LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ximaract
(cefuroxime sodium)

SE/H/1494/01/DC

This module reflects the scientific discussion for the approval of Ximaract. The procedure was finalised on 2016-05-23. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

PharmaSwiss Česká republika s.r.o. has applied for a marketing authorisation for Ximaract, 50 mg, powder for solution for injection. The active substance is cefuroxime sodium (inhibits bacterial cell wall synthesis).

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. For a well-established use (WEU) application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. In a WEU application, results of pre-clinical and clinical trials are replaced by detailed references to published scientific literature. The active substance is not considered a new active substance.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of cefuroxime are well known. No further studies are required and the applicant provides none. Instead the applicant present a non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Pharmacology

Cefuroxime is a second-generation cephalosporin. Cephalosporins interfere with the peptidoglycan synthesis of the bacterial wall by inhibiting the final transpeptidation needed for the cross-links which is bactericidal. Mechanisms for resistance development to cefuroxime are well described. These include hydrolysis by beta-lactamases, reduced affinity of penicillin-binding proteins for cefuroxime outer membrane impermeability, cell wall impermeability and drug efflux system pumps.

III.3 Pharmacokinetics

No data of the concentration profile of cefuroxime following intracameral administration in experimental animals are available from the published literature.

III.4 Toxicology

In experimental animals parenteral administration of cefuroxime had low toxicity. Cefuroxime is by weight of evidence not considered genotoxic. The lack of a carcinogenicity study is considered acceptable given the local intracameral applications and the single dose administration. Reproductive studies in animals have shown no effects on fertility, or embryo-foetal development. Cefuroxime crosses the placenta, however, no effects during pregnancy are anticipated, because systemic exposure to cefuroxime following intracameral application of a single dose is considered negligible. Cefuroxime is also excreted in the milk. Given the low systemic exposure following intracameral application adverse effects of the nursing infant at therapeutic doses are not expected.

III.5 Ecotoxicity/environmental risk assessment

It is concluded that cefuroxime (in sodium form) is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

In summary, the data presented did not reveal any additional risk or special hazard for intracameral use of cefuroxime for “Antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery”.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ximaract is a sterile ophthalmic powder for solution for intracameral injection, containing 50 mg cefuroxime. The vial is for single use. However, the volume of the reconstituted solution will be 5 ml while 0.2-0.3 ml would be needed to deliver 0.1 ml to one patient. Consequently, a use to more than one patient is expected, see further Safety.

Ximaract should be dissolved in 0.9% sodium chloride. In view of the intracameral route of delivery, the reconstituted Ximaract may be regarded as a "generic parenteral solution", but also as a locally acting locally applied product although with a different indication and the Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) is therefore considered applicable.

IV.2 Pharmacokinetics

The systemic pharmacokinetics of cefuroxime is well characterised and detailed in the SmPC for Zinacef. Since a very limited systemic exposure is expected after ocular use, only the available pharmacokinetic data of relevance for the targeted indication is addressed.

A pharmacokinetic analysis of cefuroxime after intracameral injection showed a median intracameral level of cefuroxime of 2742 mg/L 30 seconds and 756 mg/L 60 minutes after drug instillation, i.e. there was a decline of cefuroxime concentrations by almost a factor 4 the first hour after injection. This would correspond to an approximate half-life of 30 minutes which would lead to cefuroxime levels over MIC for several relevant species for up to 4- 5 hours after surgery. While the effect of fluoroquinolones is concentration-dependent, cefuroxime acts in a time-dependent manner and a sufficient duration of concentrations over MIC in the aqueous humour is thus needed. Consequently, it cannot be concluded that this is sufficient to eradicate all the target contaminants. Since it is unacceptable from an ethical view to collect aqueous samples a longer time period after surgery, the duration of time cefuroxime levels above MIC is not possible to assess in a clinical setting. Anyhow, the lack of this information is considered overruled by the efficacy data (see below)

IV.3 Pharmacodynamics

Cefuroxime is a second-generation cephalosporin β-lactam antibiotic with *in vitro* activity against a wide range of Gram-positive and Gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain Gram-negative bacteria. Analysis of isolates from postoperative endophthalmitis (POE) cases confirmed that the main identified pathogens were Gram-positive bacteria (80-90%) with coagulase-negative *Staphylococcus*, *Staphylococcus aureus and Streptococcus* spp among the most common species. MRS, penicillin-resistant *Streptococcus pneumoniae* and *Pseudomonas* spp are resistant to cefuroxime. *Pseudomonas* spp is a less common, but still relevant cause of infection. However, there are indications of a change in pattern of bacterial spectrum involved in POE. The data provided by the Applicant refers to mid and late 2000 (e.g. Fernandez-Rubio et al, 2009). An update (2013) with patients admitted for intraocular surgery, and the isolates showed that more than 80% belonged to the typical skin and mucosa flora.

