from 1 year to 18 years. Overall, the safety profile in paediatric patients was comparable to that of adult patients. For children younger than age 1, no recommendation on a posology can be made due to a lack of data.

Tobradex suspension and ointment

4.1 Therapeutic indications
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older.

4.2 Posology and method of administration
Paediatric population
Tobradex suspension and ointment may be used in children 2 years of age and older at the same dose as in adults. Currently available data is described in Section 5.1. The safety and efficacy in children younger than 2 years of age have not been established, and no data are available.

4.4 Special warnings and precautions for use
… It is advisable that the intraocular pressure be checked frequently. This is especially important in paediatric patients receiving dexamethasone-containing products, as the risk of steroid-induced ocular hypertension may be greater in children below 6 years of age and may occur earlier than a steroid response in adults. The frequency and duration of treatment should be carefully considered, and the IOP should be monitored from the outset of treatment, recognizing the risk for earlier and greater steroid-induced IOP increases in the paediatric patients.

5.1 Pharmacodynamic properties
Paediatric Population
The safety and efficacy of Tobradex eye drops and eye ointment in children have been established by broad clinical experience, but only limited data are available. In a clinical study of Tobradex suspension for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of Tobradex every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

Ocubrax

4.1 Therapeutic indications
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults.

4.2 Posology and method of administration
Paediatric population
The safety and efficacy of Ocubrax in children aged have not been established.
No data are available.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Country	Name of the medicinal product	Pharmaceutical form	Strength	Marketing Authorisation Holder
Cyprus	Tobrex	eye ointment	0.3% w/w	A.Potamitis Medicare Ltd
Cyprus	Tobrex 2X	eye drops, solution	3 mg/ml	A.Potamitis Medicare Ltd
Austria	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Ophthalmika GmbH
Austria	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Ophthalmika GmbH
Austria	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Ophthalmika GmbH
Austria	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	Alcon Ophthalmika GmbH
Bulgaria	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Bulgaria EOOD
Bulgaria	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Bulgaria EOOD
Bulgaria	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Bulgaria EOOD
Bulgaria	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	Alcon Bulgaria EOOD
Belgium	Ocubrax	eye drops solution	Tobramicyn 3 mg/ml + Diclofenac 1 mg/ml	SA Alcon-Couvreur NV
Belgium	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	SA Alcon-Couvreur NV
Belgium	Tobrex	eye ointment	Tobramicyn 3 mg/g	SA Alcon-Couvreur NV
Belgium	Tobravisc	eye drops solution	Tobramicyn 3 mg/ml	SA Alcon-Couvreur NV
Belgium	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	SA Alcon-Couvreur NV
Belgium	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	SA Alcon-Couvreur NV
Czech Republic	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon-Couvreur / Belgium
Czech Republic	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon-Couvreur / Belgium
Czech Republic	Tobrex LA	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusí / Spain

Czech Republic	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon-Couvreur / Belgium
Czech Republic	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	Alcon Pharmaceuticals (Czech Republic) s.r.o.
Cyprus	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	A.Potamitis Medicare Ltd
Cyprus	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	A.Potamitis Medicare Ltd
Cyprus	Tobrex 2x	eye drops solution	Tobramicyn 3 mg/ml	A.Potamitis Medicare Ltd
Cyprus	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	A.Potamitis Medicare Ltd
Cyprus	Tobrex	eye ointment	Tobramicyn 3 mg/g	A.Potamitis Medicare Ltd
Denmark	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Denmark
Estonia	Tobrex 2x	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi
Estonia	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Puurs
Estonia	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Puurs
Estonia	Tobradex	eye ointment	Tobramicyn 3 mg/g	Alcon Puurs
Finland	Tobrasone	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Finland
Finland	Tobrex Depot	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi
France	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Laboratoires Alcon 4, rue Henri Sainte-Claire Deville 92563 Rueil-Malmaison Cedex
France	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Laboratoires Alcon 4, rue Henri Sainte-Claire Deville 92563 Rueil-Malmaison Cedex
France	Tobrex	eye ointment	Tobramicyn 3 mg/g	Laboratoires Alcon 4, rue Henri Sainte-Claire Deville 92563 Rueil-Malmaison Cedex
France	Tobrex L.P.	eye drops solution	Tobramicyn 3 mg/ml	Laboratoires Alcon 4, rue Henri Sainte-Claire Deville 92563 Rueil-Malmaison Cedex
Germany	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Pharma GmbH, Germany

Germany	Tobramaxin	eye ointment	Tobramicyn 3 mg/g	Alcon Pharma GmbH, Germany
Germany	Tobramaxin	eye drops solution	Tobramicyn 3 mg/ml	Alcon Pharma GmbH, Germany
Greece	Tobrex 2x	eye drops solution	Tobramicyn 3 mg/ml	Alcon Laboratories Hellas S.A.
Greece	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Laboratories Hellas S.A.
Greece	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Laboratories Hellas S.A.
Greece	Thilo-Micine	eye drops solution	Tobramicyn 3 mg/ml	Pharmex S.A.
Greece	Thilo-Micine	eye ointment	Tobramicyn 3 mg/g	Pharmex S.A.
Greece	Tobrex 2x	eye drops solution	Tobramicyn 3 mg/ml	Alcon Laboratories Hellas S.A.
Greece	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Laboratories Hellas S.A
Greece	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	Alcon Laboratories Hellas S.A.
Greece	Thilomicin-Dex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Pharmex S.A.
Hungary	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Hungary Ltd.
Hungary	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Hungary Ltd.
Hungary	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Hungary Ltd.
Hungary	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	Alcon Hungary Ltd.
Hungary	Tobrexan	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi
Iceland	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Denmark
Ireland	NA	na	NA	NA
Italy	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Couvreur S.A.
Italy	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	Alcon Couvreur S.A.
Italy	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Couvreur S.A.
Italy	Tobral	eye drops, prolonged release	Tobramicyn 3 mg/ml	Alcon Italia S.p.A.

