

**Public Assessment Report
Paediatric data**

**EXOCIN (OCUFLOX)
Ofloxacin**

Marketing Authorisation Holder: Allergan

Rapporteur:	Denmark
Co-Rapporteur:	Hungary
Currently approved indication(s):	Infections caused by ofloxacin-sensitive bacteria
Pharmaceutical form(s) and strengths affected by this variation:	Eye drops, solution, 3 mg/ml
Paediatric assessment Procedure start date:	21 July 2006
Date of (Co)-Rapporteur's preliminary report (PPdAR):	29 September 2006
Date of Rapporteurs' final report (JAR):	9 March 2007
End of procedure:	13 February 2008
Date of this report:	28 July 2008

I. INTRODUCTION

Exocin (Ocuflox) was listed under the “EU worksharing project in the assessment of paediatric data”. Consequently, as a part of this procedure, the MAH submitted the requested paediatric file for Exocin eye drops, solution. The procedure started on July 21st, 2006. Denmark and Hungary had been appointed as Rapporteur and Co-rapporteur, respectively.

The paediatric file consisted of a single clinical study report, describing the results of study 190442-005: A multi-center, randomized, double-masked, parallel-group clinical study evaluating the safety and efficacy of topical ofloxacin 0.3% ophthalmic solution with that of topical trimethoprim sulfate/polymyxin B sulfate combination ophthalmic solution as a positive control, in infants, from birth to 31 days of age, with bacterial conjunctivitis.

Based on the review, the paediatric data should lead to an amendment of the currently approved SPC text. The final agreed changes to the SPC are shown in section IV at the end of this assessment report.

I.1 Scope of the variation

The MAH proposes the following to be added to Section 5.1 Pharmacodynamic Properties:

"Limited data (N = 173) are available from a double-masked comparative study of use of Exocin in neonates from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop up to 8 times daily were used for the first 2 days with four times daily dosing for 5 days thereafter. Cure rates in culture-positive patients of up to 60% were observed. No safety concerns were raised."

II. SCIENTIFIC DISCUSSION

Ofloxacin is a fluorinated 4-quinolone anti-infective with bactericidal activity against most aerobic gram-positive and gram-negative bacteria. Ofloxacin 3 mg/ml eye drops, solution are indicated for the treatment of ofloxacin-susceptible ocular infections. It has been licensed globally with the first licence being granted in France in 1989 for the treatment of bacterial conjunctivitis.

The ocular formulation is presently licensed in a number of European countries. With the exception of Ireland, Greece and Cyprus, ofloxacin is licensed for use in both adults and children with no adjustment of dose required. Where the precise age of the child is stipulated, the Summary of Product Characteristics states that the child must be aged one year or above for ofloxacin use to be licensed.

II.1 Quality aspects

N/A

II.2 Non-clinical aspects

N/A

II.3 Clinical aspects

II.3.1 Clinical pharmacology

No new clinical pharmacology data have been presented.

II.3.2 Clinical efficacy

Main study(ies)

The MAH has submitted a single clinical study report, describing the results of study 190442-005: A Multi-Center, Randomized, Double-Masked, Parallel-Group Clinical Study Evaluating the Safety and Efficacy of Topical Ofloxacin 0.3% Ophthalmic Solution with That of Topical Trimethoprim Sulfate/Polymyxin B Sulfate Combination Ophthalmic Solution as a Positive Control, in Infants, from Birth to 31 Days of Age, with Bacterial Conjunctivitis.

Study Initiation Date: 14 August 2001

Study Completion Date: 25 July 2002.

The study was undertaken at 14 US sites, 2 Mexican sites, and 2 Brazilian sites.

Methods

Infants from birth to 31 days of age with a clinical diagnosis of bacterial conjunctivitis or blepharconjunctivitis were enrolled. Patients were randomized to treatment groups in a 2:1 ratio (OCUFLOX[®] : POLYTRIM[®]) in a block size of 3. They were seen at baseline (day 0) day 3, and day 7.

Study drugs:

OCUFLOX[®] : Topical Ofloxacin 0.3% Ophthalmic Solution.

POLYTRIM[®] : Topical Trimethoprim Sulfate/Polymyxin B Sulfate Combination Ophthalmic Solution.

Dosing: For both study drugs, the dosing was as follows: For the first 48 hours, 1 drop every 2-4 hours, in each affected eye per 24-hour period, for no more than 8 doses. For the remaining 5 days of treatment, 1 drop QID per affected eye. The total duration of treatment was 7 days.

Results

The study populations were as follows:

	OCUFLOX	POLYTRIM	Total
Enrolled	119	54	173
Safety Population (SP) (a)	119	54	173
Modified Intent-To-Treat Population (MITTP) (b)	93	42	135
Per Protocol Population (PPP) (c)	81	41	122

(a): SP includes all patients who received the study medication.

(b) MITTP includes all randomized patients who were culture positive at baseline.

(c): PPP includes all randomized patients who were culture positive at baseline with no major protocol violations.

In the MITTP the success rate was 60.2% (56/93) in the OCUFLOX group and 47.6% (20/42) in the POLYTRIM group. In the PPP the success rate was 58.0% (47/81) in the OCUFLOX group and 46.3% (19/41) in the POLYTRIM group.

The MAH has provided a tabel (14.5-4.1), consisting of 43 sub-tables (each corresponding to one microbial species) showing microbial improvement in the MITTP. For each medication group the amount

of bacterial growth is shown at baseline (Grade +1, grade +2, and grade +3) and at day 7 (Grade 0, grade +1, grade +2, and grade +3). Microbial improvement was defined as bacterial eradication (grade 0) or a reduction of at least 1 grade from the baseline for the particular bacterial species. A similar set of sub-tables are presented for the PPP.

In addition the MAH has presented a summary of the susceptibility at baseline and day 7 of the microbial strains against the study drugs, as well as levofloxacin. However, this information is not stratified by clinical or microbial response.

Rapporteur's comments

1. Considering the fact that many cases of conjunctivitis, whether viral or bacterial, resolve spontaneously, one may doubt the clinical relevance of these efficacy findings in a study which did not include a placebo group and did not include viral diagnostics.

*2. This becomes particularly relevant when trying to interpret the presented results from this study. First of all, among the 43 microbial species (included a yeast strain: *Candida guilliermondii*) isolated in this study, the majority belongs to commensal flora of the skin, the oropharynx, or the nasopharynx, or even the intestine (e.g, *Enterobacter cloacae*, *Enterococcus faecalis*, *Escherichia coli*, etc.). One may seriously doubt a primary aetiological significance of these organisms, especially in the absence of virological diagnostic investigations.*

3. Furthermore, there is no information about the relationship between bacterial susceptibility to the study drugs and clinical or microbial response.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

II.3.3 Clinical safety

Patient exposure

Mean duration of exposure was 6.8 (\pm 1.40) days for the OCUFLOX[®] group and 6.9 (\pm 1.03) for the POLYTRIM[®] group. The minimum treatment duration was 1 day and the maximum treatment duration was 9 days, with the median being 7 days of treatment for both groups.

Adverse events

In the submitted study one or more adverse event (AE) was reported in 13.4% of patients treated with ofloxacin and 13.0% of patients given the comparator drug. The difference was not statistically significant and all AEs were considered not related to the study treatments.

Serious adverse events and deaths

In the submitted study there was one serious adverse event, a case of bronchitis in a child given ofloxacin ophthalmic solution, which had an uneventful course and was considered to have a non-causal relationship to the treatment. There was no deaths.

Laboratory findings

In the submitted study, no laboratory evaluation was done.

Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition

The submitted study did not include any long-term evaluation.

Co-rapporteur's comments:

Although no safety concerns have been raised during the study yet the formulation contains benzalkonium chloride which itself has a toxicity profile of which the applicant has not made any mention.

II.4 SPC

The MAH proposes the following to be added to **Section 5.1 Pharmacodynamic Properties**:

"Limited data (N = 173) are available from a double-masked comparative study of use of Exocin in neonates from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop up to 8 times daily were used for the first 2 days with four times daily dosing for 5 days thereafter. Cure rates in culture-positive patients of up to 60% were observed. No safety concerns were raised."

Rapporteur's comments:

- 1. The name of the comparator agent should be given.*
- 2. The wording of dosing for the first two days as stated in the proposal to the SmPC does not quite reflect the conditions of the study, as worded in the study report: "For the first 48 hours, 1 drop every 2-4 hours, in each affected eye per 24-hour period, for no more than 8 doses".*
- 3. The term "cure rate" should be extended to include data on clinical improvement as well as bacterial eradication (for OCUFLOX as well as POLYTRIM).*
- 4. Comparative efficacy data should be given for the most prevalent bacterial species.*
- 5. It is premature to comment in detail on the Danish SmPC apart from noting that it will need rewriting.*

RAPPORTEUR'S OVERALL CONCLUSION (PPdAR)

The Rapporteur considers that clinical efficacy has not been proven. The efficacy data as presented in the current study report are difficult to interpret, and they are not convincing. A majority of the microbial species are not considered primary pathogens in bacterial conjunctivitis. The lack of cross-tabulations of efficacy against bacterial susceptibility makes it difficult to assess whether the favourable clinical and microbial responses were actually caused by the antimicrobial treatment or if they were merely the natural history of the disease.