Although gram-positive are the most common cause of POE, prevalence of certain pathogens may vary with geographical region. The Applicant also presented data on isolates from 1987 to 2011 showing gram positive bacteria to have 93.5% sensitivity to cefuroxime. Taken together,

cefuroxime is still considered to have a fair coverage of the most important target pathogens.

The last 10-15 years use of intracameral cefuroxime has not indicated an increase in resistant strains causing endophthalmitis. After injection in the anterior chamber, this may however not be a major issue due to the single administration that gives a high local concentration. On the other hand, it is impossible to predict whether this will change if the use is further extended and the incidence rate of POE has to be continuously evaluated in future PSURs (Periodic Safety Update Report).

Also, if known that a patient have had a previous infection or reside in an environment where colonisation with MRS may be a problem, alternative prophylactic antibiotic should be considered. The Applicant states that there has been no problem with MRSA and cefuroxime use in Sweden by referring to a publication from 2002. Overall in EU, MRSA accounts for 44% of healthcare-associated infections and although MRSA does not replace susceptible Staphylococcus aurus as a causative agent for infections, it adds to the disease burden and a net increase in the infections of S. aureus. A review of observational studies in Europe between 2000-2010 showed MRSA prevalence, expressed as percentage of S. aureus blood isolates, varied over a great range, from less than 1% to greater than 20%, and above 50% in some countries (Malta, Portugal). The incidence of MRSA ocular infections is rising which is consistent with the resistance trends in non-ocular staphylococcal isolates. The Applicant concludes that MRSA POE in Europe is still scarce and POE prevention with intracameral cefuroxime in conjunction with other preventive measures remains an effective tool against POE. Overall, this is agreed and importantly, the SmPC, section 4.4 clearly outlines that in patients at risk for infections with resistant strains, e.g. MRSA alternative prophylaxis should be considered. No further update of the SmPC is requested.

No evaluation on the potential for pharmacodynamics interactions has been made. Due to the low systemic exposure after intracameral injection, no systemic interactions of relevance are expected and no local interactions have been reported over the years

IV.4 Clinical efficacy

The Applicant has not performed any clinical studies but refer to published data. In support for the preventive effect of intracameral cefuroxime, the Applicant has submitted data from the pivotal prospective, randomised and controlled ESCRS study together with a number of prospective and retrospective studies performed across Europe. Taken together, the studies involve almost 500,000 patients.

Dose-effect

Ximaract is to be administered as an intracameral injection of 1 mg. No dose-response studies with intracameral cefuroxime have been performed. While such data should have been presented or at least discussed in the clinical overview, there is a discussion on the time over MIC (see Pharmacokinetics) when injecting 1 mg of cefuroxime. Although 1 mg cefuroxime was demonstrated to lead to aqueous humour levels over MIC for several relevant species for up to 4- 5 hours after surgery, it cannot be concluded that this is sufficient to eradicate all the target contaminants. However, the overall clinical experience with 1 mg cefuroxime overrules the need for additional dose-finding, see further below.

- **Pivotal study**

The pivotal ESCRS study is a prospective randomised partially masked multicenter, cataract surgery study evaluating the effect of prophylaxis of POE in 4 treatment arms according to the below table.

Table 1. Treatments

Group A Placebo vehicle drops x 5[1] No intracameral injection	**Group B** Placebo vehicle drops x 5[1] Intracameral cefuroxime injection
Group C Levofloxacin drops 0.5% x 5[1] No intracameral injection	**Group B** Levofloxacin drops 0.5% x 5[1] Intracameral cefuroxime injection

[1] One drop 1 hour before surgery, 1 drop half an hour before surgery, 1 drop immediately post op. 1 drop 5 minutes later, and 1 drop 5 minutes later again.

The ESCRS study was performed between 2003 and 2006.

The study included all patients, also diabetics, undergoing routine cataract surgery with phacoemulsification and IOL implantation in each of the 24 units from 8 EU countries and Turkey taking part in the study. From an efficacy view, the included patient population is considered representative for the target population. The required sample size was estimated to 35,000 patients based on an estimated background incidence of POE of 0.2 %.

