Public Assessment Report

Paediatric data

Ciloxan
Ciprofloxacin

Marketing Autorisation Holder: S.A.Alcon-Couvreur N.V

Rapporteur:	**DK**
Co-Rapporteur:	**HU**
Currently approved indication(s):	**Treatment of ciprofloxacin-susceptible eye or ear infections**
Pharmaceutical form(s) and strengths affected by this variation:	**Eye drops 3 mg/ml** **Eye ointment 3 mg/g** **Ear drops 3 mg/ml**
Paediatric assessment Procedure start date:	**3 January 2006**
Date of (Co)-Rapporteur´s preliminary report:	**14 March 2006**
Date of Rapporteurs' final report:	**23 January 2007**
End of procedure:	**30 March 2007**
Date of this report:	**14 August 2008**

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I. INTRODUCTION

Ciloxan 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 Ciloxan eye drops, eye oinment and ear drops. The procedure started on January 3rd, 2006. Denmark and Hungary had been appointed as Rapporteur and Co-rapporteur, respectively.

The paediatric file consisted of the the study C-01-34, which was requested by the FDA to obtain paediatric information on ciprofloxacin eye drops for the treatment of bacterial conjunctivitis in neonates up to 1 month of age. In addition, the MAH submitted a list of clinical trials in which paediatric patients were enrolled.

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

I.1 Scope of the assessment

The present variation pertaining ciprofloxacin eye drops, eye ointment and ear drops has been submitted under the EU work sharing project assessment of paediatric data. The FDA has requested paediatric information on ciprofloxacin eye drops for the treatment of bacterial conjunctivitis (Study C-01-34). Based on data from this study the FDA, however, concluded that Ciloxan was not approvable for the treatment of bacterial conjunctivitis in neonates from birth to one month of age as the data were not sufficient to establish efficacy in neonates from birth to one month of age.

The scope of this submission is to harmonise the paediatric population for whom ciprofloxacin eye drops, eye ointment and ear drops can be used, but not to harmonise the posology and method of administration of the products.

II. SCIENTIFIC DISCUSSION

Ciprofloxacin is a fluoroquinolone antibiotic. Fluoroquinolones are broad-spectrum antibacterials with activity against gram-positive and gram-negative species. The drugs are bactericidal and work by blocking of the bacterial DNA gyrase, thereby making irreversible damage to the DNA with a following disrupting the protein synthesis.

Ciloxan (ciprofloxacin hydrochloride 3 mg/ml) are indicated for the treatment of ciprofloxacin-susceptible infections in the eye and the ear. The preparations have been approved nationally, but not in all EU countries: The eye drops solution is registered in all EU-countries but Finland, Greece, Iceland, and Malta. The eye ointment is registered except in Cyprus, Czech Republic, Estonia, Finland, Germany, Hungary, Latvia, Lithuania, Poland, Slovakia and Slovenia. The ear drops are registered in all EU-countries except Austria, Cyprus, Estonia, Finland, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Slovenia and UK. The approved therapeutic indications vary across the countries. The preparations have been approved for paediatric use in a majority of EU countries, but the age range for the approval varies across the countries. The trade names differ in some countries. A list of the approved therapeutic indications in the different countries is warranted.

The MAH has provided a survey of the approval in children in the EU-countries:

Rapporteur's summary:

Eye drops:
The eye drops are approved in 8 countries without age stipulation, in 1 country from 0 – 12 years, in 7 countries in one year and older, in 5 countries for 1 year of age and from birth to 1 month of age, in 2 countries the drug is contraindicated in children, and in 3 countries it is not registered; in 1 country the marketing authorisation has been withdrawn.

Eye ointment:
In 1 country the ointment is approved without age stipulation; in 12 countries it is approved for children of 1 year and older; in 1 country from 2 years and older; and in 13 countries it is not registered.

Ear drops:
In 7 countries (+ 2 imminent approvals) the ear drops are approved, in 4 countries no age is stipulated; in 1 country the ear drops are approved for children over 2 years; in 13 countries the ear drops are not registered.

II.1 Quality aspects

Not applicable.

II.2 Non-clinical aspects

Pre-clinical issues have not been touched upon in the submission.

Rapporteur's comment:
The MAH should present a review of the juvenile data available for the three formulations and relevant for the paediatric population – please see Other Concerns, Safety

II.3 Clinical aspects

II.3.1 Clinical pharmacology

No clinical pharmacology studies in paediatric patients have been conducted. This is justifiable because of low systemic concentration and short term exposure.

II.3.2 Clinical efficacy

Main study (C-01-34)

The C-01-34 study was requested by the FDA to obtain paediatric information on ciprofloxacin for the treatment of bacterial conjunctivitis. The objective was amended to evaluate the safety and clinical improvement rate between groups in a comparative study.

Methods:

This multi-centre study was a randomised, double-masked parallel comparison versus moxifloxacin (a 4th- generation quinolone) ophthalmic solution 0.5 % in neonates ≤ one month of age with presumed bacterial conjunctivitis. A rating ≥ 1 bulbar conjunctival injection and/or ≥ 1 conjunctival discharge/exudate in at least one eye was obligate. Patients with suspected or confirmed ophthalmia neonatorum of gonococcal, chlamydia, herpetic or chemical origin, or suspected fungal, viral or acantamoebia infection were excluded. The treatment was one drop 3 times daily for 4 days with either ciprofloxacin or moxifloxacin. Post randomisation evaluations took place at Days 2, 3, 4, 5 and 9 ("test-of-cure-visit"). The day 9 visit should monitor the patient for recurrent infection and microbiological judgement of bacterial eradication. The primary clinical efficacy variable was the clinical improvement rate of two cardinal ocular signs: Bulbar conjunctival injection and conjunctival discharge/exudate at each visit. The definition of improvement rate was the sum of the two cardinal ocular signs being at least 1 unit less than their sum at Day 1. A 4-point scale was used (absent=0, mild=1, moderate=2, severe=3). Secondary clinical efficacy variables included a.o. bacterial eradication at Day 9, clinical cure rates (the sum of bulbar conjunctival injection and conjunctival discharge/exudate being 0) at each visit. The primary microbiological efficacy variable was microbiological eradication at Day 9.

Rapporteur's comment:

The goal of the primary efficacy end point is not ambitious. A decrease of 1 out of a total of 6 possible (3+3 in each of the 2 cardinal signs) can hardly be interpreted as clinically meaningful. Clinical cure would have been more appropriate. The MAH has not discussed the choice of comparator.

In a considerable part of the EU countries the application of a quinolone to a presumed bacterial conjunctivitis is not first choice in any patient age group, as an antibiotic with a more narrow spectrum like chloramphenicol or fusidic acid is preferred. However, in view of the trial in this population being a request from the FDA, moxifloxacin as comparator could to some extent be justified.

A discussion of whether any culture identified bacteria would be the agens that elicited the clinical conjunctivitis has not been presented. It is still under debate to what extent a clinical conjunctivitis can be ascribed swab identified bacteria which is reflected by, in many cases of clinically suspected conjunctivitis no bacteria can be isolated. The MAH has not discussed this issue.

In the study report no sample size calculations or planned statistical analytical methods could be found, but a number of 200 patients with presumed bacterial conjunctivitis had to be enrolled.

Therefore, any conclusion should be drawn with caution.

Results

The ITT population was defined as all patients who received treatment and had at least 1 on-therapy visit; the MITT population was all patients who received treatment and had at least 1 on-therapy visit and who were culture positive on Day 1; the PP population included all patients who received treatment, who met in-, and exclusion criteria, and who had baseline and test-of-cure-visits (or exit if early exit); the MPP population was all patients who received treatment, who met in-, and exclusion criteria, and who had baseline and test-of-cure-visits (or exit if early exit) and were culture positive on Day 1.