CO-RAPPORTEUR'S OVERALL CONCLUSION (PPdAR)

The applicant's submission of use of ofloxacin ophthalmic solution in the treatment of bacterial conjunctivitis in infants from birth to 31 days of age has not been approved as the formulation contains the excipient benzalkonium chloride which has a toxicity profile affecting the tear film which cannot be ruled out and of which the applicant has made no mention at all. Although the study documents no safety concerns yet this particular aspect of benzalkonium chloride seems to be totally neglected by the applicant. The efficacy results of 60.2% are not sufficient to establish the efficacy of the product. The information on the excipient benzalkonium chloride which has a toxicity profile particularly attacking the tear film is missing. The applicant needs to provide publications and also toxicity data on the safety profile of the excipient.

ASSESSMENT OF REQUESTED SUPPLEMENTARY INFORMATION (JAR)

In response to the preliminary assessment reports (PPdAR) by the Rapporteur (Denmark) and the Co-rapporteur (Hungary), by day 85 additional comments were received from the Concerned Member States.

The MAH responded to the questions raised by the Rapporteur, Co-rapporteur and Concerned Member States on 15th December 2006 and submitted a new proposal for the SPC. The comments are given in the order the MAH has presented them in their response.

Issue 1, Recommendation (Rapporteur)

Based on the review of the paediatric data on safety and efficacy, the Rapporteur considers that the variation application for OCUFLOX (EXOCIN) (ofloxacin), in the treatment of bacterial conjunctivitis for the following proposed changes: to extend the indication to neonates from birth up to 31 days could be approvable provided that a satisfactory answer is given to the “other concerns” as detailed in section V.2 and that the MAH considers recommended changes for inclusion in the SPC see section VI.

Allergan response:

Allergan acknowledges the Rapporteur’s recommendation but would like to clarify that no indication extension is being requested for use of OCUFLOX/EXOCIN in neonates. However, since this preparation is at times used off-license in neonates, it is proposed to share the data available in this population by including information in section 5.1 of the Summary of Product Characteristics (SmPC). This section of the SmPC has been updated to include the observations made by the Rapporteur and Co-Rapporteur as well as the Concerned Member States.

Rapporteur’s comment:

*It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates.
Issue resolved.*

Issue 2, Clinical efficacy (Rapporteur)

The Rapporteur considers that clinical efficacy has not been proven. The efficacy data as presented in the current study report are difficult to interpret, and they are not convincing. A majority of the microbial species are not considered primary pathogens in bacterial conjunctivitis. The lack of cross-tabulations of efficacy against bacterial susceptibility makes it difficult to assess whether the favourable clinical and microbial responses were actually caused by the antimicrobial treatment or if they were merely the natural history of the disease.

Allergan response:

We take note of the feedback of the Rapporteur with respect to the limitations of the study results. As noted above, Allergan would like to clarify that an indication extension to use in neonates is not being requested. However, it is intended to share the available information in this population section 5.1. of the SmPC and this section has been updated in line with all questions and recommendations received.

Issue 3, Conditions for approval (Rapporteur)

Supplementary analyses should be provided by the MAH to document clinical efficacy. For example, the relationship between the susceptibility of the isolated bacterial strains to the study drugs and the clinical response as well as the bacterial improvement should be tabulated.

Allergan response:

We take note of the Rapporteur's feedback. It is understood that these additional analyses should be provided if an indication extension was being applied for. However as it is not our intention to ask for an indication extension, these supplementary analyses have not been performed.

Rapporteur's comment:

Allergan has not provided a table showing the relation between bacteriological and clinical response and ofloxacin susceptibility of the bacterial species.

However, it is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. In case this will be requested in the future, the suggested analysis will of course be warranted.

Issue resolved.

Issue 4, SPC (Rapporteur):

The MAH proposes the following to be added to Section 5.1. Pharmacodynamic Properties: **“Limited data (N=173) are available from a double-masked comparative study of use of Exocin in neonates from birth up to 31 days in the treatment of bacterial conjunctivities. Doses of 1 drop up to 8 times daily were used for the first 2 days with four times daily dosing for 5 days thereafter. Cure rates in culture-positive patients of up to 60% were observed. No safety concerns were raised.”**

Assessor's comments:

- 1. The name of the comparator agent should be given.**
- 2. The wording of dosing for the first two days as stated in the proposal to the SmPC does not quite reflect the conditions of the study, as worded in the study report: "For the first 48 hours, 1 drop every 2-4 hours, in each affected eye per 24-hour period, for no more than 8 doses".**
- 3. The term "cure rate" should be extended to include data on clinical improvement as well as bacterial eradication (for OCUFLOX as well as POLYTRIM).**
- 4. Comparative efficacy data should be given for the most prevalent bacterial species.**
- 5. It is premature to comment in detail on the Danish SmPC apart from noting that it will need rewriting.**

Allergan response:

➤ Allergan acknowledges the Rapporteur's recommendations and has accordingly updated the proposed wording in section 5.1. of the SmPC as follows:

1. The name of the comparator has been added. The SmPC proposal now reads: **“Limited data (N = 173) are available from a double-masked comparative study of *the* use of Exocin *versus trimethoprim sulfate and Polymixin B sulphate combination* in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis.”**

2. The wording of the dosing for the first two days has been updated to reflect the conditions as described in the study report. The SmPC proposal now reads: **“Doses of 1 drop *every 2-4 hours* (up to 8 times daily) *in each affected eye* were used for the first 2 days with four times daily dosing for 5 days thereafter.”**

3. The term “cure rate” which describes clinical improvement defined as ‘resolution of both conjunctival erythema and conjunctival discharge at day 7’ is provided for both products. Furthermore, data on bacterial eradication have been added.

The SmPC proposal now reads: **“Cure rates (*resolution of both conjunctival erythema and conjunctival discharge at day 7*) in culture-positive patients of up to 60% were observed *and 47.6% with the comparator. Complete microbial eradication was seen in 55.4% of patients treated with Exocin (50% with comparator).*”**

Tables 11.4.1.1 and 11.4.1.2.1 from the 190442-005 clinical study report supporting these statements are provided hereafter.

Table 11.4.1.1 Clinical Cure: Number (%) of Patients at Day 7 (Modified-Intent-to-Treat Population)

	OCUFLOX [®] N = 93 n (%)	POLYTRIM [®] N = 42 n (%)
Clinical Cure ^a		
Success	56 (60.2%)	20 (47.6%)
Failure	37 (39.8%)	22 (52.4%)
95% CI for success rate	(0.503, 0.702)	(0.325, 0.627)

Source: Table 14.2-1.1.

a Clinical cure "success" is defined as a score of "none" in both conjunctival erythema and discharge at day 7 and "failure" otherwise. Analysis based on the study eye.

Table 11.4.1.2.1 Microbial Improvement: Number (%) of Patients at Day 7 (Modified-Intent-to-Treat Population)

Timepoint	Bacterial grade	OCUFLOX [®] N = 93 n (%)	POLYTRIM [®] N = 42 n (%)
Baseline ^a	n	92 ^b	42
	Grade +1	2 (2.2%)	1 (2.4%)
	Grade +2	32 (34.8%)	21 (50.0%)
	Grade +3	58 (63.0%)	20 (47.6%)
Day 7 ^a	n	92 ^b	42
	Grade 0	51 (55.4%)	21 (50.0%)
	Grade +1	8 (8.7%)	5 (11.9%)
	Grade +2	21 (22.8%)	8 (19.0%)
	Grade +3	12 (13.0%)	8 (19.0%)
Microbial Improvement ^c	n	93 ^b	42
	Improvement	68 (73.1%)	27 (64.3%)
	No improvement	25 (26.9%)	15 (35.7%)

Source: Table 14.2-2.1

NOTE: Analysis is based on the study eye. For multiple species, the worst grade is used for each patient. Last observation carried forward was used for missing grade at day 7.

- a Bacterial colony grade for each patient is the worst (highest) grade across all species of the patient.
- b One patient was culture positive (not graded) due to chlamydia. This patient was not included in the analysis of microbial grade but was included in the microbial improvement analysis.
- c Microbial improvement is indicated by eradicated (grade 0) or reduced (decrease of at least 1 grade) from baseline across all species present at baseline.

4. Comparative efficacy data have been given for the most prevalent bacterial species (*Staphylococcus epidermidis*). The SmPC proposal now reads: “ ... ***The most prevalent bacterial species was *Staphylococcus epidermidis*. Microbial improvement in this species, defined as bacterial eradication or reduction by at least 1 grade, was seen in 62.5% with Exocin and 64.5% with comparator.***”

This text is based upon the data presented in Table 14.5-4.1 from the Clinical Study report shown below (study 190442-005), where ‘microbial improvement’ was defined as bacterial eradication (grade 0) or reduction (decrease by at least 1 grade) from baseline.