The two primary endpoints in the study were to evaluate the events of 'presumed endophthalmitis' and the events of 'proven endophthalmitis' (culture or PCR), while a secondary endpoint evaluated potential risk factors for POE. Due to the two primary endpoints and the multiple group comparisons, there is an issue regarding multiplicity which was not accounted for.

There were further frequent interim analyses (monthly to test for futility/safety issues, quarterly to test for efficacy) without any control of the type 1 error spending function. This is not appropriate and the statistical strength as well as the size of the effect will thus be difficult to conclude on, see further below.

At one of the interim analyses including approximately 40 % of the planned number of patients, it was determined to terminate the study early due to a signal of efficacy. In this interim dataset (13,700 patients in total), 23 patients that were not treated with cefuroxime presented with presumed endophthalmitis (16 proven) while in the two groups that received cefuroxime 5 cases were identified (3 proven). For the presumed endophthalmitis, there was consequently a 4.6-fold reduction in risk (p =0.002). For the proven cases the risk reduction was 5.3 (p=0.008).

In the final dataset, there were few deviations from the protocol resulting in very similar ITT (n=16,211) and PP (n=15,971) populations. Loss to follow up was limited to 2 % (392 patients) due to failure to attend scheduled appointments, death, and incomplete data reports. Due to the few deviations and the limited loss to follow up, the absence of details is considered acceptable.

Efficacy outcome: Results of the primary endpoints are summarised in the figure and tables below.

Figure 1. Total patient numbers and endophthalmitis incidence rates in each of the 4 groups in the study based on ITT and PP analysis.

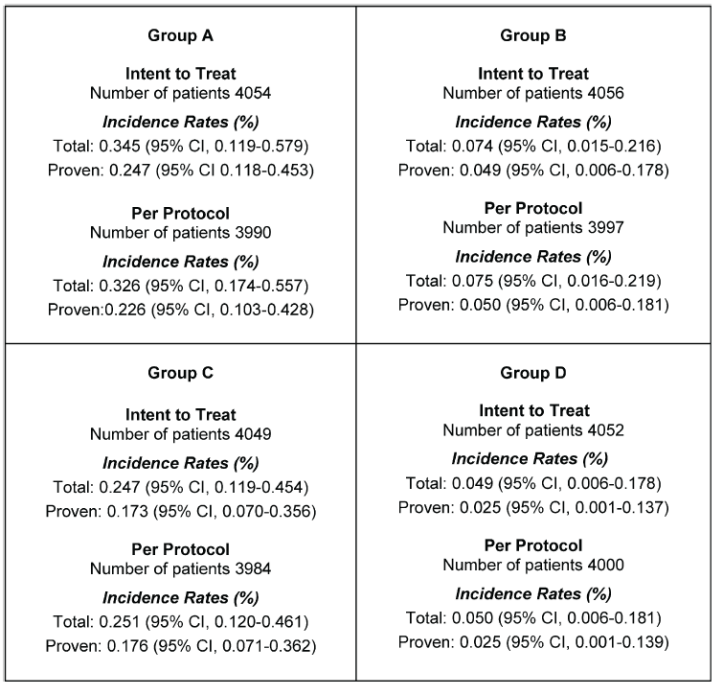

Table 2. Postoperative endophthalmitis incidence with or without the additional use of topical antibiotic – Final outcome

	Group A[1]	**Group B[1]**	**Group C[1]**	**Group D[1]**
	No cefuroxime	Intracameral cefuroxime	No cefuroxime	Intracameral cefuroxime
	Perioperative placebo eyedrops x 5[2]	Perioperative placebo eyedrops[2]	Perioperative levofloxacin eyedrops[2]	Perioperative levofloxacin eyedrops[2]
Followed-up number	4054	4056	4049	4052
Total reported endophthalmitis	14	3	10	2
Proven infective endophthalmitis	10	2	7	1

[1] All patients received preoperative povidone iodine and postoperative topical levofloxacin for 6 days.
[2] Perioperative eye drops consisted in: 1 drop 1h before surgery, 1 drop 30min before surgery and 3 drops at 5-minute intervals commencing immediately at the end of surgery.

Figure 2. Bacteriological results relating to all endophthalmitis cases (proven and non-proven) in patients recruited to the study.