Rapporteur's comment:

It is not stated which of these populations are planned to serve as the primary analysis population.

A number of 209 (107:102 for ciprofloxacin: moxifloxacin) patients of whom 142 were culture positive were enrolled and available for ITT and safety analysis. A number of 142 (70:72) were evaluable for MITT analysis, and 197 (98:99) encompassed the PP data set, and 137 (67:70) patients were available for MPP analysis. A total of 8 patients, all in the moxifloxacin group, were withdrawn because of non-compliance (1), parent decision (2), treatment failure (4) and Investigator decision (1). The average age was 16.4 days (range 2-30). Of the population 51% were male and 49 % were female. The patients were well balanced regarding mean age, sex, race, iris colour and study eye.

The primary efficacy parameter for the ITT population is depicted inn the table below:

Table 14.2.1.1.-1: ITT - Clinical Improvement Rate for Moxifloxacin 0.5% vs. CILOXAN

		Treatment							
		Moxi		CILOXAN					
Visit	Clinical Improvement	N	%	N	%	P-Val[a]	Delta	LCL[b]	UCL[b]
Day 2	Yes	68	63.6	58	56.9	0.3232	6.6887	-6.5608	19.9381
	No	39	36.4	44	43.1				
Day 3	Yes	80	74.8	76	74.5	0.9660	0.2566	-11.5446	12.0577
	No	27	25.2	26	25.5				
Day 4	Yes	90	84.1	90	88.2	0.3887	-4.1231	-13.4546	5.2083
	No	17	15.9	12	11.8				
Day 5	Yes	88	86.3	96	94.1	0.0596	-7.8431	-15.9333	0.2470
	No	14	13.7	6	5.9				
Ophth Exit	Yes	99	93.4	97	95.1	0.5987	-1.7018	-8.0192	4.6156
	No	7	6.6	5	4.9				

[a] Chi-square test of independence (or Fishers Exact test if N<5).
[b] 95% Conf. Limits for Moxi-CILOXAN.

As for microbiological efficacy, out of the 142 patients who were culture positive 85 % were rated as microbiological successes at the test-of-cure-visit with ciprofloxacin versus 87 % with moxifloxacin (MITT data set, results are not provided for the ITT population).

Rapporteur's comment:
The more relevant efficacy variable, clinical cure - which is, regrettably, not defined in the study report - (at Day 5??) is according to the FDA assessment and the Expert Report 61 % in the ciprofloxacin group. But this figure is not consistent with the figures presented in the Study report for either the ITT, MITT or the PP population at Day 5. ***The MAH should clarify.***
The FDA has stated that the clinical cure rate of 61 % is approximately 10 percent points less than the generally observed clinical cure rate with placebo of 70 %. The MAH has argued that the population of neonates may react less than older populations because of an immature immune system, and because many of the included patients may have obstructed tear duct (dacryostenosis). However, in the latter case the MAH should have excluded such patients from study participation. Moreover, only a single case of obstruct tear duct was reported. Hence, the argumentation of the MAH is hypothetical and cannot be regarded as valid.

RAPPORTEUR'S EFFICACY CONCLUSION FOR STUDY C-01-34
Presently, this trial does not prove convincing efficacy in the population of neonates in the age ≤ 1 month of age with presumed bacterial conjunctivitis. At this point, it is premature to indicate if we share the negative position of the FDA, and that there are insufficient data to support the wording regarding efficacy in the proposed SPC text for the eye drops.

II.3.3 Clinical safety

Patient exposure
A number of 102 patients were exposed to ciprofloxacin, with a mean and median duration of 4.0 days.

Adverse events
The most frequently reported related and not related adverse events with ciprofloxacin were rhinitis 3.9 %, oral monilla (2.9 %), vomiting (2.9 %), rash (2.9%), and surgical/medical procedure (2.9 %). With moxifloxacin the corresponding features were tearing (2.8 %) and rash (2.8 %). The ocular adverse events related to study medication were eye hyperaemia (1.0 %) and lid oedema (1.0 %) with ciprofloxacin, and lid hyperaemia (1.9 %) with moxifloxacin. Non-ocular events not related to treatment were not reported. An ocular adverse event not related to therapy was eye haemorrhage.

Rapporteur's comment:
No surprising findings are reported, with the exception of one case of eye haemorrhage. The MAH should describe this case.

No clinically relevant changes in ocular safety parameters (pupils, red light reflex, anterior segment) were observed.

As for vital signs a few deviations in the values of systolic diastolic blood pressure, which were not likely to be of any clinical importance, particularly in view of the large physiological variations for this age group.

Serious adverse events and deaths
No deaths and no treatment related serious adverse events were reported. Two serious not-related adverse events were noted, one pylorus stenosis and one case of fever, both in the moxifloxacin group.

Laboratory findings
N/A

Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition
Not available.

Rapporteur's comment:
It is acceptable that such data have not been submitted as the treatment with ciprofloxacine eye drops, ointment or ear drops is only of short duration.

RAPPORTEUR'S SAFETY CONCLUSION FOR STUDY C-01-34
Analysis of the safety of ciprofloxacin eye drops in neonates ≤ 1 month of age did not give rise to new concerns. However, one case of eye haemorrhage, coded as not related to therapy, should be explored by the MAH.

MAH's proposal for SPC:

Section 4.4

Ciloxan Eye Drops – Proposed Section for Use in Children
Use in Children
Children 1 year of age and above
The dosage is the same as for adults.
Children from birth to 1 month of age
For the treatment of bacterial conjunctivitis:
Instill one drop into the conjunctival sac(s) of the affected eye(s) three times daily for four days.
Safety and effectiveness of CILOXAN 3 mg/ml eye drops were determined in 102 children less than 1 month of age. No serious adverse event was reported in these patients.

Ciloxan Eye Oinment – Proposed Section for Use in Children
Use in Children
Children 1 year of age and above
The dosage is the same as for adults.
Safety and effectiveness of CILOXAN 3 mg/g eye oinment were determined in 192 children between the ages of one to 12 years. No serious adverse event was reported in these patients. These clinical studies have indicated that dosage modifications are not required for children.

Ciloxan Ear Drops – Proposed Section for Use in Children
Use in Children
The dose is 3 drops of CILOXAN in the ear canal twice daily for children 1 year of age and older.
For patients requiring the use of an otowick the dose can be doubled for the first administration only.
Safety and efficacy of CILOXAN was determined in 139 children between the ages of one and twelve years of age. No serious adverse events were reported in this group of patients.

Rapporteur's comment:
Section 4.2 would be the appropriate section. Evaluation of the wording must await the MAH's response.

RAPPORTEUR'S OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Apart from the study (C-01-34), which was requested by the FDA, only insufficient material has been provided, i.e. a list of conducted trials recruiting paediatric patients, an outdated expert statement on paediatric data for the Ciloxan eye drops (1995), the original expert reports (1994 and 2000) for the products, some PSURs and a considerable number of original study reports.
Final conclusions cannot be drawn until the MAH has submitted a review with the available data, including relevant analyses of efficacy. Likewise, a review of relevant safety data including analyses of all reported related and not related adverse events for safety data in all paediatric patients and including an integrated PSUR review should be submitted.