Table 14.5-4.1 (Page 27 of 43)
Microbial Improvement: Number (Percent) of Patients at Day 7 by Species
(Modified Intent-to-Treat Population)

Species			OCUFLOX (N=93)	POLYTRIM (N=42)
<i>Staphylococcus epidermidis</i>	Baseline	Bacterial Colony Grade		
		N	48	31
		Grade +1	10 (20.8%)	5 (16.1%)
		Grade +2	23 (47.9%)	22 (71.0%)
		Grade +3	15 (31.3%)	4 (12.9%)
	Day 7	Bacterial Colony Grade		
		N	27	16
		Grade 0	0 (0.0%)	0 (0.0%)
		Grade +1	7 (25.9%)	4 (25.0%)
		Grade +2	17 (63.0%)	8 (50.0%)
		Grade +3	3 (11.1%)	4 (25.0%)
		Microbial Improvement [a]		
		N	48	31
		Improvement	30 (62.5%)	20 (64.5%)
	No Improvement	18 (37.5%)	11 (35.5%)	

5. At this stage of the procedure, we are proposing a EU harmonised wording for section 5.1 of the SmPC.

It will be noted that, in addition to updates proposed by the Rapporteur, the revised text also contains a number of changes resulting from the assessments of the other Concerned Member States.

➤ The proposed revised SmPC (Section 5.1.) now reads as follows:

“5.1 Pharmacodynamic Properties

Limited data (N = 173) are available from a double-masked comparative study of ***the*** use of Exocin ***versus trimethoprim sulfate and Polymixin B sulphate combination*** in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop ***every 2-4 hours*** (up to 8 times daily) ***in each affected eye*** were used for the first 2 days with four times daily dosing for 5 days thereafter.

Cure rates (***resolution of both conjunctival erythema and conjunctival discharge at day 7***) in culture-positive patients of up to 60% were observed ***and 47.6% with the comparator. Complete microbial eradication was seen in 55.4% of patients treated with Exocin (50% with comparator). The most prevalent bacterial species was *Staphylococcus epidermidis*. Microbial improvement in this species, defined as bacterial eradication or reduction by at least 1 grade, was seen in 62.5% with Exocin and 64.5% with comparator.***

The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.

No safety concerns were raised ***with Exocin. Notably, no deterioration in corneal appearance was observed throughout the 7-day treatment period.***

Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus.”

Rapporteur's comment:

The changes proposed by the Applicant are acknowledged except for the following:

- 1. "Bacterial Colony Grade" has not been defined.*
- 2. The following section "Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus" should be changed and amended to: "Topical antimicrobial treatment is not indicated for eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae. Current guidelines indicate that systemic antimicrobial treatment is necessary in patients with eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae".*
- 3. The applicant has not included in the response the fact that they have added a tabulation of efficacy against various bacterial species, as requested by the Rapporteur. However, this table has actually been provided as part of the response to questions put forward by the UK.*
- 4. The clinical significance of Staphylococcus epidermidis is highly questionable.*

Issue 5, Recommendation (Co-rapporteur):

Based on the review of the paediatric data on safety and efficacy, the Co-Rapporteur considers that the variation application for Ofloxacin Ophthalmic solution 0.3%, in the treatment of bacterial conjunctivitis in neonates aged from 0 to 31 days, for the following proposed changes <scope of variation> cannot be approved because of the toxicity of the excipient benzalkonium chloride affecting the tear film and corneal epithelial barrier function of which the applicant has made no mention at all. The other reason for the approval not being granted is the efficacy studies do not show statistically significant difference from the comparator.

Allergan Response:

Allergan acknowledges the Co-Rapporteur's recommendation but would like to clarify that no indication extension is being requested for use of OCUFLOX/EXOCIN in neonates. However, since this preparation is at times used off-license in neonates, it is proposed to share the data available in this population by including information in section 5.1 of the Summary of Product Characteristics (SmPC). This section of the SmPC has been updated to include the observations made by the Co-Rapporteur and Rapporteur as well as the Concerned Member States.

Specifically, in response to the concern raised by the Co-Rapporteur, UK and Ireland, a review of available data pertaining to corneal appearance and histology has been carried out. A toxicology study (90-3608) in 36 neonate male and female Beagle dogs (six/sex/dose) has been performed (see Abstract in appendix 1)

Neonate dogs (3 months of age at initiation of dosing) were given 0, 0.3%, 0.5% or 1% ofloxacin topically (ocular), 4 times daily for one month. Gross ocular observations (weekly), ophthalmological examinations including fluorescein staining (for evaluation of corneal toxicity) at the end of treatment and recovery periods and histopathological evaluations of the ocular tissues revealed no significant drug-related effects. Each of the formulations tested in this study contained 0.005% BAK concentration, being the same concentration as is found in the formulation used in clinical practice.

Furthermore, examination of the ocular surface during the clinical study 190442-005 was performed. Ocular examinations were conducted at baseline (day 0), day 3, and day 7 to determine the conditions of the conjunctiva, lids, and cornea. The worst-case reading was recorded at each study visit for each variable. The corneal assessments were made according to the following ratings:

Condition of Cornea:

The investigator used a 2-point scale to evaluate corneal appearance:

- Normal (0) = normal, transparent, and clear
- Abnormal (+1) = abnormal, not transparent and clear

The results did not suggest that there was deterioration in the appearance of the corneal surface. Therefore, the ocular response (no drug-related ocular irritation or corneal toxicity) in neonate dogs to ofloxacin is similar to that of the response of infants given 0.3% Ocuflax.

In order to allow the prescriber to make a fully informed decision should he consider prescribing ofloxacin in this patient population, it is proposed to provide this information in Section 5.1 of the SmPC As follows: “ No safety concerns were raised *with Exocin. Notably, no deterioration in corneal appearance was observed throughout the 7-day treatment period.*”

Rapporteur’s comment:

The response is accepted. The Applicant made studies in which neonate dogs were given ofloxacin eyedrops in each eye four times daily for a month, i.e. far longer than the intended treatment period in humans. The study formulation contained the same concentration (0.005%) of benzalkonium chloride as the preparation intended for use in humans. Observations in humans did not reveal corneal damage. The Applicant notes in the SmPC that efficacy has not been proven. Issue resolved.

Issue 6, Request for supplementary information, Major objections (Co-rapporteur):

The major objections include the toxicity profile of benzalkonium chloride regarding which the applicant needs to submit tox data. The efficacy results of 60.2 % are not sufficient to establish the efficacy of the product.

Allergan Response:

Safety concern:

A non-clinical toxicology study (90-3608) was performed in 36 neonate male and female Beagle dogs (six/sex/dose) (see Abstract in appendix 1). The dogs were 3 months of age at initiation of dosing and were given 0, 0.3%, 0.5% or 1% ofloxacin topically (ocular), 4 times daily for one month. Each of the formulations tested in this study contained 0.005% BAK concentration, being the same concentration as is found in the formulation used in clinical practice.

The solution was instilled into the lower conjunctival sac of the left eye and the right eye served as the untreated control. The animals were dosed four times a day for one month followed by a one month recovery.

Careful weekly ocular examinations were conducted during the dosing phase. At the end of one month on test, four dogs from each group were euthanized. Thereafter, one animal per sex per group was sacrificed on each day of the scheduled necropsy timetable. Two dogs per sex per group were maintained for one month recovery and euthanized at the end of this period.

The assessments showed only minimal conjunctival irritation either unilaterally or bilaterally in both the control and treated animals. A similar incidence of these findings was observed during the pre-test, treatment and recovery phases of the study. The observations were not considered treatment related since they were seen in all doses groups before the treatment as well as during the recovery phase.

It is of note that there were no iritis or corneal observations at any time during the study.

At autopsy there were no microscopic abnormalities in any organs or tissues examined that could be attributed to the ocular exposure of the animals to the test compound ofloxacin.

The reassuring results from the non-clinical study were reproduced in the clinical setting of study 190442-005. The study revealed that at baseline, corneal appearance was rated as normal in 97.5% (116/119) of patients treated with OCUFLOX and 96.3% (52/54) of patients treated with POLYTRIM.

At day 3, corneal appearance was rated as normal in 100.0% (113/113) of patients treated with OCUFLOX and 96.2% (51/53) of patients treated with POLYTRIM. Although 6 patients treated with OCUFLOX discontinued study treatment between baseline and day 3, all 3 patients who had abnormal corneal appearance at baseline remained in the study and had normal corneal appearance by day 3. By day 7, corneal appearance continued to be normal in 100.0% (113/113) of patients treated with

OCUFLOX and 98.1% (51/52) of patients treated with POLYTRIM. The differences between the groups were not statistically significant ($p > 0.101$).

Efficacy concern:

In line with the observation that efficacy results of 60.2 % are not considered sufficient to establish the efficacy of the product, the following text is proposed in Section 5.1 of the SmPC: ***“The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.”***

Rapporteur’s comment:

The response is accepted. The Applicant made studies in which neonate dogs were given ofloxacin eyedrops in each eye four times daily for a month, i.e. far longer than the intended treatment period in humans. The study formulation contained the same concentration (0.005%) of benzalkonium chloride as the preparation intended for use in humans. Observations in humans did not reveal corneal damage. The Applicant notes in the SmPC that efficacy has not been proven.

Co-rapporteur’s comment:

The response given to our objections about benzalkonium chloride requires more clarifications.

We propose to include the following sentence to the SmPC Section 4.8. and 5.3.:

“The eye drops contains benzalkonium chloride, as preservative material.

In the scientific literature emerged that benzalkonium chloride has adverse effects affecting the tear film and corneal epithelial barrier function.

A toxicology study (90-3608) in 36 neonate male and female Beagle dogs (six/sex/dose), and examination of the ocular surface during the clinical study 190442-005 was performed by Allergan. No deterioration in corneal appearance was observed throughout the 7-day treatment period.”