Group A Placebo vehicle drops x 5* No intracameral injection	Group B Placebo vehicle drops x 5* Intracameral cefuroxime injection
2 *Streptococcus pneumoniae* 1 *Streptococcus salivarius* 1 *Streptococcus suis* 1 *Streptococcus mitis, Staphylococcus epidermidis* 1 *Staphylococcis aureus, Staphylococcus epidermidis, Propionibacterium acnes* 3 *Staphylococcus epidermidis*† 1 *Propionibacterium acnes* 4 Non-proven †One removed for *PP* analysis	2 *Staphylococcus epidermidis* 1 Non-proven
Group C **Levofloxacin drops 0.5% x 5*** **No intracameral injection**	**Group D** **Levofloxacin drops 0.5% x 5*** **Intracameral cefuroxime injection**
1 *Streptococcus salivarius* 1 *Streptococcus sanguinis* 1 *Streptococcus oralis* 1 *Staphylococcus aureus* 2 *Staphylococcus epidermidis* 1 *Staphylococcus hominis/haemolyticus* 3 Non-proven	1 *Staphylococcus warneri* 1 Non-proven

*One drop 1 hour before surgery, 1 drop half an hour before surgery, 1 drop immediately postoperation, 1 drop 5 minutes later, and 1 drop 5 minutes later again. All groups received povidone–iodine 5% (Betadine) before surgery and were prescribed levofloxacin 0.5% eyedrops from days 1 to 6 after surgery 4 times daily.

Thus, the incidence rates (ITT) of presumed endophthalmitis in the groups receiving cefuroxime were 0.074 % in the group that received perioperative placebo eye drops and 0.049% in the group that received perioperative levofloxacin. In the two groups receiving no intracameral cefuroxime, the corresponding incidence rates (ITT) were 0.345% and 0.247% in the perioperative placebo and levofloxacin eye drop groups, respectively. This translated into a risk reduction of 4.9 for presumed POE (95% CI 1.87-12.9, p=0.001) and 5.9 for proven POE (95% CI 1.72 – 20.0, p=0.005) (Table 3, Table 4). Besides the risk reduction by the use of intracameral cefuroxime, this study demonstrated that other risk factors for the development of POE included the clear corneal procedure, surgical complications (only for presumed cases) and silicone IOLs (secondary endpoint), see Table below.

Table 3. Risk Factors for Total Endophthalmitis (proven + non-proven) (Logistic Regression; ITT set)

Risk Factor	**Total Endophthalmitis**		
	OR	**95 %**	**p-value**
Age (years)	1.02	0.98-	0.311
Sex (female, male)	1.79	0.86-	0.121
Surgeon experience level (1, 2, 3)	2.01	1.02-4.0	0.046
Site of incision (scleral tunnel, clear	5.88	1.34-	0.019
Any surgical complications (absent,	4.95	1.68-	0.004
IOL optic material (acrylic, silicone)	3.13	1.47-	0.003
Cefuroxime injection (absent, present)	**4.92**	**1.87-**	**0.001**
Levofloxacin eye drops perioperative	**1.41**	**0.67-**	**0.368**

Source: ESCRS Endophthalmitis Study Group (2007); CI: confidence interval; IOL: intraocular lens; OR: Odds ratio

Table 4. Risk Factors for Proven Endophthalmitis (Logistic Regression; ITT set)

Risk Factor	**Total Endophthalmitis**		
	OR	**95 % CI**	**p-value**
Age (years)	1.01	0.96-	0.773
Sex (female, male)	2.70	1.07-6.8	0.035
Surgeon experience level (1, 2, 3)	2.86	0.99-	0.053
Site of incision (scleral tunnel, clear	7.43	0.97-	0.054
Any surgical complications (absent, present)	-	-	-
IOL optic material (acrylic, silicone)	4.10	1.66-	0.002
Cefuroxime injection (absent, present)	**5.86**	**1.72-**	**0.005**
Levofloxacin eye drops perioperative	**1.51**	**0.62-3.7**	**0.368**

Source: ESCRS Endophthalmitis Study Group (2007); CI: confidence interval; IOL: intraocular lens; OR: Odds ratio

However, as for the multiplicity issues with regards to endpoints and multiple comparisons, the interim analyses with an inadequate control of the type I error hampers the interpretation of the outcome of the study and therefore, the effect must be weighed against the supportive studies discussed below. The ESCRS study has also been criticised for the higher than expected rate (0.35%) of cases of endophthalmitis in the group not receiving cefuroxime and peri-operative levofloxacin (0.25% for those receiving peri-operative levofloxacin only). The Applicant interprets that the CI 95% (0.119% and 0.579%) for total endophthalmitis is within the background incidence rate of POE in Europe when no perioperative antibiotic prophylaxis was given. However, rates reported in other studies have often been for patients receiving various additional forms of prophylaxis, some of which have would be expected to be of benefit. The Applicant also points to a likely underreporting of POE cases in the retrospective evaluations. These arguments are acknowledged.