Italy	Tobral	eye drops solution	Tobramicyn 3 mg/ml	Alcon Italia S.p.A.
Italy	Tobral	eye ointment	Tobramicyn 3 mg/g	Alcon Italia S.p.A.
Latvia	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Puurs
Latvia	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Puurs
Latvia	Tobradex	eye ointment	Tobramicyn 3 mg/g	Alcon Puurs
Latvia	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Puurs
Lithuania	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Puurs
Lithuania	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Puurs
Lithuania	Tobrex LA	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi
Lithuania	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml	
Luxembourg	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	SA Alcon-Couvreur NV
Luxembourg	Tobrex	eye ointment	Tobramicyn 3 mg/g	SA Alcon-Couvreur NV
Luxembourg	Tobravisc	eye drops solution	Tobramicyn 3 mg/ml	SA Alcon-Couvreur NV
Luxembourg	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	SA Alcon-Couvreur NV
Luxembourg	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	SA Alcon-Couvreur NV
Malta	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Couvreur Belgium
Malta	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Couvreur Belgium
Netherlands	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	SA Alcon-Couvreur NV
Netherlands	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	SA Alcon-Couvreur NV
Netherlands	Tobrex	eye ointment	Tobramicyn 3 mg/g	SA Alcon-Couvreur NV
Netherlands	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	SA Alcon-Couvreur NV
Norway	Tobrasone	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Norway
Norway	Tobrex Depot	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi
Poland	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	s.a. Alcon-Couvreur n.v.

Poland	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	s.a. Alcon-Couvreur n.v.
Poland	Tobrex	eye ointment	Tobramicyn 3 mg/g	s.a. Alcon-Couvreur n.v.
Poland	Tobrexan	eye drops solution	Tobramicyn 3 mg/ml	s.a. Alcon-Couvreur n.v.
Portugal	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Portugal - Produtos e Equipamentos Oftalmológicos, Lda.
Portugal	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Portugal - Produtos e Equipamentos Oftalmológicos, Lda.
Portugal	Tobrexan	eye drops solution	Tobramicyn 3 mg/ml	Alcon Portugal - Produtos e Equipamentos Oftalmológicos, Lda.
Portugal	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Portugal - Produtos e Equipamentos Oftalmológicos, Lda.
Romania	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	S.A.Alcon-Couvreur NV, Rijksweg 14, B-2870, Puurs, Belgium
Romania	Tobrex	eye ointment	Tobramicyn 3 mg/g	S.A.Alcon-Couvreur NV, Rijksweg 14, B-2870, Puurs, Belgium
Romania	Tobrex 2x	eye drops solution	Tobramicyn 3 mg/ml	S.A.Alcon-Couvreur NV, Rijksweg 14, B-2870, Puurs, Belgium
Romania	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	S.A.Alcon-Couvreur NV, Rijksweg 14, B-2870, Puurs, Belgium
Romania	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	S.A.Alcon-Couvreur NV, Rijksweg 14, B-2870, Puurs, Belgium
Slovak Republic	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	S.A.Alcon-Couvreur N.V.
Slovak Republic	Tobrex	eye ointment	Tobramicyn 3 mg/g	S.A.Alcon-Couvreur N.V.
Slovak Republic	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	S.A.Alcon-Couvreur N.V.
Slovak Republic	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	S.A.Alcon-Couvreur N.V.
Slovak Republic	Tobravisc	eye drops solution	Tobramycin 3 mg/ml (depot formulation)	S.A.Alcon-Couvreur N.V.
Slovenia	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	SA Alcon-Couvreur NV
Slovenia	Tobrex	eye ointment	Tobramicyn 3 mg/g	SA Alcon-Couvreur NV
Slovenia	Tobrex 2x	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusí, SA

Slovenia	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	SA Alcon-Couvreur NV
Slovenia	Tobradex	eye ointment	Tobramicyn 3 mg/g + Dexamethasone 1 mg/g	SA Alcon-Couvreur NV
Spain	Ocubrax	eye drops solution	Tobramicyn 3 mg/ml + Diclofenac 1 mg/ml	Alcon Cusi, S.A.
Spain	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Cusi, S.A.
Spain	Tobrex	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi, S.A.
Spain	Tobrex	eye ointment	Tobramicyn 3 mg/g	Alcon Cusi, S.A.
Spain	Tobrexan	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi, S.A.
Sweden	Tobrex Depot	eye drops solution	Tobramicyn 3 mg/ml	Alcon Cusi
Sweden	Tobrasone	eye drops suspension	Tobramicyn 3 mg/ml	Alcon Sweden
UK	Tobradex	eye drops suspension	Tobramicyn 3 mg/ml + Dexamethasone 1 mg/ml	Alcon Laboratories UK, Ltd.
UK	Tobravisc	eye drops solution	Tobramicyn 3 mg/ml	Alcon Laboratories UK, Ltd.