Issue 7, Conditions for the approval (Co-rapporteur):

The applicant’s submission can be accepted only when the applicant has submitted the tox data on benzalkonium chloride. The applicant also needs to provide some publications on the excipient which particularly has a toxicity profile attacking the tear film.

Allergan Response:

The relevant toxicology data have been summarised above. However, it must be re-iterated that Allergan has not applied for an indication extension in neonates and only wishes to update the Pharmacodynamics section of the Summary of Product Characteristics.

Rapporteur’s comment:

It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. Furthermore, animal studies and human observations did not indicate corneal damage.

Issue resolved.

Issue 8, SPC (Co-rapporteur):

Section 5.1: Limited data (N=173) are available from a double masked comparative study of use of Exocin in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop up to 8 times daily being used for the first 2 days followed by four times daily dosing for 5 days thereafter. Cure rates in culture positive patients of up to 60% were observed. No safety concerns were raised.

Comments: Cure rates of only 60% not enough to establish the efficacy of the product.

Allergan Response:

➤ In light of the comments from the Co-Rapporteur, the text of Section 5.1 of the SmPC has been updated.

It will be noted that, in addition to updates proposed by the Co-Rapporteur, the revised text also contains a number of changes resulting from the assessments of the Rapporteur and other Concerned Member States.

➤ The proposed revised SmPC (Section 5.1.) now reads as follow.

“5.1 Pharmacodynamic Properties

Limited data (N = 173) are available from a double-masked comparative study of *the* use of Exocin *versus trimethoprim sulfate and Polymixin B sulphate combination* in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop *every 2-4 hours* (up to 8 times daily) *in each affected eye* were used for the first 2 days with four times daily dosing for 5 days thereafter.

Cure rates (*resolution of both conjunctival erythema and conjunctival discharge at day 7*) in culture-positive patients of up to 60% were observed *and 47.6% with the comparator. Complete microbial eradication was seen in 55.4% of patients treated with Exocin (50% with comparator). The most prevalent bacterial species was Staphylococcus epidermidis. Microbial improvement in this species, defined as bacterial eradication or reduction by at least 1 grade, was seen in 62.5% with Exocin and 64.5% with comparator.*

The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.

No safety concerns were raised *with Exocin. Notably, no deterioration in corneal appearance was observed throughout the 7-day treatment period.*

Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus.”

Rapporteur’s comment:

It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates.

Co-rapporteur’s comment:

We endorse the changes performed in the SmPC mentioning the following subjects:

- No therapeutic indication or dosing instructions pertaining to the neonatal population will be provided in Section 4.1 and 4.2 of the Summary of Product Characteristics.

- Since this preparation is at times used off-license in neonates, it is proposed to share the data available in this population by including information in section 5.1 of the Summary of Product Characteristics (SmPC)

Issue resolved.

Issue 9, Clinical efficacy (CMS):

Efficacy has not adequately demonstrated in the single trial presented, to allow an indication to be included in the SPC for use in neonates with bacterial conjunctivitis. There are doubts about the appropriateness of the comparator used and, in addition, the cure rate observed with Exocin appears to be too low to be of clinical usefulness.

Allergan Response:

Allergan acknowledges the comments from the assessor but would like to clarify that no indication extension is being requested for use of OCUFLOX/EXOCIN in neonates. However, since this preparation is at times used off-license in neonates, it is proposed to share the data available in this population by including information in section 5.1 of the Summary of Product Characteristics (SmPC). This section of the SmPC has been updated to include the cure rate incidence of both ofloxacin as well as the comparator product.

Study 190442-005 was conducted in the United States, Mexico and Brazil in 2002. The trimethoprim sulfate and Polymixin B sulphate combination was chosen as the comparator because it was the most common antibiotic used for paediatric patients at the time. Although no topical antibiotic was and still is not indicated for neonatal conjunctivitis (0-31 days), Polytrim is indicated for paediatric patients as young as 2 months old in the United States. Since the combination gives excellent coverage for organisms generally found responsible for paediatric conjunctivitis and has also been shown to be extremely safe, it was considered the most appropriate comparator for this study.

It is judged that should a prescriber consider use of ofloxacin in this patient population, the proposed updating of Section 5.1 of the SmPC will allow this decision to be made in a fully informed manner.

Rapporteur's comment:

*It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. Furthermore, Allergan has noted in the SmPC that efficacy has not been proven. In the possible event that Allergan in the future should apply for an indication extension for use in neonates, the data from the POLYTRIM study are quite insufficient to demonstrate efficacy:
Issue resolved.*

Issue 10, Clinical efficacy (CMS)

Further analysis, in respect of a tabulation of efficacy against isolated bacterial strains in the study should be provided.

Allergan Response:

Table 11.4.1.2.2 hereafter, extracted from the Clinical Study Report, lists the incidence of microbial improvement (eradication or reduction by at least one grade from baseline) for the most prevalent bacterial strains. Since the purpose of this variation is not to apply for an indication for use in neonates with bacterial conjunctivitis to be included in the SPC, it is considered that these results are of academic interest only.

Table 11.4.1.2.2 Microbial Improvement: Number (%) of Patients at Day 7 Based on Bacterial Species Present at Day 0 in Either Treatment Group (Modified-Intent-to-Treat Population)

Bacterial Species	Microbial Improvement ^a	OCUFLOX [®] N = 93 n (%)	POLYTRIM [®] N = 42 n (%)
<i>Staphylococcus aureus</i>			
	n	16	7
	Improvement	13 (81.3%)	6 (85.7%)
	No improvement	3 (18.8%)	1 (14.3%)
<i>Staphylococcus epidermidis</i>			
	n	48	31
	Improvement	30 (62.5%)	20 (64.5%)
	No improvement	18 (37.5%)	11 (35.5%)
<i>Streptococcus mitis</i>			
	n	16	9
	Improvement	15 (93.8%)	8 (88.9%)
	No improvement	1 (6.3%)	1 (11.1%)
<i>Streptococcus oralis</i>			
	n	16	6
	Improvement	16 (100.0%)	4 (66.7%)
	No improvement	0 (0.0%)	2 (33.3%)

Source: Table 14.5-4.1.

NOTE: Analysis is based on the study eye. For multiple species, the worst grade is used for each patient. Last observation carried forward was used for missing grade at day 7.

a Microbial improvement defined as eradicated (grade 0) or reduced (decrease of at least 1 grade) from baseline.

Rapporteur’s comment:

The clinical significance of the oral commensal flora (Streptococcus mitis and Streptococcus oralis), as well as Staphylococcus epidermidis is highly questionable. In fact, only the figures for Staphylococcus aureus are of interest. Moreover, the differences in improvement rate between the two regimens are not statistically significant. Thus, although this table of data do not add to the confidence in the efficacy of OCUFLOX/EXOCIN, it is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. Issue resolved.

Issue 11, Clinical safety (CMS):

Further data leading to reassurance is required regarding the safety of the dose of the preservative benzalkonium chloride contained in the product, with respect to its effect upon the corneal epithelium in neonates (i.e those aged 0-31 days).

Allergan Response:

In order to address the question from the assessor the data available from both the non-clinical and clinical studies have been reviewed focusing on ocular safety.

A non-clinical toxicology study (90-3608) was performed in 36 neonate male and female Beagle dogs (six/sex/dose) (see Abstract in appendix 1). The dogs were 3 months of age at initiation of dosing and were given 0, 0.3%, 0.5% or 1% ofloxacin topically (ocular), 4 times daily for one month. Each of the

formulations tested in this study contained 0.005% BAK concentration, being the same concentration as is found in the formulation used in clinical practice.

The solution was instilled into the lower conjunctival sac of the left eye and the right eye served as the untreated control. The animals were dosed four times a day for one month followed by a one month recovery.

Careful weekly ocular examinations were conducted during the dosing phase. At the end of one month on test, four dogs from each group were euthanized. Thereafter, one animal per sex per group was sacrificed on each day of the scheduled necropsy timetable. Two dogs per sex per group were maintained for one month recovery and euthanized at the end of this period.

The assessments showed only minimal conjunctival irritation either unilaterally or bilaterally in both the control and treated animals. A similar incidence of these findings was observed during the pre-test, treatment and recovery phases of the study. The observations were not considered treatment related since they were seen in all doses groups before the treatment as well as during the recovery phase.

It is of note that there were no iritis or corneal observations at any time during the study.

At autopsy there were no microscopic abnormalities in any organs or tissues examined that could be attributed to the ocular exposure of the animals to the test compound ofloxacin.

The reassuring results from the non-clinical study were reproduced in the clinical setting of study 190442-005. The study revealed that at baseline, corneal appearance was rated as normal in 97.5% (116/119) of patients treated with OCUFLOX and 96.3% (52/54) of patients treated with POLYTRIM.

At day 3, corneal appearance was rated as normal in 100.0% (113/113) of patients treated with OCUFLOX and 96.2% (51/53) of patients treated with POLYTRIM. Although 6 patients treated with OCUFLOX discontinued study treatment between baseline and day 3, all 3 patients who had abnormal corneal appearance at baseline remained in the study and had normal corneal appearance by day 3. By day 7, corneal appearance continued to be normal in 100.0% (113/113) of patients treated with OCUFLOX and 98.1% (51/52) of patients treated with POLYTRIM. The differences between the groups were not statistically significant ($p > 0.101$).