Among the proven cases of endophthalmitis, there were 11 cases of staphylococci, eight cases of streptococci, two cases of *Propionibacterium acnes*, one complex of salmonella, *Escherichia coli* and *E. shigella* and one case of *Gemella haemolysins*. The three proven cases in the cefuroxime-treated groups were all staphylococci. The visual outcome of these patients ranged from 20/20 to 20/80. All eight cases of streptococci occurred in the non-injected groups; their visual acuity ranged from 20/20 to no light perception. This is an important

outcome in view of the very poor visual outcomes that has been reported after endophthalmitis of streptococcal origin.

Taken together, the limitations of the pivotal study make an accurate estimation of the true treatment effect of cefuroxime difficult, i.e. it is a risk that the 5-fold decrease in the rate of endophthalmitis is an overestimate. However, the study does give a support of a preventive effect of cefuroxime that will be weighed together with the supportive studies below.

- **Supportive studies**

In the majority of the supportive studies, a comparison with the reported incidence rate before starting cefuroxime prophylaxis with that observed after prophylaxis was initiated. In two fully prospective studies, a comparison with concomitant control, i.e. where part of the study populations could for some reason not be given cefuroxime (e.g. allergy), was performed. The studies are summarised below.

Table 5. Overview of ESCRS Study and Supportive Studies for Intracameral Cefuroxime as Prophylaxis of Postoperative Endophthalmitis

Study / Author	**Period, Country**	**Study Design**	**Number of Patients**	**Number of Patients Receiving Intracameral Cefuroxime**	**Number of patients Receiving no Intracameral Cefuroxime**	**Infection Rate in Patients Receiving Intracameral Cefuroxime Group**	**Infection Rate in Ratients Receiving no Intracameral Cefuroxime**
ESCRS Study 2007	Sept 2003 to Jan 2006 Multi-national	multicenter randomized partially masked placebo controlled P3 study	ITT: 16,211 PP: 15,971	ITT: 8,108 PP: 7,997	ITT: 8,103 PP: 7,974	PP: 0.063% total infections 0.038% proven infections	PP: 0.289% total infections 0.201% total infections
Wejde et al., 2005b	1999 to 2001 Sweden	prospective survey	158,679	151,874	6,805	0.053 %	0.22 %
Garcia-Saenz et al., 2010	Jan 1999 to Sept 2005* Oct 2005 to Dec 2008**, Spain	cross-sectional descriptive study	13652	**7057	*6595	**0.043%	*0.59%
Gualino et al,, 2010	2007 to 2008 France	retrospective analysis	3,316	3,316	-	0.06 %	-

Díez et al., 2009	Oct 2003 to Sept 2008 Spain	retrospective analysis	4,281	4,281	-	0.11 %	-
Yu-Wai-Man et al., 2008	Jan 2000 to Dec 2006 England	retrospective cohort study	36,743	17,318	19,425 Sub-conjunctival Cefuroxime	0.046 %	0.139 % Sub-conjunctival Cefuroxime
Montan et al., 2002b	1990 to 2000 Sweden	non-controlled retrospective observa-tional study	66,280	32,180	34,102	0.06 %	0.26 %
Lundström et al., 2007	Jan 2002 to Dec 2004 Sweden	prospective comparative study	225,471	223,156	2,315	0.045 %	0.35 %
TOTAL				455,176			
TOTAL				455,176			

ITT: Intent to treat; PP: Per protocol

The supportive data presented by the Applicant indicate that in Europe, the incidence rate of POE when intracameral cefuroxime was not used was reported to be in a range of 0.14-0.59%, i.e. within the range of the 0.25-0.35% background incidence among those not receiving intracameral cefuroxime in the ESCRS-study. Overall, the supportive studies pointed to a 3 to 13-fold reduction of risk for a POE after initiation of intracameral treatment with cefuroxime and give support to a risk-reduction in the range of the 5-fold reduction observed in the pivotal study.

Among the supportive studies, the two prospective studies reported by Wejde (2005a) and Lundström (2007) are of special interest. In these studies, reporting was made to the Swedish cataract register. This is a registry that has collected prospective data on cataract operations performed in Sweden since 1992. Behndig et al (2011) reported that the Swedish National Cataract Register now contains data from more than one million cataract surgery procedures, representing 95.6% of the surgeries performed in Sweden during 1992-2009, and EOP has continuously decreased to below 0.04%. Since 1998, all ophthalmic units have committed to report every incident of POE to the registry.

