SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

APROKAM 50 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of cefuroxime (as 52.6 mg of cefuroxime sodium).

After reconstitution with 5 ml of solvent (see section 6.6), 0.1 ml solution contains 1 mg of cefuroxime.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection [powder for injection].

White to almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents, including guidance on the antibiotic prophylaxis on eye surgery.

4.2 Posology and method of administration

Intracameral use. One vial for single-use only.

Posology

Adults:

The recommended dose is 0.1ml of reconstituted solution (see section 6.6), i.e. 1mg of cefuroxime.

DO NOT INJECT MORE THAN THE RECOMMENDED DOSE (see section 4.9).

Paediatric population:

The optimal dose and the safety of APROKAM have not been established in the paediatric population.

Elderly:

No dose adjustment is necessary.

Patients with hepatic and renal impairment:

Considering the low dose and the expected negligible systemic exposure to cefuroxime using APROKAM, no dose adjustment is necessary.

Method of administration

APROKAM must be administered after reconstitution by intraocular injection in the anterior chamber of the eye (intracameral use), by an ophthalmic surgeon, in the recommended aseptic conditions of cataract surgery. Only sodium chloride 9 mg/ml (0.9 %) solution for injection must be used when reconstituting APROKAM (see section 6.6).

After reconstitution, APROKAM should be inspected visually for particulate matter and discoloration prior to administration.

Slowly inject 0.1ml of the reconstituted solution into the anterior chamber of the eye at the end of the cataract surgery.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to cefuroxime or to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

Treatment with APROKAM is for intracameral use only.

Special care is indicated in patients who have experienced an allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur.

In patients at risk for infections with resistant strains, e.g. those with known previous infection or colonisation with MRSA (Methicillin-resistant *Staphylococcus aureus*), alternative prophylactic antibiotic should be considered.

In the absence of data for 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 2000 corneal endothelial cells), APROKAM should only be used after careful risk/benefit assessment.

The use of cefuroxime should not be regarded as an isolated measure but other circumstances are also of importance like prophylactic antiseptic treatment.

Corneal endothelial toxicity has not been reported at the recommended concentration of cefuroxime; nevertheless, this risk cannot be excluded and in the post-surgical surveillance, physicians should have in mind this potential risk.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

Since the systemic exposure is expected to be negligible, systemic interactions are unlikely.

No incompatibility with most commonly used products in cataract surgery was reported in literature.

4.6 Fertility, pregnancy and lactation

Fertility:
There are no data on the effects of cefuroxime sodium on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

Pregnancy:
There are limited amount of data from the use of cefuroxime in pregnant woman. Animal studies do not show any harmful effects on embryonal and foetal development. Cefuroxime reaches the embryo/foetus via the placenta. No effects during pregnancy are anticipated, since systemic exposure to cefuroxime using APROKAM is negligible. APROKAM can be used during pregnancy.

Breastfeeding:
Cefuroxime is expected to be excreted in human milk in very small quantities. Adverse effects at therapeutic doses are not expected after APROKAM use. Cefuroxime can be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

No particular adverse effects were reported in the literature when cefuroxime is administered as intraocular injection except the following:

Eye disorders
Not known (cannot be estimated from the available data): Macular oedema.

Immune system disorders
Very rare (<1/10,000): Anaphylactic reaction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

The reported cases of overdose are those described in the literature after incorrect dilution and non-authorised use of cefuroxime intended for systemic administration.

Inadvertent high-dose (3-fold the recommended dose) intracameral cefuroxime was administered to 6 patients following an incorrect dilution due to homemade cefuroxime dilution protocol. These injections did not cause any detectable adverse effect in any patient even on ocular tissues.

Toxicity data were available following intracameral injection, during cataract surgery, of 40 to 50-fold the recommended dose of cefuroxime in 6 patients after a dilution error. Initial mean visual acuity was 20/200. Severe anterior segment inflammation was present, and retinal optical coherence tomography showed extensive macular oedema. Six weeks after surgery, mean visual acuity reached 20/25. Macular optical coherence tomography profile returned to normal. A 30% decrease of scotopic electroretinography was, however, observed in all patients.

Administration of incorrectly diluted cefuroxime (10-100mg per eye) to 16 patients resulted in ocular toxicity including corneal oedema resolving in weeks, transient raised intraocular pressure, loss of corneal endothelial cells and changes in the electroretinography. A number of these patients had permanent and severe vision loss.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

Pharmacotherapeutic group: Sensory Organs - Ophthalmologicals - Antiinfectives - Antibiotics

ATC code: S01AA27

Mechanism of action

Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

PD/PK (pharmacodynamics/pharmacokinetics) relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

After intracameral injection of 1 mg cefuroxime, cefuroxime levels in the aqueous humour were over MIC for several relevant species for up to 4- 5 hours after surgery.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram-negative bacterial species;
- reduced affinity of penicillin-binding proteins for cefuroxime;
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative bacteria;
- bacterial drug efflux pumps.

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime.

Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.

Beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefuroxime despite apparent in vitro susceptibility.

Breakpoints:

The list of micro-organisms presented hereafter has been targeted to the indication (see section 4.1).

APROKAM should be used for intracameral application only and should not be used to treat systemic infections (see section 5.2); clinical breakpoints are not relevant for this route of administration. Epidemiological cut-off values (ECOFF), distinguishing the wild-type population from isolates with acquired resistance traits are as follows:

	ECOFF (mg/L)
Staphylococcus aureus	≤ 4
Streptococcus pneumoniae	≤ 0.125
E. coli	≤ 8
Proteus mirabilis	≤ 4
H. influenzae	≤ 2

Susceptibility of staphylococci to cefuroxime is inferred from the methicillin susceptibility.

The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.

Information from clinical trials

An academic prospective randomized partially masked multicentre cataract surgery study was performed on 16,603 patients. Twenty-nine patients (24 in "without cefuroxime" groups and 5 in "intracameral cefuroxime" groups) presented with endophthalmitis, of whom 20 (17 in "without cefuroxime" groups and 3 in "intracameral cefuroxime" groups) were classified as having

proven infective endophthalmitis. Among these 20 proven endophthalmitis: 10 patients are in group “placebo eye drops and without cefuroxime”, 7 patients in group “levofloxacine eye drops and without cefuroxime”, 2 patients in group “placebo eye drops and intracameral cefuroxime” and 1 patient in group “levofloxacine eye drops and intracameral cefuroxime. The administration of intracameral cefuroxime prophylactic regimen at 1mg in 0.1ml sodium chloride 9mg/ml (0.9%) solution for injection was associated with a 4.92-fold decrease in the risk for total postoperative endophthalmitis.

Two prospective studies (Wedje 2005 and Lundström 2007) and 5 retrospective studies were supportive to the pivotal ESCRS study further substantiating the efficacy of intracameral cefuroxime in postoperative endophthalmitis.

5.2 Pharmacokinetic properties

The systemic exposure following intracameral injection has not been studied but is expected to be negligible.

After intracameral injection at the recommended single dose of 0.1ml of a 10mg/ml solution of cefuroxime in cataract patients, the mean intracameral level of cefuroxime was 2614 ± 209mg/l (10 patients) 30 seconds and 1027 ± 43mg/l (9 patients) 60 minutes after drug administration.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Intravitreal injection of 1 mg cefuroxime in albino rabbits resulted in levels of 19-35mg/l and 600-780mg/l after 30min following injection in the aqueous and in the vitreous, respectively. Levels after 6 h decreased to 1.9-7.3 and 190-260mg/l respectively in these two structures. There was no increase in the intraocular pressure during the first 3 days. Histopathology showed no degenerative changes compared to saline.

ERG: a-, b- and c- waves diminished up until 14 days both in the control and antibiotic-injected eyes.

Recovery occurred and may be slower than in control. ERG showed no definite changes suggestive of retinal toxicity up to 55 days after intravitreal administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months.

After reconstitution: the product should be used immediately after reconstitution and not reused.

6.4 Special precautions for storage

Store below 25ºC.

Keep the vial in the outer carton, in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

8ml type I glass vial, stoppered with bromobutyl stopper and sealed with flip-off cap.

Box of 1×50mg, 10×50mg or 20×50mg vials.

Box of 10×50mg vials together with 10 5-micron sterile filter needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

APROKAM must be administered by intracameral injection, by an ophthalmic surgeon in the recommended aseptic conditions of cataract surgery.

VIAL IS FOR SINGLE USE ONLY.

USE ONE VIAL FOR ONE PATIENT. Stick the flag label of the vial on the patient's file.

To prepare the product for intracameral administration, please adhere to the following instructions:

1. Withdraw flip-off cap.
2. Before inserting a sterile needle, the outer part of the rubber stopper of the vial should be disinfected.
3. Push the needle vertically into the centre of the vial stopper, keeping the vial in an upright position. Then, inject into the vial 5ml of sodium chloride 9mg/ml (0.9%) solution for injection using aseptic technique.
4. Shake gently until the solution is free from visible particles.

5. Assemble a sterile needle (18G x 1½", 1.2mm x 40mm) with 5-micron filter (acrylic copolymer membrane on a non-woven nylon) onto a 1ml sterile syringe. Push this syringe vertically into the centre of the vial stopper, keeping the vial in an upright position.
6. Aseptically aspire at least 0.1ml of the solution.
7. Disconnect the 5-micron filter needle from the syringe and assemble the syringe with an appropriate anterior chamber cannula.
8. Carefully expel the air from the syringe and adjust the dose to the 0.1ml mark on the syringe. The syringe is ready for injection.

The reconstituted solution should be visually inspected and should only be used if it is a colourless to yellowish solution free from visible particles. It has a pH and osmolality close to the physiological values (pH about 7.3 and osmolality about 335mosmol/kg).

After use, discard the remaining of the reconstituted solution. Do not keep it for subsequent use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Discard used needles in a sharps container.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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