Based upon these results, it can be concluded that there is no adverse effect upon the corneal epithelium in neonates following use of Exocin for up to 7 days. This is reflected in the update to Section 5.1 of the SmPC.

Rapporteur's comment:

*The response is accepted. The Applicant made studies in which neonate dogs were given ofloxacin eyedrops in each eye four times daily for a month, i.e. far longer than the intended treatment period in humans. The study formulation contained the same concentration (0.005%) of benzalkonium chloride as the preparation intended for use in humans. Observations in humans did not reveal corneal damage
Issue resolved.*

Issue 12, SPC (CMS):

The statements proposed by the MAH in Section 5.1 of the SPC should be amended in line with the Rapporteur's comments.

In addition, we propose that a statement should be included in Section 5.1 of the SPC to inform prescribers that in neonates with eye infection caused by chlamydia or the gonococcus, that current guidelines indicate that systemic antimicrobial treatment is necessary.

In addition, we propose that a statement should be included in Section 4.2 of the SPC to state that in neonates (aged 0-31 days) with bacterial conjunctivitis, data are limited and that efficacy has not been demonstrated.

Allergan Response:

All requests made by the Rapporteur and the CMS have been incorporated into the updated text of Section 5.1 of the SmPC as proposed below. The update also includes recommendations made by the Co-Rapporteur and the other Concerned Member States. It is proposed that this section mentions the availability of limited data in neonates and the fact that efficacy has not been demonstrated.

Furthermore, in line with the European Commission Guideline on Summary of Product Characteristics (October 2005), section 4.2 will also be updated to add: "Experience of use of Exocin in the treatment of ophthalmia neonatorum is limited (see Section 5.1)".

The proposed revised SmPC (Section 5.1) therefore now reads:

"5.1 Pharmacodynamic Properties

Limited data (N = 173) are available from a double-masked comparative study of *the* use of Exocin *versus trimethoprim sulfate and Polymixin B sulphate combination* in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop *every 2-4 hours* (up to 8 times daily) *in each affected eye* were used for the first 2 days with four times daily dosing for 5 days thereafter.

Cure rates (*resolution of both conjunctival erythema and conjunctival discharge at day 7*) in culture-positive patients of up to 60% were observed *and 47.6% with the comparator. Complete microbial eradication was seen in 55.4% of patients treated with Exocin (50% with comparator). The most prevalent bacterial species was Staphylococcus epidermidis. Microbial improvement in this species, defined as bacterial eradication or reduction by at least 1 grade, was seen in 62.5% with Exocin and 64.5% with comparator.*

The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.

No safety concerns were raised *with Exocin. Notably, no deterioration in corneal appearance was observed throughout the 7-day treatment period.*

Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus."

Rapporteur's comment:

The changes proposed by the Applicant are acknowledged except for the following:

- 1. "Bacterial Colony Grade" has not been defined.*
- 2. The following section "Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus" should be changed and amended to: "Topical antimicrobial treatment is not indicated for eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae. Current guidelines indicate that systemic antimicrobial treatment is necessary in patients with eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae".*
- 3. The applicant has not included in the response the fact that they have added a tabulation of efficacy against various bacterial species, as requested by the Rapporteur. However, this table has actually been provided as part of the response to questions put forward by the UK.*
- 4. The clinical significance of Staphylococcus epidermidis is highly questionable.*

Issue 13, Clinical efficacy / SPC (CMS):

With reference to the Rapporteur's Assessment Report dated Sep 29, 2006, we endorse the overall conclusion of the RMS, and agrees that, in overall, clinical efficacy has not been proven. No indication or dosing instruction can be given in Sections 4.1 and 4.2.

Allergan Response:

Allergan agrees that no indication or dosing instructions pertaining to the neonatal population should be provided in Section 4.1 and 4.2 of the Summary of Product Characteristics.

Rapporteur's comment:

Response accepted. It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates.

Issue resolved.

Issue 14, Clinical safety (CMS):

The MAH should clarify the issue in relation to corneal epithelium / eye safety for new born to 31 days old regarding the excipient benzalkalonim chloride.

Allergan Response:

In order to address the question from the assessor the data available from both the non-clinical and clinical studies have been reviewed focusing on ocular safety.

A non-clinical toxicology study (90-3608) was performed in 36 neonate male and female Beagle dogs (six per sex per dose) (see Abstract in appendix 1). The dogs were 3 months of age at initiation of dosing and were given 0, 0.3%, 0.5% or 1% ofloxacin topically (ocular), 4 times daily for one month. Each of the formulations tested in this study contained 0.005% BAK concentration, being the same concentration as is found in the formulation used in clinical practice.

The solution was instilled into the lower conjunctival sac of the left eye and the right eye served as the untreated control. The animals were dosed four times a day for one month followed by a one month recovery.

Careful weekly ocular examinations were conducted during the dosing phase. At the end of one month on test, four dogs from each group were euthanized. Thereafter, one animal per sex per group was sacrificed on each day of the scheduled necropsy timetable. Two dogs per sex per group were maintained for one month recovery and euthanized at the end of this period.

The assessments showed only minimal conjunctival irritation either unilaterally or bilaterally in both the control and treated animals. A similar incidence of these findings was observed during the pre-test, treatment and recovery phases of the study. The observations were not considered treatment related since they were seen in all doses groups before the treatment as well as during the recovery phase.

It is of note that there were no iritis or corneal observations at any time during the study.

At autopsy there were no microscopic abnormalities in any organs or tissues examined that could be attributed to the ocular exposure of the animals to the test compound ofloxacin.

The reassuring results from the non-clinical study were reproduced in the clinical setting of study 190442-005. The study revealed that at baseline, corneal appearance was rated as normal in 97.5% (116/119) of patients treated with OCUFLOX and 96.3% (52/54) of patients treated with POLYTRIM.

At day 3, corneal appearance was rated as normal in 100.0% (113/113) of patients treated with OCUFLOX and 96.2% (51/53) of patients treated with POLYTRIM. Although 6 patients treated with OCUFLOX discontinued study treatment between baseline and day 3, all 3 patients who had abnormal corneal appearance at baseline remained in the study and had normal corneal appearance by day 3. By day 7, corneal appearance continued to be normal in 100.0% (113/113) of patients treated with

OCUFLOX and 98.1% (51/52) of patients treated with POLYTRIM. The differences between the groups were not statistically significant ($p > 0.101$).

Based upon these results, it can be concluded that there is no adverse effect upon the corneal epithelium in neonates following use of Exocin for up to 7 days. This is reflected in the update to Section 5.1 of the SmPC.

Rapporteur's comment:

The response is accepted. The Applicant made studies in which neonate dogs were given ofloxacin eyedrops in each eye four times daily for a month, i.e. far longer than the intended treatment period in humans. The study formulation contained the same concentration (0.005%) of benzalkonium chloride as the preparation intended for use in humans. Observations in humans did not reveal corneal damage. Issue resolved.

Issue 15, Clinical efficacy (CMS):

The Applicant has compared Ofloxacin with Polytrim which is licensed for treatment of conjunctivitis and shown to be non inferior although both Ofloxacin and Polytrim had poor overall very poor clinical cure rates. The Applicant should justify the choice of comparator and why a more commonly used comparator or another intra ocular preparation with a higher cure rate was not chosen. It would seem the comparator chosen was insufficient. A clinical cure rate of 60 % is insufficient for the indication sought by the MAH.

Allergan Response:

Study 190442-005 was conducted in the United States, Mexico and Brazil in 2002. The trimethoprim sulfate and Polymixin B sulphate combination was chosen as the comparator because it was the most common antibiotic used for paediatric patients at the time. Although no topical antibiotic was and still is not indicated for neonatal conjunctivitis (0-31 days), Polytrim is indicated for paediatric patients as young as 2 months old in the United States. Since the combination gives excellent coverage for organisms generally found responsible for paediatric conjunctivitis and has also been shown to be extremely safe, it was considered the most appropriate comparator for this study.

Allergan acknowledges the comments of the assessor but would like to clarify that no indication extension is being requested for use of OCUFLOX/EXOCIN in neonates.

Rapporteur's comment:

The Rapporteur agrees with the CMS that a clinical cure rate is insufficient and that the comparator POLYTRIM is badly chosen. However, it is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. In case this will be requested in the future, more convincing data than those from the POLYTRIM study would be needed. Issue resolved.

Issue 16, Clinical efficacy (CMS):

We agree the current indication for treatment of children from birth to 31 days old is not approvable.

Allergan Response:

Allergan agrees with the comment of the assessor but would like to clarify that no indication extension is being requested for use of OCUFLOX/EXOCIN in neonates.

Rapporteur's comment:

It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. Issue resolved.

Issue 17, Clinical efficacy and safety (CMS):

The (Co-)Rapporteurs's recommendations cannot be entirely endorsed. We have the following additional comments:

- **The questions (Other Concerns) of the Rapporteur concerning efficacy in the evaluated condition are very relevant and the answers should be awaited before reaching definitive conclusion. We do not support the objection of Co-Rapporteur concerning efficacy. Superiority above the comparator is not a requirement for approval in tested infection. Furthermore, the MAH is not claiming an indication extension based on provided study, only a brief paragraph on this study is proposed to be added under section 5.1. See also our additional comment below concerning 5.1.**
- **The safety of the eye drops containing the excipient benzalkonium chloride could be of concern in neonates/infants, however, both approved products contain this preservative and have been used safely for years including young children although not as such documented in the neonates.**

Allergan Response:

With regard to efficacy, we acknowledge the comments from the assessor and would indeed like to confirm that no indication extension is being requested for use of OCUFLOX/EXOCIN in neonates.