The information submitted to the registry is fairly detailed and include for example, prophylactic regimen, type of surgery and IOL, communication anterior chamber/vitreous (e.g.

posterior capsule break). In addition, the Swedish ophthalmologists are very familiar with the data reporting which contributes to the high quality of data. Despite the limitations with regards to the lack of randomization between prophylactic protocols and the lack of a full characterisation of risk factors of the study populations, these prospective studies that showed that the use of intracameral cefuroxime reduced the risk of POE with 3.6 (95% CI 2.29-5.81, p<0.001) and 7.2 (95% CI 3.71-14.11, p<0.001). Consequently, the prospective studies certainly support a relevant effect of preventive effect of intracameral cefuroxime and thus support that the outcome of the ESCRS study is of a reasonable magnitude.

IV.5 Clinical safety

Taken together, almost half a million patients have been exposed to intracameral cefuroxime in the published pivotal ESCRS study and the supportive clinical studies referred to in this application. In the pivotal study, although reported age and prevalence of diabetes seemed representative for the target population, only limited information with regards to other demographics of exposed patients can be retrieved and the reporting of adverse events (AEs) is scarce. However, clinical experience especially from the large studies originating from Sweden both from one single-site (Montan et al 2002) and from the Swedish National Cataract Registry (Wejde et al 2005; Lundström et al 2007) is reassuring with regards to exposure in the proposed target population.

In addition, data from registries covering a vast number of procedures conducted under antibiotic prophylaxis (more than a million alone from the Swedish registry (see Behndig et al 2011, Behndig et al., 2013) also indicates a substantial positive development with a decrease in complications and improved outcome.

However, there was no information provided for the rate of AEs reported neither in the publications issued for the results of the ESCRS study and this information was very limited in the publications of the supportive studies. Only in the study by Diez, it was concluded that no anterior toxic segment syndrome or corneal oedema on discharge (between 1 and 1.5 months) were observed. The number of cases of cystic macular oedema with visual repercussion did not seem to increase either.

Although the size of the total safety population is very large and reassuring – there are limited reports of adverse reactions from the ESCRS and supportive studies or other sources to confirm the reassuring safety profile. Nevertheless, despite this deficiency, the benefits of using cefuroxime in cataract compensate.

There is a risk of hypersensitivity reactions to cefuroxime administered into the anterior chamber of the eye. Studies suggest that anaphylactic reactions to cephalosporin are rare (frequency 0.0001 to 0.1%), however, deaths have been reported. Therefore, the proposed wording of section 4.3 Contraindications; “hypersensitivity to cefuroxime or to the cephalosporin group of antibiotics” and section 4.4 Special warnings and precautions for use; “special care is indicated in patients who have experienced and allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur”, is endorsed. A warning with regards to hypersensitivity to penicillin or any beta-lactam drug would suffice in view of the vast number of studies failing to conclusively establish that penicillin allergy increases the risk of an allergic reaction to cephalosporins.

There is also a potential risk for cefuroxime-induced toxicitiy on corneal endothelial cells. This was addressed specifically in a small published study (n=90, 1:1) comparing subjects that received cefuroxime with those who did not (Montan et al. 2002a). The decline in the number of endothelial cells was less pronounced in cefuroxime-treated patients; however, the

difference did not attain statistical significance. Another potential issue is that of toxic effects on the retina, especially in case of perioperative break of the posterior lens capsule. This was investigated using optical coherence tomography (OCT) in a study with sixty-two patients (cefuroxime vs. vehicle) (Gupta et al., 2005). No increased macular thickness secondary to the use of intracameral cefuroxime four weeks to six weeks postoperatively was found.

In recent literature articles (Ciftci et al, 2013, Le Dû et al, 2014), eye inflammation, cystoid macular oedema and macular oedema have been associated with of intracameral prophylactic administration of cefuroxime following cataract surgery as reported in the PSUR of Aprokam, while these reports may well be confounded by the surgical procedure as well as overdose. The Applicant's position is that ocular toxicity (macular oedema, eye inflammation) were essentially related to administration of higher doses than recommended and do not warrant an addition in the Risk Management Plan (RMP). However, these safety topics will continue to be under review as a potential signal and take the actions needed in case of any further information that warrants updates of the RMP or the label.