ASSESSMENT OF REQUESTED SUPPLEMENTARY INFORMATION (JAR)

During the procedure a need for additional information has been identified and a List of Questions was generated. The applicant responded to these questions as detailed below:

ISSUE 1 (Rapporteur)
CLINICAL EFFICACY
The MAH should submit a clear and concise review with the available data, including relevant analyses of efficacy (for the different efficacy populations). The reviews should contain the studies that the MAH states to contain the principal efficacy data: C-91-74 and C-01-34 for the eye drops, study C-91-29 for the eye ointment and study C-98-18 for the ear drops.

RESPONSE: Alcon has undertaken a review of the available data including relevant analyses of efficacy for the different efficacy populations studied in the requested studies. Additionally in respect of CILOXAN Ear Drops a study is assessed which has not previously been submitted, namely, study C-99-59 (a study conducted in patients with acute otitis media with tympanostomy tubes, AOMT). This study has been included to address concerns raised by the Rapporteur, Co-Rapporteur and some Member States regarding the safety of CILOXAN Ear Drops in patients with perforated tympanic membranes.

Rapporteur's summary and comments:

The MAH has forwarded a review of data:

Ciloxan Eye Drops:

C-01-34:

The trial was a randomised active controlled, double-masked study of Ciloxan or Mofloxacin eye drops dosed 3 times daily for 4 days in paediatric patients from birth to one month of age with (presumed) bacterial conjunctivitis.
As noted in the initial assessment the study is influenced by several shortcomings. The MAH now clarifies that in the initial submission a "day 5 early cure rate" was used as the primary analysis (please note that the treatment period in this study was only 4 days). However, in the Response the day 9 test-of -cure, i.e. when bulbar injection and conjunctival discharge/exudates was absent, is referred to as more relevant for comparison across studies (in the Response called the modified ITT data set).
This endpoint was obtained in an acceptable proportion of the patients, which encompassed 107 patients in the Ciprofloxacin group and 102 in the Mofloxacin group. At the test of cure visit 78 % of the patients in the Ciprofloxacin group and 79 % in the Mofloxacin group obtained this rating. In accordance herewith, the eradication rate for pre-therapy pathogens was 85 % and 87 %, respectively. The pre-treatment culture-positive rate was 68 %, which is unremarkable in this population of presumed bacterial conjunctivitis patients.

In conclusion, although there are methodological deficiencies in the trial design and initial reporting, the clinical treatment response in the neonatal group is satisfactory, and we consider the therapeutic indication acceptable.

C-91-74:
This randomised active controlled study in patients between 1 and 12 years with bacterial conjunctivitis compared Ciloxan eye drops with Tobrex (tobramycin 0.3 %) eye drops dosed 1-2 drops every 2 hours on day 1 and 2 followed by 1-2 drops every 4 hours on days 3 to 7.

As the eye drops are already approved in the vast majority of EU countries in the age from 1 year and above only the former study is of major interest in the present context.
The proposed extrapolation between the age of one month and one year for the use of the eye drops is an uncontroversial pragmatic step as the effect and adverse event profile is similar in all exposed age groups.

Ciloxan eye ointment:
In study C-91-29 children in the age from 1 to 12 years with bacterial conjunctivitis were treated for 7 days 3 times daily on days 1 and 2, thereafter 2 times daily.
The Physician's impression of clinical cure at day 7 (efficacy data set, N= 133) was 95.5 % and 91.3 % for Ciloxan and Tobrex, with an eradication rate of 86.2 % and 83.3 %, respectively.

In conclusion, as in the 14 Member states where this formulation is approved, the majority already has the age "one year and above" for the use of the ointment, no concerns are raised.

Ciloxan Ear Drops:

C-98-18:
This study recruited patients of one year or older with a clinical diagnosis of acute otitis externa (AOE). A number of 139 patients aged up to 11 years (166 were above that age, incl. adults) were included in a randomised double blind comparison between Ciloxan ear drops, Ciprodex (ciloxan and dexamethason), and Corticosporin ear drops (neomycin, polymyxine B and hydrocortisone), which were administered twice daily for 7 days.

C-99-59:
This study in paediatric patients of 6 months to 12 years with tympanostomy tubes (AOMT) is submitted to support the indication of suppurative otitis media in those countries where it is already approved.

The submitted study C-99-59 does not address the question about ototxicitiy in the inner ear after topical application. Audiometric investigations of the study populations are not valuable in this context as the comparator drug also contains ciprofloxacin. However, this issue is addressed in the non-clinical part of the Response; please see assessment of Issue 3.

As the use of Ciloxan ear drops in children with tympanostomy tube is controversial in some member states the study can be regarded just as support in those countries where this indication is approved (but might in fact be the documentation in these countries?).

Issue resolved

ISSUE 2 (Rapporteur)
CLINICAL SAFETY: The MAH should submit a clear and concise review of relevant safety data as mentioned in the Overall Conclusion. The reviews should contain both the studies that the MAH states to contain the principal efficacy data: C-91-74 and C-01-34 for the eye drops, study C-91-29 for the eye ointment and study C-98-18 for the ear drops, and all other paediatric available safety data presented in a way to facilitate overview.

SUMMARY OF RESPONSE: A review of the relevant safety data is provided .This review reflects the safety data observed in the principal studies and from post-marketing experience. From the review of the safety data no safety concerns were identified for paediatric patients exposed to CILOXAN Eye Drops, Eye Ointment, or Ear Drops based upon a review of adverse events and an assessment of ocular, otic, and systemic safety parameters.

The data presented in the Summary of Clinical Safety supports the following conclusions:
• CILOXAN Eye Drops is safe and well-tolerated in paediatric patients. Clinical study safety data in paediatric patients with bacterial conjunctivitis support the use of CILOXAN Eye Drops in paediatric patients as young as newborn infants.
• CILOXAN Eye Ointment is safe and well-tolerated in paediatric patients. Clinical study safety data in paediatric patients with bacterial conjunctivitis support the use of CILOXAN Eye Ointment in paediatric patients as young as 1 year of age.

• CILOXAN Ear Drops is safe and well-tolerated in paediatric patients with otitis externa. Clinical study safety data support the use of CILOXAN Ear Drops in paediatric patients as young as1 year of age.
• CILOXAN Ear Drops is safe and well-tolerated in paediatric patients with tympanostomy tubes or perforated tympanic membranes.

Rapporteur's summary and comments:

Rapporteur's summary of the MAH response, which, as requested, reviews data from studies C-91-29, C-91-74, C-01-34 and C-08-18 contributing paediatric data, and post-marketing data from the period January 1 2001 to March 31 2006. In addition, data from study C-99-59 have now been submitted.

<u>Ciloxan Eye Drops:</u>
A total of 97 newborn children received eye drops. No treatment related adverse events were reported, and similar, not-related adverse events were reported in the Ciloxan and in the comparator group.
In the age group 28 days – 23 months 58 patients received Ciloxan eye drops with 2 treatment related adverse events: ocular hyperaemia and lid oedema. Otitis media and rhinitis were the most frequently reported not-related adverse events in this age group.
In the 2-11 years age group 96 children received the eye drops. Ocular pruritus, ocular hyperaemia, ocular discharge and dry eye occurred as treatment related adverse events in 1.0 % - 2.1 %. Otitis media and infection were reported as not-related adverse events.
In adolescents, 12-17 years, 5 patients received the eye drops with no treatment-related adverse events and one related, namely rhinitis, reported.

For the post marketing period 6 reports are available: Two cases of urticaria, 1 case of eye irritation, but for none of these cases the outcome was reported. Furthermore, 1 case of urticaria, 1 of generalised erythema and 1 of mydriasis and papillary disorder, all of which resolved.

<u>Ciloxan Eye Ointment:</u>
No newborn patients received eye ointment.