Regarding the potential concern on the safety of the eye drops containing the excipient benzalkonium chloride in neonates/infants a review of available data pertaining to corneal appearance and histology has been carried out. A toxicology study (90-3608) in 36 neonate male and female Beagle dogs (six/sex/dose) has been performed (see Abstract in appendix 1)

Neonate dogs (3 months of age at initiation of dosing) were given 0, 0.3%, 0.5% or 1% ofloxacin topically (ocular), 4 times daily for one month. Gross ocular observations (weekly), ophthalmological examinations including fluorescein staining (for evaluation of corneal toxicity) at the end of treatment and recovery periods and histopathological evaluations of the ocular tissues revealed no significant drug-related effects. Each of the formulations tested in this study contained 0.005% BAK concentration, being the same concentration as is found in the formulation used in clinical practice.

Furthermore, examination of the ocular surface during the clinical study 190442-005 was performed. Ocular examinations were conducted at baseline (day 0), day 3, and day 7 to determine the conditions of the conjunctiva, lids, and cornea. The worst-case reading was recorded at each study visit for each variable. The corneal assessments were made according to the following ratings:

Condition of Cornea:

The investigator used a 2-point scale to evaluate corneal appearance:

- Normal (0) = normal, transparent, and clear
- Abnormal (+1) = abnormal, not transparent and clear

The results did not suggest that there was deterioration in the appearance of the corneal surface. Therefore, the ocular response (no drug-related ocular irritation or corneal toxicity) in neonate dogs to ofloxacin is similar to that of the response of infants given 0.3% Ocuflax.

This is in keeping with the observation made by The Netherlands (and France) that products containing the preservative benzalkonium chloride, at this concentration, have been used safely in similar populations.

Rapporteur's comment:

The response is accepted. The Applicant made studies in which neonate dogs were given ofloxacin eyedrops in each eye four times daily for a month, i.e. far longer than the intended treatment period in humans. The study formulation contained the same concentration (0.005%) of benzalkonium chloride as the preparation intended for use in humans. Observations in humans did not reveal corneal damage.

It is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates.

We agree with the CMS point of view, that "Superiority above the comparator is not a requirement for approval in tested infection". However, an efficacy of 60% would in any case be considered unacceptable. Issue resolved.

Issue 18, SPC (CMS):

Section 5.1 of the SPC

We endorse the proposed changes in the Variation by the Rapporteur.

We propose the addition of a concluding statement as follows “The results of this study are not sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum”.

Allergan Response:

The recommendations of the Rapporteur and those of the CMS have all been incorporated into the updated text of Section 5.1 of the SmPC, including the following sentence addition: ***“The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.”***

Furthermore, recommendations from the Co-Rapporteur and other Concerned Member States have also been included.

The proposed revised SmPC (Section 5.1.) now reads:

“5.1 Pharmacodynamic Properties

Limited data (N = 173) are available from a double-masked comparative study of ***the*** use of Exocin ***versus trimethoprim sulfate and Polymixin B sulphate combination*** in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop ***every 2-4 hours*** (up to 8 times daily) ***in each affected eye*** were used for the first 2 days with four times daily dosing for 5 days thereafter.

Cure rates (***resolution of both conjunctival erythema and conjunctival discharge at day 7***) in culture-positive patients of up to 60% were observed ***and 47.6% with the comparator. Complete microbial eradication was seen in 55.4% of patients treated with Exocin (50% with comparator). The most prevalent bacterial species was Staphylococcus epidermidis. Microbial improvement in this species, defined as bacterial eradication or reduction by at least 1 grade, was seen in 62.5% with Exocin and 64.5% with comparator.***

The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.

No safety concerns were raised ***with Exocin. Notably, no deterioration in corneal appearance was observed throughout the 7-day treatment period.***

Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus.”

Rapporteur’s comment:

The changes proposed by the Applicant are acknowledged except for the following:

- 1. "Bacterial Colony Grade" has not been defined.*
- 2. The following section "Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus" should be changed and amended to: "Topical antimicrobial treatment is not indicated for eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae. Current guidelines indicate that systemic antimicrobial treatment is necessary in patients with eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae".*
- 3. The applicant has not included in the response the fact that they have added a tabulation of efficacy against various bacterial species, as requested by the Rapporteur. However, this table has actually been provided as part of the response to questions put forward by the UK.*
- 4. The clinical significance of Staphylococcus epidermidis is highly questionable.*

Issue 19, Clinical efficacy / SPC (CMS):

The unique study available to support the mention “conjunctivitis” in the SPC suffers from significant limitations:

- we consider that the microbial documentation submitted in this study is not sufficient to validate a bacterial efficacy for OCUFLOX in neonates; an adequate microbial documentation from clinical data targeted on species in line with neonatal infections (Gonococcus, Chlamydia, Staphylococcus aureus, Haemophilus, Streptococcus pneumoniae) should be submitted;

Allergan Response:

We concur with the feedback of the assessor with respect to the limitations of the study results. However, we wish to draw attention to the fact it is not Allergan’s intention to apply for an indication for use in neonates with bacterial conjunctivitis. However, since this preparation is at times used off-license in neonates, it is proposed to share the data available in this population by including information in section 5.1 of the Summary of Product Characteristics (SmPC).

In particular this section will include the text: *The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.*

For interest the efficacy tables from the clinical study 190442-005 for Staphylococcus aureus, all Haemophilus strains and Streptococcus pneumoniae are provided.

Table 14.5-4.1 (Page 14 of 43)
Microbial Improvement: Number (Percent) of Patients at Day 7 by Species
(Modified Intent-to-Treat Population)

Species			OCUFLOX (N=93)	POLYTRIM (N=42)
Haemophilus haemolyticus	Baseline	Bacterial Colony Grade		
		N	1	0
		Grade +1	0 (0.0%)	0 (0.0%)
		Grade +2	0 (0.0%)	0 (0.0%)
		Grade +3	1 (100.0%)	0 (0.0%)
	Day 7	Bacterial Colony Grade		
		Grade 0	0 (0.0%)	0 (0.0%)
		Grade +1	0 (0.0%)	0 (0.0%)
		Grade +2	0 (0.0%)	0 (0.0%)
		Grade +3	0 (0.0%)	0 (0.0%)
		Microbial Improvement [a]		
		N	1	0
	Improvement	1 (100.0%)	0 (0.0%)	
No Improvement	0 (0.0%)	0 (0.0%)		

Table 14.5-4.1 (Page 15 of 43)
Microbial Improvement: Number (Percent) of Patients at Day 7 by Species
(Modified Intent-to-Treat Population)

Species			OCUFLOX (N=93)	POLYTRIM (N=42)
Haemophilus influenzae	Baseline	Bacterial Colony Grade		
		N	4	3
		Grade +1	0 (0.0%)	0 (0.0%)
		Grade +2	0 (0.0%)	2 (66.7%)
		Grade +3	4 (100.0%)	1 (33.3%)
	Day 7	Bacterial Colony Grade		
		N	0	1
		Grade 0	0 (0.0%)	0 (0.0%)
		Grade +1	0 (0.0%)	0 (0.0%)
		Grade +2	0 (0.0%)	0 (0.0%)
		Grade +3	0 (0.0%)	1 (100.0%)
		Microbial Improvement [a]		
	N	4	3	
Improvement	4 (100.0%)	2 (66.7%)		
No Improvement	0 (0.0%)	1 (33.3%)		

Table 14.5-4.1 (Page 16 of 43)
 Microbial Improvement: Number (Percent) of Patients at Day 7 by Species
 (Modified Intent-to-Treat Population)

Species			OCUFLOX (N=93)	POLYTRIM (N=42)	
Haemophilus parainfluenzae	Baseline	Bacterial Colony Grade			
		N	2	0	
		Grade +1	1 (50.0%)	0 (0.0%)	
		Grade +2	0 (0.0%)	0 (0.0%)	
			Grade +3	1 (50.0%)	0 (0.0%)
	Day 7	Bacterial Colony Grade			
		N	0 (0.0%)	0 (0.0%)	
		Grade +1	0 (0.0%)	0 (0.0%)	
		Grade +2	0 (0.0%)	0 (0.0%)	
		Grade +3	0 (0.0%)	0 (0.0%)	
		Microbial Improvement [a]			
		N	2	0	
		Improvement	2 (100.0%)	0 (0.0%)	
	No Improvement	0 (0.0%)	0 (0.0%)		

Table 14.5-4.1 (Page 23 of 43)
 Microbial Improvement: Number (Percent) of Patients at Day 7 by Species
 (Modified Intent-to-Treat Population)