Preparation of the product involves only one dilution step in contrast to the two dilution steps used in the ESCRS study. It is assumed that this will reduce the risk of medication errors. In addition, since the present formulation is intended for single-patient use only, the risk of bacterial spread from a contaminated vial used for multiple patients is expected to be reduced. However, the 5 ml volume of diluted product would still allow administration to more than one patient if a separate syringe and needle is used. From a clinical view, the Applicant has amended the wording of the SmPC, section 4.2 further to highlight this issue.

Patients aged <18 years were excluded from the ESCRS study. However, reports of use of cefuroxime in children undergoing cataract surgery for congenital or developmental cataract were found in the literature. It is endorsed that use in children <18 years should be included in the RMP as missing information and appropriately addressed in the SmPC.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan (version 1.1), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ximaract.

Safety specification
The safety concerns listed by the Applicant are shown in **Error! Reference source not found.**below. The safety profile of the cefuroxime is considered to be well established.

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions including anaphylactic reactions
Important potential risks	Corneal toxicity
	Retinal toxicity
	Medication error
	Off-label use
Important missing information	Use in children <18 years
	Use in special patient groups (patients with severe risk of infection, patients with

	complicated cataracts, patients having combined operations with cataract surgery, patients with severe thyroid disease, patients with less than 2,000 corneal endothelial cells)

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

In order to prevent medication errors Section 4.2 Posology and method of administration reads: "The recommended dose is 0.1 ml of reconstituted solution (see section 6.6), i.e.1 mg of cefuroxime THE RECOMMENDED DOSE MUST NOT BE EXCEDED (see section 4.9)".

Summary of the RMP
The list of ongoing safety concerns is acceptable. Routine pharmacovigilance activities are considered sufficient. No additional risk minimisation activities are proposed. Overall, this is acceptable.

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly. **Issue is resolved**.
The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Intracameral cefuroxime has been used extensively off-label in several EU countries to prevent POE after cataract surgery which translates into a lack of pharmacovigilance activities.

In 2012, Aprokram 50 mg Powder for Solution for Injection, the first medicinal product of this well-known antibiotic for intracameral use, was approved via the Decentralised Procedure (SE/H/1080/01). The proposed indication and posology for Ximaract 50 mg Powder for Solution for Injection is the same as Aprokam's.

Ximaract is reconstituted in one step under sterile conditions to get a single use and reproducible solution for injection intended for one patient only.

Cefuroxime has a fair antibiotic coverage against most species of relevance for the targeted indication, i.e. mainly *Staphylococcus* and *Streptococcus* spp. This is supported by recent data from different regions in Europe. The effect of cefuroxime on streptococci is of special importance in view of the very poor visual outcomes reported in the review on endophthalmitis of streptococcal origin. In addition, recommendations regarding the use of alternative prophylactic antibiotics when resistance may be a problem are included in the SPC, section 4.4 and section 5.1 which is appropriate.

In support for the preventive effect of intracameral cefuroxime, the Applicant has submitted data from the pivotal prospective, randomised and controlled ESCRS study together with a number of prospective and retrospective studies performed across Europe.

The pivotal ESCRS study involving approximately 16,000 patients demonstrated decreased an incidence rate of presumed endophthalmitis in the two groups receiving intracameral cefuroxime. The rates were of 0.074 % in the group that received perioperative placebo eye drops and 0.049% in the group that received perioperative levofloxacin in addition to the cefuroxime injection. The corresponding figure in the group that received no cefuroxime or perioperative levofloxacin was 0.345%, while the rate in the group that received perioperative levofloxacin only was 0.247%. This translated into a risk reduction with the use of cefuroxime of 4.9 for presumed POE (95% CI 1.87- 12.9, p=0.001). A similar difference was observed with regards to the risk reduction for proven POE (OR 5.9, 95% CI 1.72 – 20.0, p=0.005).

Seven supportive studies, whereof 5 retrospective and 2 prospective, performed across Europe, all together involving approximately 450, 000 patients, pointed to a 3 to 13-fold reduction of risk for a POE after initiation of intracameral treatment with 1 mg cefuroxime. These studies give support to a risk-reduction in the range of the 5-fold reduction observed in the pivotal study. Among these studies, the two prospective studies are of specific value to support an effect of cefuroxime in the prevention of POE. These studies that showed that the use of intracameral cefuroxime reduced the risk of POE with a factor of 3.6 (95% CI 2.29-5.81, p<0.001) and 7.2 (95% CI 3.71-14.11, p<0.001). Consequently, the prospective studies certainly support a relevant effect of preventive effect of intracameral cefuroxime.