For the age group 28 days to 23 months (N=24) no treatment related adverse events were reported. In the age group 2 – 11 years (N=77) treatment related adverse events were ocular pruritus, ocular discomfort and decreased visual acuity. Not-related adverse events were otitis media, pharyngitis, and increased cough. Each of these adverse events was reported for 1.3 % to 2.6. %.
For the adolescents, 12-17 years, 2 patients were treated with Ciloxan eye ointment without any reports of treatment related or unrelated adverse events

In the post-marketing information for the period January 1, 2001 to March 31, 2006 no cases of adverse events in paediatric patients were reported.

<u>Ciloxan Ear drops:</u>
External otitis indication:
No Patients in the newborn received Ciloxan Ear Drops.
In the age group 28 days to 23 months 2 children received ear drops with no treatment related adverse events reported.
In the age spectrum 2 - 11 years 137 paediatric patients were treated. Ear pruritus, headache and dermatitis were reported as treatment related, all with a frequency of 0.7 %, and otitis media, otitis externa, headache, infection, cold syndrome, vomiting and pharyngitis were noticed as not-related adverse events.
For the adolescents, 12-17 years, a number of 54 patients were treated with Ciloxan ear drops without any reports of treatment related adverse events.
Post-tympanostomy acute otitis media and otorrhea indication:
Study C-99-59 was a randomised, single-blind comparison of ciloxan and ciprofloxacin+dextamethason 0.1 % ear drops that were administered twice daily for 7 days in patients from 6 months to 12 years of

age. A total of 98 patients received Ciloxan ear drops. Treatment-related adverse events were ear pain, ear discomfort, ear pruritus, ear precipitate and crying, each occurring in 1.0% - 3.1 %.

In the post-marketing period two cases in patients aged 13 and 2 years, respectively, were identified of which one was hypersensitivity (resolved), the other case was described as medication residue and drug ineffective (outcome not reported).

In conclusion, no alarming adverse events were reported in the exposed paediatric population. For the three Ciloxan formulations, i.e. eye drops, eye ointment and ear drops, the safety pattern is unremarkable and consistent with what could be expected.

Issue resolved.

ISSUE 3 (Rapporteur)

CLINICAL SAFETY: To meet the few countries with a paediatric contraindication for the eye drops the MAH should justify 1) that no risk in human paediatric exists for premature epiphyseal closure of long bones and 2) toxicity in the inner ear in case of perforated tympanic membrane.

RESPONSE: There have been concerns expressed related to the safety of fluoroquinolones in paediatric patients because of musculoskeletal changes that were observed in immature animals who were administered systemic fluoroquinolones. The Applicant has conducted a comprehensive literature search to identify related publications and is unaware of any musculoskeletal issues related to the topical administration of fluoroquinolones.

Plasma levels of ciprofloxacin, drawn within 30 minutes after administration of eye drops at several points during a seven-day topical dosing schedule for the treatment of conjunctivitis, ranged from nonquantifiable to mean peak levels of 4.7 ng/ml. The mean peak plasma level of ciprofloxacin obtained after topical dosing is approximately 450-fold less than that observed following a single 250 mg oral dose of ciprofloxacin, indicating a wide margin of safety for topical ocular administered ciprofloxacin (Leibowitz, 1991).

A review was conducted of the safety findings from 1795 children who received 2030 treatment courses of intravenous or oral ciprofloxacin. The average doses of intravenous and oral ciprofloxacin in the study population were 8 and 25 mg/kg/day, respectively. Treatment associated events were reported in 10.9% of children receiving oral ciprofloxacin compared to 18.9% among intravenous recipients. Overall arthralgia occurred during 31 ciprofloxacin treatment courses (1.5%) with the majority of events resolving without intervention and being of mild to moderate severity. More than 60% of arthralgia episodes were in children with cystic fibrosis. This study concluded that the adverse event pattern in children receiving ciprofloxacin was similar to that observed in adults (Hampel et al., 1997). A review of the nonclinical data, which demonstrate a lack of risk in children in respect of premature epiphyseal closure of the long bones and toxicity in the inner ear in the presence of a perforated tympanic membrane is provided.

Rapporteur's comment:
Topical administration of ciprofloxacin eye drops does not raise concern of premature epiphyseal closure of the long bones as the safety margin is large.

The potential for ototoxicity has been studied in the guinea pig. The rapid maturation timeline of guinea pigs (full reproductive function has been reported in as little as 30 days after birth) precludes the conduct of specific juvenile studies in this ototoxicity model. However, the study was initiated with animals as young as feasible (3 to 5 weeks of age). Therefore, the lack of ototoxicity in this model is considered to support the safety of CILOXAN Ear Drops in both adult and paediatric populations.

Rapporteur's comment
This study has been assessed the non-clinical section.

With respect to the potential toxicity in the inner ear, in the case of perforated tympanic membrane, the efficacy and safety of CILOXAN Ear Drops in children from 6 months to 12 years of age has been demonstrated in C-99-59 (a study conducted in patients with acute otitis media with tympanostomy tubes, AOMT).

Rapporteur's comment:
This study has been briefly commented in Issue 2.

Co-Rapporteur's suggestion:
The Company is advised to consider adding a short paragraph on the absence of ototoxicity following middle ear application in guinea pigs even though these findings were made in sexually mature animals and to mention that only juvenile animals are sensitive to the degenerative effect of fluoroquinolones.

Rapporteur's comment: We accept this proposal.

Rapporteur's assessment of MAH Response:
For comments to the clinical study C-99-59 see Issue 2.
The potential ototoxicity of ciprofloxacin has been investigated in animals without indication that greater than therapeutic doses of ciprofloxacin had adverse effects on hearing function or cochlear hair cell histology even though the drug was shown to penetrate to the inner ear when applied locally to the round window membrane.
In conclusion, the submitted non-clinical data suggest that there is no appreciable risk of ototoxicity in children treated with ciprofloxacin ear drops, even in the case of a perforated tympanic membrane.

Issue resolved

ISSUE 4 (Co-rapporteur)
CLINICAL SAFETY
A few articles were published about the "lack of ciprofloxacin ototoxicity". J.Claes investigated the ototoxicity of topical ciprofloxacin on guinea pigs. However no experiments were performed on juvenile animals. (J.Claes et al. 1991. Lack of Ciprofloxacin Ototoxicity after Repeated Ototopical Application. Antimicrobial Agents and Chemotherapy, May 1991. p. 1014-1016.)
In our opinion it is necessary to investigate the effects of topical fluorokinolons (in concentration according the ear drops) on the structure of middle ear in juvenile animals. Until this condition is not fulfilled we recommend that the CILOXAN Ear Drops, Solution cannot be used in children with otitis media with or without perforated tympanic membrane.
There are no data about occurrence of the ear damage or hear loss caused by topical fluorokinolon. However the bone, joint or tendon damage can occur several weeks or month after the end of therapy. After such a long period it is not inevitable to realize the relation between the symptom and the treatment. The possibility of this kind of damage is only theoretic at the moment, but the exclusion of this would be a satisfaction.

RESPONSE: There have been concerns expressed related to the safety of fluoroquinolones in paediatric patients because of musculoskeletal changes that were observed in immature animals who were administered systemic fluoroquinolones. The Applicant has conducted a comprehensive literature search to identify related publications and is unaware of any musculoskeletal issues related to the topical administration of fluoroquinolones.

The systemic absorption of ciprofloxacin when administered topically is negligible. Plasma levels of ciprofloxacin, drawn within 30 minutes after administration of eye drops at several points during a seven-day topical dosing schedule for the treatment of conjunctivitis, ranged from nonquantifiable to mean peak levels of 4.7 ng/ml. The mean peak plasma level of ciprofloxacin obtained after topical dosing is

approximately 450-fold less than that observed following a single 250 mg oral dose of ciprofloxacin, indicating a wide margin of safety for topical ocular administered ciprofloxacin (Leibowitz, 1991).