Species			OCUFLOX (N=93)	POLYTRIM (N=42)	
Staphylococcus aureus	Baseline	Bacterial Colony Grade			
		N	16	7	
		Grade +1	0 (0.0%)	2 (28.6%)	
		Grade +2	7 (43.8%)	1 (14.3%)	
			Grade +3	9 (56.3%)	4 (57.1%)
	Day 7	Bacterial Colony Grade			
		N	5	2	
		Grade 0	0 (0.0%)	0 (0.0%)	
		Grade +1	1 (20.0%)	1 (50.0%)	
		Grade +2	1 (20.0%)	0 (0.0%)	
		Grade +3	3 (60.0%)	1 (50.0%)	
		Microbial Improvement [a]			
		N	16	7	
	Improvement	13 (81.3%)	6 (85.7%)		
No Improvement	3 (18.8%)	1 (14.3%)			

Table 14.5-4.1 (Page 40 of 43)
 Microbial Improvement: Number (Percent) of Patients at Day 7 by Species
 (Modified Intent-to-Treat Population)

Species			OCUFLOX (N=93)	POLYTRIM (N=42)	
Streptococcus pneumoniae	Baseline	Bacterial Colony Grade			
		N	4	3	
		Grade +1	0 (0.0%)	0 (0.0%)	
		Grade +2	1 (25.0%)	1 (33.3%)	
			Grade +3	3 (75.0%)	2 (66.7%)
	Day 7	Bacterial Colony Grade			
		N	2	2	
		Grade 0	0 (0.0%)	0 (0.0%)	
		Grade +1	0 (0.0%)	1 (50.0%)	
		Grade +2	1 (50.0%)	0 (0.0%)	
		Grade +3	1 (50.0%)	1 (50.0%)	
		Microbial Improvement [a]			
		N	4	3	
	Improvement	3 (75.0%)	2 (66.7%)		
No Improvement	1 (25.0%)	1 (33.3%)			

However, since no data are available for use in neonates with Gonococcus or Chlamydia infections the following text has been added:

Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus.

Rapporteur's comment:

Only the data regarding Staphylococcus aureus and possibly Streptococcus pneumoniae are considered relevant, while the data for oral commensals are sparse as well as irrelevant. However, it is acknowledged that Allergan does not request an indication extension for use of OCUFLOX/EXOCIN in neonates. In case such a request is put forward in the future, more convincing data will be needed. Issue resolved.

- the choice of the comparator cannot be considered adequate; POLYTRIM is unknown in European countries such as in France and we do not know the performance of this topical antibiotic; as we note, this study has been conducted in countries other than European ones, this can explain this situation; but consequently we have some doubts about the appropriateness of the comparator used in this study;

Allergan Response:

Study 190442-005 was conducted in the United States, Mexico and Brazil in 2002. The trimethoprim sulfate and Polymixin B sulphate combination was chosen as the comparator because it was the most common antibiotic used for paediatric patients at the time. Although no topical antibiotic was and still is not indicated for neonatal conjunctivitis (0-31 days), Polytrim is indicated for paediatric patients as young as 2 months old in the United States. Since the combination gives excellent coverage for organisms generally found responsible for paediatric conjunctivitis and has also been shown to be extremely safe, it was considered the most appropriate comparator for this study.

Rapporteur's comment:

We agree that the comparator is irrelevant seen from an European perspective. The results of the study reveals that EXOCIN appeared to have the same relatively low efficacy rate as POLYTRIM. It is not Allergan's intention to apply for an indication for use in neonates with bacterial conjunctivitis. In the event that this might later be the case, the POLYTRIM study would not be suitable as a documentation of efficacy. Issue resolved.

- the investigated schedule can be considered as intensive for the first 48 hours: "For the first 48 hours, 1 drop every 2-4 hours in each affected eye per 24 hour period, maximum 8 doses/24-hour period/eye; for the remaining 5 days of treatment, 1 drop QID per affected eye" ; such a posology is not validated for conjunctivitis; we cannot exclude that the dosage mentioned at this time in the French Exocin MAA allowed in adults and children (without limitation for a specific population) should be sufficient for the treatment of conjunctivitis during the whole treatment duration : "2 drops x 4/day in each affected eye". Consequently the Applicant should justify the schedule chosen for OCUFLOX in this study.

Allergan Response:

The dosage regimen used in the study was chosen to deliver maximal effect as rapidly as possible to the affected eye. It is appreciated that the regimen is in excess of that presently approved in France. However, since no indication is sought and the results of the study are being shared for information only, the more aggressive dosing regimen, with its reassuring safety profile, could be considered of great interest to the prescriber.

Rapporteur's comment:

It is not Allergan's intention to apply for an indication for use in neonates with bacterial conjunctivitis. In the event that this might later be the case, Allergan will have to document this posology compared to more conventional posologies. Issue resolved.

Issue 20, Clinical safety (CMS):

Regarding the safety documentation considering the PSURs, the Applicant should provide a safety review targeted on corneal perforations in all patients whatever the age in order to permit a more accurate assessment. Moreover, the MAH should discuss these results.

Allergan Response:

Allergan acknowledges the comments from the assessor based upon the review of the PSURs which were submitted with the dossier. It is of note that this question was also raised by the Irish Medicines Board (IMB) at the time of the Renewal Application. Allergan was requested to comment on the reports of corneal perforations associated with use of fluoroquinolones. This was duly provided and included a thorough review of all the literature as well as the Allergan safety data base. This document is presented in Appendix 2. It concludes with a recommendation to add wording to SmPC Section 4.4 regarding the possible risk of the occurrence of corneal perforation in patients with corneal epithelial defect or corneal ulcer who receive treatment with Exocin. The proposed wording for inclusion in SmPC Section 4.4 is as follows:

“Clinical and non-clinical publications have reported the occurrence of corneal perforation in patients with pre-existing corneal epithelial defect or corneal ulcer, when treated with topical fluoroquinolone antibiotics. However, significant confounding factors were involved in many of these reports, including advanced age, presence of large ulcers, concomitant ocular conditions (e.g. severe dry eye), systemic inflammatory diseases (e.g. rheumatoid arthritis), and concomitant use of ocular steroids or non-steroidal anti-inflammatory drugs. Nevertheless, it is necessary to advise caution regarding the risk of corneal perforation when using product to treat patients with corneal epithelial defects or corneal ulcers.”

Once the changes are agreed with the IMB, Allergan had plans to roll-out this SmPC variation across the other European licences for EXOCIN in order to ensure regional harmonisation of the safety information for this product. Whilst this adverse effect has not been reported in the study of the neonatal population, in line with the assessor’s comment, Allergan does consider that this is a significant issue. Therefore it is proposed that this change to the SmPC is reviewed during this EU Working-Sharing Project of Assessment of Paediatric Data procedure for Exocin/Ocuflox (ofloxacin).

Rapporteur’s comment:

*Allergan has provided a literature review and a review of the Allergan safety data base. It concludes with a recommendation to add wording to SmPC Section 4.4 regarding the possible risk of the occurrence of corneal perforation in patients with corneal epithelial defect or corneal ulcer who receive treatment with Exocin, as stated above. The proposed wording is considered sufficient.
Issue resolved.*

Issue 21, SPC (CMS):

The SPC proposal should be amended in line with the above comments. No therapeutic indication or dosing instruction regarding neonates should be given in 4.1 and 4.2 SPC sections.

Allergan Response:

Allergan agrees that no therapeutic indication or dosing instructions pertaining to the neonatal population will be provided in Section 4.1 and 4.2 of the Summary of Product Characteristics.

Rapporteur’s comment:

*Response accepted. It is not Allergan’s intention to apply for an indication for use in neonates with bacterial conjunctivitis.
Issue resolved.*

Issue 22, SPC (CMS):

If any statement is considered to be mentioned in the SPC, this should be a precautionary statement warranting the prescribers on the risk of rhino-pharyngeal passage. In this field, we would propose to only include a very limited statement which can contribute to the occurrence and the diffusion of bacterial resistance as follows: “The use of this drug in children should take into account, particularly in cases of repeated use, the risk of a rhino-pharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.”

Allergan Response:

Allergan acknowledges the comments from the assessor relating to potential for bacterial resistance. This potential exists not only in children and since this is not invariably related to ‘rhino-pharyngeal passage’, the following general statement, already present in a number of the SmPCs of the Concerned Member States, would address this issue: ‘As with other anti infectives, prolonged use may result in overgrowth of non-susceptible organisms.’

It is also considered that this concept is already present in the French SmPC in section 5.1. as part of the following text: « Chez les malades traités au long cours ou atteints d’une infection nosocomiale, une surveillance micro biologique particulière s’impose, à la recherche d’une émergence de résistance, notamment parmi les Staphylocoques et les Pseudomonas. »

Review of all national SmPCs reveals that this concept is already addressed in each country. Therefore, Allergan does not consider that any change to any national SmPC is required.

Rapporteur’s comment:

Response accepted. The following statement, already present in a number of the SmPCs of the Concerned Member States, sufficiently warns against the risk of resistance development: ‘As with other anti infectives, prolonged use may result in overgrowth of non-susceptible organisms.’

Issue resolved.

Issue 23, SPC (CMS):

If some information for neonates has to be given in the SPC (even if an acceptable dossier is submitted), we suggest to introduce a sentence in line with the very limited experience in this population: “The clinical experience in neonates is very limited”.

Allergan Response:

As noted above, Allergan is not seeking an indication extension. However, since this preparation is at times used off-license in neonates, it is proposed to share the data available in this population by including information in section 5.1 of the Summary of Product Characteristics (SmPC).