Uncertainties of the benefits

Some bacteria like coagulase-negative staphylococci and *Propionibacterium acnes* are known to have the potential to form a biofilm on surgical implants and cefuroxime's ability to prevent biofilm formation since the significance of biofilm-forming bacteria in POE is not known. The pivotal ESCRS study has a number of flaws. The study has been criticised for not administering the topical 4th generation fluoroquinolones, for lack of adjustments of

multiplicity (two primary endpoints, 4 treatment groups) and for the many interim analysis without an adequate handling of the type I error that lead to an early termination of the study. This makes the sizes of the p-values and, consequently, the estimation of the size of the effect uncertain and the outcome is weighed together with the supportive studies.

Risks
The safety profile of intracameral cefuroxime appears reassuring and the total number of patients exposed in the pivotal and supportive clinical studies is very large, reaching almost 500 000 exposed patients. The main risks identified are those of very rare hypersensitivity reactions that can be fatal, while there are potential risks for corneal endothelial cell toxicity and retinal toxicity, the latter especially in case of perioperative break of the posterior lens capsule. However, the risk of endothelial cell toxicity and retinal toxicity has only been reported as a result of overdose of cefuroxime (40-50-fold the recommended dose) and the risks at the recommended dose are therefore only potential.

Uncertainties of the risks
Although the safety profile appears reassuring, the reporting of adverse events from the published studies is scarce.

Ximaract is for single use. However, the volume of the reconstituted solution will be 5 ml while 0.2-0.3 ml would be needed to deliver 0.1 ml to one patient. Consequently, it is questioned whether the 5 ml of the reconstituted content of cefuroxime will be used only to one patients.

In recent literature articles (Ciftci et al, 2013; Le Dû et al, 2014), eye inflammation, cystoid macular oedema and macular oedema have been associated with intracameral prophylactic administration of cefuroxime following cataract surgery as reported in the PSUR of Aprokam, while these reports may well be confounded by the surgical procedure as well as overdose. The events will be kept under future review.

Importance of the benefits vs. the risks
The pivotal ESCRS study has a number of limitations which makes the estimation of the size of the 5-fold risk reduction of POE uncertain. Seven supportive studies performed across Europe, all together involving approximately 440, 000 patients, pointed to a 3 to 13-fold reduction of risk for a POE after initiation of intracameral treatment with cefuroxime. In view of a risk reduction in a similar range in the two supportive studies that were prospective (odds ratios 3.6 and 7.2) and thus given considered of high importance, a relevant effect of preventive effect of intracameral cefuroxime is supported.

In the ESCRS publication presenting the pivotal study (2007), the benefit of cefuroxime was translated as follows: “Assuming a conservative average of 2.5 million cataract operations per year and a background incidence rate (without the use of perioperative antibiotics) of 0.3%, 75 000 cases of endophthalmitis could be expected to occur in Europe during the next 10 years. Based on these assumptions, the introduction of perioperative intracameral cefuroxime in cataract surgery across Europe could reduce the number of endophthalmitis infections by approximately 60 000 cases over the coming decade.”

In view of the reported 2.5 million operations performed in France, Germany, Italy, Spain, and the United Kingdom in 2003, the above estimate is certainly conservative. On the other hand, considering the established use of perioperative topical antibiotics, an incidence rate of POE would rather expected to be in the range of 0.2% leading to an estimate of 5,000 yearly cases of POE in the above countries. Taking the ESCRS study and the key supportive studies

together, the use of intracameral cefuroxime may indicate that this number could be reduced to a range between 700 and 1,400 patients. This is of a clear benefit considering the poor visual outcome after an endophthalmitis.

Although there are clear limitations in the reporting of adverse events in the published studies, the overall experience over the last 10 years (especially in Sweden) including the almost half a million patients that were part of studies submitted with this application indicate that the intracameral injection of 1 mg cefuroxime is well tolerated. The main risk appears to be that of hypersensitivity reactions, although rare, it may be fatal.

Currently the identified risk of hypersensitivity and the potential risks include the risks of ocular toxicity and retinal toxicity are adequately addressed in the SPC.

Conclusion
The benefit/risk for Ximaract (cefuroxime sodium) 50 mg powder for solution for injection, is assessed as positive. The application is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Ximaract, 50 mg, powder for solution for injection was positively finalised on 2016-05-23.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se