A review was conducted of the safety findings from 1795 children who received 2030 treatment courses of intravenous or oral ciprofloxacin. The average doses of intravenous and oral ciprofloxacin in the study population were 8 and 25 mg/kg/day, respectively. Treatment associated events were reported in 10.9% of children receiving oral ciprofloxacin compared to 18.9% among intravenous recipients.
Overall arthralgia occurred during 31 ciprofloxacin treatment courses (1.5%) with the majority of events resolving without intervention and being of mild to moderate severity. More than 60% of arthralgia episodes were in children with cystic fibrosis. This study concluded that the adverse event pattern in children receiving ciprofloxacin was similar to that observed in adults (Hampel et al., 1997).

A review of the nonclinical data, which demonstrate a lack of risk in children in respect of premature epiphyseal closure of the long bones and toxicity in the inner ear in the presence of a perforated tympanic membrane, is provided in Module 2, Section 2.4 and the data from Alcon studies and the literature is summarised in Section 2.6.6.

Alcon has conducted studies to support the topical ocular and topical otic routes of administration. The GLP regulated toxicity studies included in this submission specifically address the risk of ocular and joint toxicity (arthropathy) following topical ocular administration and the risk of ototoxicity following application into the middle ear.

The topical ocular study included in this submission was conducted in juvenile dogs to address risks associated with ciprofloxacin exposure in paediatric patients and demonstrates the safety of topical ocular ciprofloxacin in this population.

The potential for ototoxicity has been studied in the guinea pig. The rapid maturation timeline of guinea pigs (full reproductive function has been reported in as little as 30 days after birth) precludes the conduct of specific juvenile studies in this ototoxicity model. However, the study was initiated with animals as young as feasible (3 to 5 weeks of age). Therefore, the lack of ototoxicity in this model is considered to support the safety of CILOXAN Ear Drops in both adult and paediatric populations.

With respect to the potential toxicity in the inner ear, in the case of perforated tympanic membrane, the efficacy and safety of CILOXAN Ear Drops in children from 6 months to 12 years of age has been demonstrated in C-99-59 (a study conducted in patients with acute otitis media with tympanostomy tubes, AOMT). This study is reviewed in Module 2, Section 2.5 (CILOXAN Ear Drops) and a copy of the report is located in Module 5, Section 5.3.5.1. This study demonstrated the safety and efficacy of CILOXAN Ear Drops in this paediatric population.

We consider that the data available, both nonclinical and clinical, support the safe use of ocular and otic administration of ciprofloxacin in the paediatric population and also the use of CILOXAN Ear Drops in paediatric patients with otitis media, with or without perforated tympanic membranes.

Co-rapporteur's assessment:

CILOXAN Ear Drops
After careful consideration of the MAH's and Agencies answers and proposals our opinion is as follows:
We ***agree with the opinion of French Agencies: general practitioner and paediatricians can treat children's ear infections.***

We ***don't agree*** *with the indication to give CILOXAN Ear Drops to children with* ***otitis and with tympanoplasty tubes.***
Although we understand the argument of Alcon "in children with otitis media with tympanostomy tubes treated with ciprofloxacin….plasma concentration of ciprofloxacin were not detected", however the

concentration of ciprofloxacin in the middle ear in this cases is much higher than the plasma level. Considering this fact the local effect of ciprofloxacin should be checked
If hear impairment occurs several weeks after the ciprofloxacin treatment the relationship of the two facts can be easily overlooked. It would be valuable to carry out a follow up investigation clarifying this problem.
To summarize our concerns about the pediatric use of Ciloxan Ear Drops, it would be important to clarify the possible long-term effects of ciprofloxacin on the inner ear.

ALCON Clinical Study Report 003:65:0102
Protocol No.: C-99-59

The study was approximately two weeks in duration with four scheduled visits; Visit 1 on Day 1 (baseline), Visit 2 on Days 3-5 (during treatment), Visit 3 on Days 8-10 (end of treatment) and Visit 4 on Days 14-17 (post-treatment or test of cure). At the screening/baseline visit (Day 1), the purpose, risks and benefits of the study were explained and the informed consent executed. Subject to the determination of eligibility,

As it can be seen, the study C-99-59 was not a long-term one.

Rapporteur's comments:
We share the Co-Rapporteur's view that long term consequences of the use of Ciloxan ear drops have not been investigated in this study. However, considering the negative outcome of the animal studies and considering that long term therapy involving direct exposure of Ciloxan ear drops to the middle ear are not the intension we would not demand a long term study, respecting that therapeutic indications have been decided nationally. Anyway, a therapeutic indication concerning ears with non-intact tympanic membrane will not be granted in countries where not already approved.

ISSUE 5 (Rapporteur)
CLINICAL SAFETY
In Study C-01-34 one case of eye haemorrhage was reported with ciprofloxacin. The MAH should describe this case.

RESPONSE: One adverse event of eye haemorrhage was reported in the CILOXAN Eye Drops group. On Study Day 3, patient C0134.3452.0636, an 11 day old infant, experienced an event described as scleral haemorrhage in the left eye. This adverse event, which was attributed to eye rubbing and therefore assessed as not related to study drug, was mild in intensity, lasted 1 day, resolved without treatment, and did not interrupt patient continuation in the study.

Rapporteur's assessment:
The MAH has described the case, and no alarming findings are identified.

Issue resolved

ISSUE 6 (Co-rapporteur)
CILOXAN EYE DROPS
MAJOR OBJECTIONS
The indications for children under the age of 1 year cannot be accepted.

RESPONSE: Paediatric patients with bacterial conjunctivitis were treated with CILOXAN Eye Drops as part of two well-controlled clinical studies (C-91-74 and C-01-34). In these studies, the percentages of paediatric patients graded as clinically cured were 87% for C-91-74 at Day 7 and 78% for C-01-34 at Day 9. The eradication rate of pre-therapy pathogen(s) was 90% for C-91-74 at Day 7 and 85% for C-01-34 at Day 9.

Results observed for clinical cure in any paediatric age subgroup (newborn, infant and toddlers, children and adolescents) are similar to the outcomes observed in the overall paediatric population. Likewise, results observed for eradication of the pre-therapy pathogen(s) in any paediatric age group are similar to the outcomes observed in the overall paediatric population.
Overall, the data from these studies support the efficacy of CILOXAN Eye Drops in the treatment of paediatric patients as young as newborns.

A total of 230 paediatric patients received CILOXAN Eye Drops as part of study C-91-74 and C-01-34. Treatment-related adverse events reported for CILOXAN Eye Drops occurred infrequently (an incidence of 1.0% or less). All of the events were mild or moderate in intensity, resolved with or without treatment, and did not interrupt patient continuation in the study. With the exception of ocular hyperaemia and ocular pruritus, all ocular adverse events related to therapy were single patient reports. A review of the treatment-related ocular adverse events revealed no safety concerns in the paediatric population exposed to CILOXAN Eye Drops.

A review of adverse events occurring in newborn infants (0 to 27 days), infants/toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 17 years) revealed similarities to types of adverse events that would be expected in the non-paediatric population. While no patients between 1 month and 1 year of age were evaluated in the clinical trials for CILOXAN Eye Drops, the safety profile for patients in this age range is expected to be similar to that for patients between 1 and 2 years of age (evaluated in C-91-74) and to that of patients less than 1 month of age (evaluated in C-01-34).
In summary, there are no safety concerns regarding the adverse events that would preclude the use of CILOXAN Eye Drops in paediatric patients and Alcon considers that the efficacy and safety data support the use of CILOXAN Eye Drops in patients below the age of 1 year.

Co-rapporteur's assessment:

<u>CILOXAN Eye Drops</u>
We agree with the proposal of the MAH concerning the section 4.2 provided the section 4.4 contains the warning suggested by the French Agencies "The clinical experiment in children less than one year old, particularly in neonates is very limited."

Rapporteur's comment to Co-Rapporteur: We consider a warning less appropriate in view of the age spectrum 0-27 days, 28 days - 23 months, 2 years - 16 years, which we accept, and the amended text in 4.8.

Section 4.8
We don't agree with the opinion of Alcon about the adverse event caused by benzalconium-chlorid reported by Kovoor. It is true these findings are neither specific to CILOXAN nor to pediatric patients. However the eye drop contains benzalconium-chlorid and so in the SPC must be included the side effects due to benzalconium-chlorid.
We agree that this information can be included during the national step.

<u>CILOXAN Eye Ointment</u>
We accept the answers of Alcon

ISSUE 7 (Co-rapporteur)
CILOXAN EYE DROPS
CLINICAL SAFETY
Some supplementation is necessary in the Sections 4.3, 4.4, 4.8, 5.3.

RESPONSE: Proposals for these sections of the SPC have been made by the Co-rapporteur and responses are detailed in the SPC overview document.

ISSUE 8 (Co-rapporteur)
CILOXAN EYE DROPS
OTHER CONCERNS
The paediatric indication is acceptable only above one year of age. We suggest some changes for the SPC that must be included / changed.

RESPONSE: With reference to use of CILOXAN Eye Drops in children under the age of one year please see previous response to Issue 6.
With reference to the SPC, changes proposed by the Co-rapporteur are reviewed in the SPC overview.

ISSUE 9 (Co-rapporteur)
CILOXAN EAR DROPS
OTHER CONCERNS
The applicant must submit a full SPC proposal. We have written some point that ought to be included in it.

RESPONSE: As has been described in the initial submission of data in respect of the paediatric exercise there are national SPCs in place across the EU for CILOXAN Eye Drops, CILOXAN Eye Ointment and CILOXAN Ear Drops. These SPCs are quite divergent. Alcon does not consider that the paediatric exercise should be taken as a means of harmonising the entire SPC for each product across the EU. Alcon proposes that each national SPC will remain as it is currently approved with the exception of some sections detailed for each product in the SPC overview. The specific SPC points which have been proposed by the Co-rapporteur are addressed in this section.

Co-rapporteur's assessment and comments:
Issue 7, 8, 9: We accept the further proposals (not mentioned above).

ISSUE 10 (CMS)
CILOXAN EYE DROPS: How will patients between the ages of 1 month and 1 year be treated? Are there any available data in this age group?

SUMMARY OF RESPONSE: Please see response to Issue 6. While there are no available clinical data in paediatric patients between 1 month and 1 year of age, the efficacy and safety profile of CILOXAN Eye Drops in neonates and in patients from 1 to 12 years of age is similar. Therefore, the efficacy and safety in patients between 1 month and 1 year of age should also be similar. CILOXAN Eye Drops is indicated in some Member States without age restriction and no particular concern has emerged from its clinical usage in any paediatric age group. It is proposed that CILOXAN Eye Drops be indicated in paediatric patients from birth.

Rapporteur's assessment of MAH Response:
The extrapolation from data obtained in neonates from 0-27 days to patients from 1 year and above seems acceptable in view of the similar therapeutic response and adverse events pattern in the different age groups.
Issue resolved

NON-CLINICAL INPUT

Introduction

During the review of available ciprofloxacin paediatric data by the EU Paediatric Work Sharing Group, safety concerns were raised in relation to the risk of arthropathy following topical administration and the risk of ototoxicity following accidental application into the middle ear. In addition, it was suggested that section 5.3 of the SPCs be amended to include language addressing the available juvenile animal data, if any, pertaining to these risks.

In response to these concerns, the Company has prepared an overview and summary of the non-clinical toxicology studies that were conducted to address the above risks and resubmitted the underlying non-clinical study reports filed in the original eye drop, eye ointment or ear drop application, as applicable. The Company has also submitted a proposal for amending section 5.3 of the SPCs as requested.

Non-clinical studies addressing the risk of arthropathy

It is well known that fluoroquinolones accumulate in the cartilage of developing bone, affecting its growth. Thus, ciprofloxacin has been shown to cause degenerative changes in articular cartilage in rats treated orally with doses ≥ 500 mg/kg/day and in juvenile dogs at oral doses ≥ 30 mg/kg/day.

The potential systemic toxicity of ophthalmic solutions of ciprofloxacin was investigated in a GLP study sponsored by the Company (TR #054:3320:1088). Three groups of 2 male and 2 female Beagle dogs were treated in the eye 4 times daily for 1 month with 60 μL of a preparation containing 0, 3 or 7.5 mg/mL of ciprofloxacin. These dogs were 8 weeks old at the start of the study, that is, juvenile. Developing bones and articular tissue were examined both grossly during necropsy and microscopically. No significant effect was found on the growth of bone or on the articular surface of long bones. Toxicokinetic investigations did not reveal measurable levels of ciprofloxacin in plasma. It was therefore concluded that the low level of systemic ciprofloxacin exposure resulting from topical administration of ciprofloxacin implies a negligible risk of arthropathy in paediatric patients.

Non-clinical studies addressing the risk of ototoxicity

As shown in the table below, a number of studies reported in the literature have been conducted to investigate the ototoxicity of ciprofloxacin or structurally related compounds following direct application to the outer or middle ear of experimental animals. Taken together, these studies demonstrate that although repeated local administration to the middle ear results in measurable concentrations in the inner ear, ciprofloxacin and structurally related substances have no observable effect on the structure or function of the cochlea.

In a separate GLP study sponsored by the Company (TR #175:30:0800), groups of 10 guinea pigs of either sex were implanted with a cannula delivering test material directly at the round window niche. These groups were injected twice daily through the cannula with 10 μL of various test materials including, but not limited to, saline solution (negative control), neomycin solution 100 mg/mL (positive control) and ciprofloxacin solution 3 mg/mL. Auditory brainstem response (ABR) was recorded at 2, 8 and 16 kHz after 2 and 4 weeks of dosing. Following the last ABR test, animals were sacrificed, the middle ear opened and examined grossly and the cochlea collected for microscopy. Treatment with ciprofloxacin had no effect on auditory function and was not associated with gross or microscopic lesions that differed from those observed in the negative controls. On the other hand, treatment with neomycin resulted in profound hearing loss at all frequencies and a marked loss of hair cells in the cochlea.

Authors	Species	Test Article and Posology	Study Conclusions
Brownlee et al. (5)	Guinea pigs	7.5 mg/ml ciprofloxacin (0.1 ml, twice daily for seven days)	No effect on hair cell histopathology or auditory brainstem response.
Prieskorn, et al. (6)	Guinea pigs	2 mg/ml ciprofloxacin (10 µl, twice daily for 30 days)	No effect on hair cell histopathology or auditory brainstem response.
Claes et al. (7)	Guinea pigs	2 mg/ml ciprofloxacin (Gelfoam soaked with test article applied to the round window membrane bilaterally once daily for 5 days)	No effect on auditory function.
Barlow et al. (8)	Guinea Pigs	10 mg/ml ofloxacin[a] (0.2 ml, once daily for 7 days)	No hair cell loss detected in the inner ear.
Black et al. (9)	Guinea Pigs	3 mg/ml ofloxacin[a] (10 µl, twice daily for 30 days)	No effect on ABRs, no loss of inner ear hair cells and no adverse effect on vestibular function
Kato et al. (2)	Guinea pigs	3 mg/ml ofloxacin[a,b] (0.1 ml once daily for 30 days)	No effect on humeral trochlea, femoral condyle or osseous tissue (tympanic cavity with auditory tube)
Bagger-Sjoback et al. (3)	Chinchillas	0.1 mg/ml ciprofloxacin (Single-dose of gelfoam soaked with test article applied to the round window membrane either unilaterally or bilaterally)	After 1 hr and 15 minutes of treatment with ciprofloxacin impregnated gelfoam, the mean concentration of ciprofloxacin within the perilymph was 0.165 µg/ml. Therefore, when locally applied to the middle ear, ciprofloxacin has the capacity to enter the inner ear.
Dohar et al. (10)	Cynomolgus monkeys[c]	2 mg/ml ciprofloxacin (3 drops, twice daily for 4 weeks)	No adverse effect on auditory function (ABR) or cochlear hair cell histopathology

[a] Fluoroquinolone closely related to ciprofloxacin.
[b] Animals 4 weeks old (juvenile) at study initiation.
[c] Animals with experimentally induced chronic suppurative otitis media and tympanostomy tubes in place.

Rapporteur's comment:

Fluoroquinolones are known to accumulate in the cartilage of developing bones, causing degenerative lesions (arthropathy). Juvenile dogs are sensitive to this effect and develop arthropathy at oral doses ≥ 30 mg/kg/day. However, in juvenile dogs treated in the eye with up to 1.8 mg ciprofloxacin/day for 1 month, systemic absorption was negligible and there was no noticeable effect on the growth of bone or on the articular surface of long bones.

The potential ototoxicity of ciprofloxacin was investigated in 6 independent studies, including 4 in guinea pigs, 1 in chinchillas and 1 in the cynomolgus monkey. Taken together, these studies indicate that greater than therapeutic doses of ciprofloxacin has no adverse effects on hearing function or cochlear hair cell histology even though the drug was shown to penetrate to the inner ear when applied locally to the round window membrane. For technical reasons these studies were conducted in sexually mature animals, but there are no developmental reasons why these findings cannot be extrapolated to younger age groups.

In conclusion, the submitted non-clinical data suggest that there is no appreciable risk of arthropathy in children treated with ciprofloxacin eye drops at therapeutic doses, or of arthropathy or ototoxicity in children treated with ciprofloxacin ear drops, even in the case of a perforated tympanic membrane.

Section 5.3 of the SPCs

Following the comments made by some Member States during the review process, the Company has agreed to elaborate on the potential risk for arthropathy in section 5.3 of the SPCs for CILOXAN eye drops, eye ointment and ear drops.

The Company has proposed the following text for the eye drops and ointment:

"Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal.

A one month topical ocular study with ciprofloxacin 3 mg/ml eye drops, solution in immature beagle dogs did not demonstrate any articular lesions. Likewise there is no evidence that the ophthalmic dosage form has any effect on the weight bearing points.

Additionally, in 634 children treated orally with ciprofloxacin, clinical and radiological monitoring did not reveal any skeletal toxicity."

Rapporteur's comment:
The last paragraph should be deleted as section 5.3 should not contain clinical data. Otherwise, the Company proposal is acceptable.

The Company has proposed the following text for the ear drops:

"Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal. This dose is
greater than 270 times the proposed otic clinical dose if a 10-kg child is treated with 0.27 mg ciprofloxacin into each ear twice a day.

A one month topical ocular study with ciprofloxacin 3 mg/ml eye drops, solution in immature beagle dogs did not demonstrate any articular lesions. Likewise there is no evidence that the ophthalmic dosage form has any effect on the weight bearing points.

Additionally, in 634 children treated orally with ciprofloxacin, clinical and radiological monitoring did not reveal any skeletal toxicity."

Rapporteur's comment:
The last paragraph should be deleted as section 5.3 is not supposed to contain clinical data. For the first two paragraphs, the Company proposal is acceptable. The Company is advised to consider adding a short paragraph on the absence of ototoxicity following middle ear application in guinea pigs even though these findings were made in sexually mature animals.

REGARDING THE SPC

It should be emphasised that the nationally approved therapeutic indication(s) and posology should be preserved and only the age range for which the three formulations are recommended should be harmonised.

The MAH has revised the SPC proposal for the three formulations as follows:

Alcon considers that the data available on CILOXAN Eye Drops, Eye Ointment and Ear Drops support the following indications:

CILOXAN Eye Drops
Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12-16 years)
Treatment of superficial infections of the eye caused by bacteria susceptible to ciprofloxacin, including corneal abscess, corneal ulcers, conjunctivitis and blepharitis.

CILOXAN Eye Ointment

Adults and children 1 year and above

Treatment of superficial infections of the eye caused by bacteria susceptible to ciprofloxacin, including corneal abscess, corneal ulcers, conjunctivitis and blepharitis.

CILOXAN Ear Drops

Adults and children 1 year and above

Acute otitis externa and acute flare up of otitis media caused by bacteria susceptible to ciprofloxacin.

FROM THE MAH RESPONSE: The review of the paediatric submission by the Rapporteur, Co-Rapporteur and some Member States has been divergent in terms of the indications and also the extent of revision of the SPCs, which should be implemented.
Alcon does not consider that the paediatric exercise should be taken as a means of harmonising the entire SPC for each product across the EU and also recognises the different approaches taken by regulatory authorities in respect of antibiotics.
Accordingly Alcon proposes that each national SPC remain as currently approved with the exception of the sections detailed for each product.
The sections of the national SPCs will be modified, where necessary, to include the information detailed below. Following incorporation of this information, modification of other sections of the national SPCs will be undertaken as required.

Rapporteur's comment:
We acknowledge this position.
Apart from the comment to Section 5.3, the revised SPC is acceptable.
The Company is advised to consider adding a short paragraph on the absence of ototoxicity following middle ear application in guinea pigs even though these findings were made in sexually mature animals and to mention that only juvenile animals are sensitive to the degenerative effect of fluoroquinolones.

RAPPORTEUR'S CONCLUSION ON SPC

It is out of scope of the current project to change the therapeutic indications, as also stated by the MAH. The Company suggests keeping the (different) indications and the posology approved nationally. So, with the exception of the eye drops for which investigation between in patients in the age of one month and one year is lacking, the specified age ranges reflect the paediatric groups, which have been investigated in the single indication. The extrapolation between the age of one month and one year for the use of the eye drops is an uncontroversial pragmatic step as the effect and adverse event profile is similar in all exposed age groups. In conclusion, the revised SPC text for section 4.1 is acceptable provided that the current therapeutic indications are kept nationally. The amendments required by some member states have been implemented.

DISCUSSION ON FINAL SPC FOLLOWING CIRCULATION OF THE JAR:

It was considered by one CMS that Ciloxan eye ointment efficacy and safety should be similar as those assessed with Ciloxan eye drops, and for the same ages, since this pharmaceutical form should be of particular interest in infants. The applicant was requested to discuss this issue to take the opportunity of the paediatric worksharing procedure to implement a harmonised wording on the use of this ointment in children less than 1 year, which in the CMS opinion would represent an optimization of the treatment as compared to the eye drops for this target population. The Rapporteur could however not agree with the extrapolation of the age limit below 1 year for the oinment for consistency with the limit for the eye drops. The Rapporteur did not consider an extrapolation from eye drops to eye oinment justified in the population below 1 year of age in spite of the possible practical advantage, since there is no available data to support such an extrapolation. In order to solve this issue, the applicant committed to submit information on an investigation of Ciloxan oinment in children less than 1 year of age.

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ciloxan is indicated for the treatment of ciprofloxacin-susceptible infections in the eye and the ear. As a part of the EU work sharing procedure in the assessment of paediatric data, the MAH submitted available data in children for Ciloxan eye drops, eye oinment and ear drops. The submitted data consisted of the study C-01-34, which was requested by the FDA to obtain paediatric information on ciprofloxacin eye drops for the treatment of bacterial conjunctivitis in neonates up to 1 month of age. In addition, a review of relevant safety and efficacy data was submitted by the MAH in response to the request for supplementary information as proposed by the Rapporteur. The reviews concerned the studies C-01-34, C-91-74 (Ciloxan eye drops), C-91-29 (Ciloxan eye ointment) and C-98-18, C-99-59 (Ciloxan ear drops), which the MAH had stated to contain the principal efficacy data.

There are national SPCs in place across the EU for Ciloxan eye drops, Ciloxan eye ointment and Ciloxan ear drops and these are quite divergent in terms of indication and posology. It was considered out of scope of the paediatric worksharing procedure to change the therapeutic indications and posology and it was agreed to only harmonise the age range for which the three formulations are recommended. With the exception of the eye drops for which investigation in patients between the age of one month and one year is lacking, the specified age ranges reflect the paediatric groups, which have been investigated in the single indication. The extrapolation between the age of one month and one year for the use of the eye drops was considered an uncontroversial pragmatic step.

No alarming adverse events were reported in the exposed paediatric population. For the three Ciloxan formulations, i.e. eye drops, eye ointment and ear drops, the safety pattern is unremarkable and consistent with what could be expected.

In conclusion, the safety and efficacy data support the use of Ciloxan eye drops in children from birth and the use of Ciloxan eye ointment / Ciloxan ear drops in children aged 1 year and above.

During the review of available ciprofloxacin paediatric data safety concerns were raised in relation to the risk of arthropathy following topical administration and the risk of ototoxicity following accidental application into the middle ear. Consequently, section 5.3 of the SPCs was amended to include language addressing the available juvenile animal data pertaining to these risks.

A consensus was found between member states to introduce other relevant statements with regard to the paediatric use in section 4.4, 4.8, and 5.2. In addition, the final proposed SPC includes some general information as required by some member states (section 4.1, 4.3, 4.4 and 4.8). On 30 March 2007 agreement on the SPC was reached and the procedure was finalised. The final proposed changes for the SPCs for the three formulations are presented in section IV.

Commitments made during the paediatric worksharing procedure:
In response to a request from one concerned member state, the applicant committed to submit information on an investigation of Ciloxan oinment in children less than 1 year of age.

Subsequently at a meeting with this concerned member state, the place of Ciloxan within the anti infective ophthalmic products was discussed and the limited place of Ciloxan ointment for the treatment of children was recognised

After discussion, no adequate additional investigation in paediatric population can be proposed. Consequently the concerned member state considered that the commitment regarding eye ointment experience in children less than one year old can be withdrawn due to acknowledged questionable feasibility of reliable clinical investigation in this target population. It can be concluded that no further information has to be provided by the Applicant.

IV. PROPOSED CHANGES IN THE SPC

Each national SPC should remain as currently approved with the exception of the sections detailed on the following pages for each product.

The sections of the national SPCs will be modified, where necessary, to include the information detailed. Following incorporation of this information, modification of other sections of the national SPCs will be undertaken as required.

CILOXAN Eye Drops

Section 4.1
Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 – 16 years)
Indication as per current national approval

The following text will be included:
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Section 4.2
Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 – 16 years)
Posology as per national approval.

Section 4.3
Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to quinolones.

Section 4.4
The clinical experience in children less than one year old, particularly in neonates is very limited. The use of CILOXAN eye drops in neonates with ophthalmia neonatorum of gonococcal or chlamydial origin is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition.

When using CILOXAN eye drops one should take into account the risk of a rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systematically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions.

As with all antibacterial preparations prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.

Ciprofloxacin should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Section 4.8
With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.

In isolated cases blurred vision, decreased visual acuity, and medication residue have been observed with ophthalmic ciprofloxacin.

Paediatric population:
Safety and effectiveness of CILOXAN 3 mg/ml eye drops were determined in 230 children between the ages of 0 and 12 years of age. No serious adverse drug reaction was reported in this group of patients.

Section 5.2
There are no pharmacokinetic data available in respect of use in children.

Section 5.3
Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal.

A one month topical ocular study with ciprofloxacin 3 mg/ml eye drops, solution in immature beagle dogs did not demonstrate any articular lesions. Likewise there is no evidence that the ophthalmic dosage form has any effect on the weight bearing points.

CILOXAN Eye Ointment

Section 4.1
CILOXAN eye ointment will be indicated for adults and children as follows:
Adults and children 1 year and above

Indication as per current national approval

The following text will be included:
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Section 4.2
Adults and children 1 year and above
Posology as per national approval.

Section 4.3
Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to quinolones.

Section 4.4
There is no experience in children less than 1 year old.

When using CILOXAN eye ointment one should take into account the risk of a rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systematically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions.

As with all antibacterial preparations prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.

Ciprofloxacin should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Section 4.8
Safety and effectiveness of CILOXAN 3 mg/g eye ointment were determined in 103 children between the ages of one and 12 years of age. No serious adverse drug reaction was reported in these patients.

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.

Section 5.2
There are no pharmacokinetic data available in respect of use in children.

Section 5.3
Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal.

A one month topical ocular study with ciprofloxacin 3 mg/ml eye drops, solution in immature beagle dogs did not demonstrate any articular lesions. Likewise there is no evidence that the ophthalmic dosage form has any effect on the weight bearing points.

CILOXAN Ear Drops

Section 4.1
Adults and children 1 year and above:
Indication as per current national approval

The following text will be included:
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Section 4.2
Adults and children 1 year and above:
Posology as per national approval.

Section 4.3
Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to quinolones.

Section 4.4
Efficacy and safety in children less than one year old have not been assessed.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systematically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions.

In otic use meticulous medical monitoring is required in order to be able to determine in a timely manner the possible necessity of other therapeutic measures.

As with all antibacterial preparations prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.

Ciprofloxacin should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Section 4.8

Paediatric population:
Safety and efficacy of CILOXAN 3 mg/ml ear drops was determined in 193 children between the ages of one and 12 years of age. No serious adverse drug reaction was reported in this group of patients.

In otic use the ingredients rarely are sensitising. However as with any substance that is applied to the skin, an allergic reaction to any of the ingredients of the preparation can always occur. With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.

Section 5.2

In children with otitis media with tympanostomy tubes treated with ciprofloxacin 3 mg/ml solution (3 drops three times daily for 14 days), plasma concentrations of ciprofloxacin were not detected (limit of quantification 5 ng/ml). In children with suppurative otitis with perforated tympanic membrane, treated by ciprofloxacin 2 mg/ml solution (twice daily for 7-10 days), no circulating plasma concentration of ciprofloxacin up to the limit of quantification 5 ng/ml was detected. No significant systemic passage of ciprofloxacin is expected under the normal conditions of use.

Section 5.3

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal. This dose is greater than 270 times the proposed otic clinical dose if a 10-kg child is treated with 0.27 mg ciprofloxacin into each ear twice a day.

While the joints of some species of juvenile animals are sensitive to the degenerative effects of fluoroquinolones (primarily the dog), young adult guinea pigs dosed in the middle ear with ciprofloxacin for one month exhibited no drug related structural or functional changes of the cochlear hair cells and no lesions in the ossicles.