It is agreed that the experience in neonates is limited and this is reflected in the updated proposed wording of Section 5.1 with the following revised sentence:

“Limited data (N = 173) are available from a double-masked comparative study of *the* use of Exocin *versus trimethoprim sulfate and Polymixin B sulphate combination* in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. .”

In addition, the following sentence is also proposed:

The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.

Furthermore, in line with the European Commission Guideline on Summary of Product Characteristics (October 2005), section 4.2 will also be updated to add: “Experience of use of Exocin in the treatment of ophthalmia neonatorum is limited (see Section 5.1)”.

Section 5.1 of the proposed revised SmPC has also included recommendations from the Rapporteur, Co-Rapporteur and the other Concerned Member States and now reads:

“5.1 Pharmacodynamic Properties

Limited data (N = 173) are available from a double-masked comparative study of *the* use of Exocin *versus trimethoprim sulfate and Polymixin B sulphate combination* in neonates aged from birth up to 31 days in the treatment of bacterial conjunctivitis. Doses of 1 drop *every 2-4 hours* (up to 8 times daily) *in each affected eye* were used for the first 2 days with four times daily dosing for 5 days thereafter.

Cure rates (*resolution of both conjunctival erythema and conjunctival discharge at day 7*) in culture-positive patients of up to 60% were observed *and 47.6% with the comparator. Complete microbial eradication was seen in 55.4% of patients treated with Exocin (50% with comparator). The most prevalent bacterial species was Staphylococcus epidermidis. Microbial improvement in this species, defined as bacterial eradication or reduction by at least 1 grade, was seen in 62.5% with Exocin and 64.5% with comparator.*

The study results of this study are not considered sufficient to establish the efficacy of ofloxacin eye drops (0.3%) in ophthalmia neonatorum.

No safety concerns were raised *with Exocin. Notably, no deterioration in corneal appearance was observed throughout the 7-day treatment period.*

Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus.”

Rapporteur’s comment:

The changes proposed by the Applicant are acknowledged except for the following:

- 1. "Bacterial Colony Grade" has not been defined.*
- 2. The following section "Topical antimicrobial treatment is not indicated for eye infection caused by chlamydia or gonococcus" should be changed and amended to: "Topical antimicrobial treatment is not indicated for eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae. Current guidelines indicate that systemic antimicrobial treatment is necessary in patients with eye infection caused by Chlamydia trachomatis or Neisseria gonorrhoeae".*
- 3. The applicant has not included in the response the fact that they have added a tabulation of efficacy against various bacterial species, as requested by the Rapporteur. However, this table has actually been provided as part of the response to questions put forward by the UK.*
- 4. The clinical significance of Staphylococcus epidermidis is highly questionable.*

RAPPORTEUR’S OVERALL CONCLUSION (JAR)

Based on the review of the paediatric data on safety and efficacy, the Rapporteur considers that:

1. No data have been submitted that document the efficacy in neonatal conjunctivitis
2. However, it is acknowledged that Allergan does not seek in indication extension to include the use of OCUFLOX/EXOCIN in neonatal conjunctivitis.
3. The submitted data on safety are considered adequate.
4. The Rapporteur requests the following changes to be made in the Applicant's revised SmPC (deletions are shown by ~~strike-through characters~~, and amendments are shown by underlined characters).

If the SmPC is revised according to our suggestions, no further issues remain:

SmPC, section 4.2

Experience of use of Exocin in the treatment of ophthalmia neonatorum is limited and efficacy has not been proven (see Section 5.1)

SmPC, section 5.1

The most prevalent bacterial species was *Staphylococcus epidermidis*. The clinical significance of *Staphylococcus epidermidis* in conjunctivitis is highly questionable. Microbial improvement in this species

SmPC, section 5.1

Topical antimicrobial treatment is not indicated for eye infection caused by ~~chlamydia~~ *Chlamydia trachomatis* or ~~gonococcus~~ *Neisseria gonorrhoeae*. Current guidelines indicate that systemic antimicrobial treatment is necessary in patients with eye infection caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

DISCUSSIONS ON SPC FOLLOWING CIRCULATION OF THE JAR

Following circulation of the JAR, further comments regarding the SPC were received from a CMS:

Section 5.1 : it is proposed to delete the whole Rapporteurs' proposed information regarding the single study in neonates, and to mention the limitations of this investigation in 4.4 SPC section.

We suggest to delete therapeutic recommendations in a sub-paediatric population (treatment of ophtalmia neonatorum, such as eye infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in neonates) and to replace them in 4.4 SPC section.

Section 4.2 : the proposed wording « *Experience of use of Exocin in the treatment of ophtalmia neonatorum is limited and efficacy has not been proven (see section 5.1)* » should be deleted because no particular therapeutic indication is allowed in neonates.

Section 4.4 : information in this section should take into account the following points :

- the limitations of the submitted study,
- the risk of a rhino-pharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance,
- the basis of the wording proposed by the MAH related to the occurrence of corneal perforations,
- the interest to mention information on benzalkonium chloride in ofloxacin topical ophtalmic Marketing Authorisations which contain this preservative (multi-doses).

Consequently it is suggested to mention the following text :

“Data are very limited to establish efficacy and safety of ofloxacin eye drops 0.3% in the treatment of conjunctivitis in neonates.

The use of ofloxacin eye drops in neonates with ophtalmia neonatorum of gonococcal or chlamydial origin is not recommended as it has not been evaluated in such patients. Neonates with ophtalmia neonatorum should receive appropriate treatment for their condition.

When using this drug, one should take into account the risk of a rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

~~*Clinical and non-clinical publications have reported the occurrence of corneal perforations in patients with pre-existing corneal epithelial defect or corneal ulcer, when treated with topical fluoroquinolone antibiotics has been reported. Caution should be exercised, especially in patients with*~~ *However, significant confounding factors were involved in many of these reports, including advanced age, presence of large ulcers, concomitant ocular conditions (e.g. severe dry eye), systemic inflammatory diseases (e.g. rheumatoid arthritis), and concomitant use of ocular steroids or non-steroidal anti-inflammatory drugs. Nevertheless, it is necessary to advise caution regarding the risk of corneal perforation when using product to treat patients with corneal epithelial defects or corneal ulcers.*

The multidose eye drop presentation contains the preservative benzalkonium chloride, which may cause eye irritation. Contact lenses should be removed prior to application and wait at least 15 minutes before

reinsertion. Benzalkonium chloride is known to discolour soft contact lenses” (if this preservative has to be considered in the topical ophthalmic pharmaceutical form).

Section 4.8: no specific information related to safety data concerning undesirable effects due to benzalkonium chloride is useful.

Section 5.3 : the Co-rapporteur’s proposed wording is not accepted.

These CMS comments were supported by the Rapporteur with minor modifications in the wording. Consequently, the MAH revised the SPC in line with the above comments and this is reflected in the final agreed changes for the SPC.

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

As a part of the EU work sharing procedure in the assessment of paediatric data, the MAH submitted available data in children for Exocin eye drops, solution 3 mg/ml.

The MAH provided a single clinical study report, describing the results of study 190442-005: A multi-center, randomized, double-masked, parallel-group clinical study evaluating the safety and efficacy of topical ofloxacin 0.3% ophthalmic solution with that of topical trimethoprim sulfate/polymyxin B sulfate combination ophthalmic solution as a positive control, in infants, from birth to 31 days of age, with bacterial conjunctivitis.

From an efficacy point of view no conclusion can be drawn from presented data. In line with this conclusion, the MAH did not claim an indication extension for the use of Exocin in neonates. The proposal of the MAH was to share the data available for the neonate population by including information about the study in section 5.1 of the SPC. This approach was first supported by the Rapporteur and several Member States. However, another Member State considered that the level of information was not sufficient to support any statement in section 5.1 of the SPC with regards to the use in neonates. A consensus was finally reached to delete the proposed information regarding the single study in neonates in section 5.1 of the SPC and to mention the limitations of this investigation in section 4.4. Additional changes to section 4.4 were discussed and it was agreed to introduce relevant statements.

On 13 February 2008 the Member States reached an agreement about the SPC and the procedure was closed. The final agreed changes for the SPC is presented in section IV.

IV. FINAL AGREED CHANGES IN THE SPC

Section 4.4 Special Warnings and Precautions for Use

'Data are very limited to establish efficacy and safety of ofloxacin eye drops 0.3% in the treatment of conjunctivitis in neonates.'

'The use of ofloxacin eye drops in neonates with ophthalmia neonatorum caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis* is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.'

'When using Exocin eye drops the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance should be considered. As with other anti infectives, prolonged use may result in overgrowth of non-susceptible organisms.'

'Clinical and non-clinical publications have reported the occurrence of corneal perforation in patients with pre-existing corneal epithelial defect or corneal ulcer, when treated with topical fluoroquinolone antibiotics. However, significant confounding factors were involved in many of these reports, including advanced age, presence of large ulcers, concomitant ocular conditions (e.g. severe dry eye), systemic inflammatory diseases (e.g. rheumatoid arthritis), and concomitant use of ocular steroids or non-steroidal anti-inflammatory drugs. Nevertheless, it is necessary to advise caution regarding the risk of corneal perforation when using product to treat patients with corneal epithelial defects or corneal ulcers.'

'The multidose eye drop presentation contains the preservative benzalkonium chloride, which may cause eye irritation.'

'Exocin contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses and discolour them. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration'