

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

EXIME-750 (Cefuroxime for Injection USP 750mg)

2. Qualitative and quantitative composition

Each vial contains sterile Cefuroxime sodium USP equivalent to cefuroxime 750mg.

3. Pharmaceutical form

Powder for injection

A White powder filled in clear glass vials.

4. Clinical particulars

4.1 Therapeutic indications

Antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery.

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

Posology:

Intracameral use. One vial for single-use only. Posology

Adults: The recommended dose is 0.1ml of reconstituted solution, i.e. 1mg of cefuroxime.

DO NOT INJECT MORE THAN THE RECOMMENDED DOSE.

Paediatric population: The optimal dose and the safety of CEFUROXIME INJECTION 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 CEFUROXIME INJECTION, no dose adjustment is necessary.

Method of administration

CEFUROXIME INJECTION 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 CEFUROXIME INJECTION. After reconstitution, CEFUROXIME INJECTION 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.

4.3 Contraindications

Hypersensitivity to cefuroxime or to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

Treatment with CEFUROXIME INJECTION 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, CEFUROXIME INJECTION 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

Pregnancy:

There is 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 CEFUROXIME INJECTION is negligible. CEFUROXIME INJECTION can be used during pregnancy.

Breast-feeding:

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

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.

4.7 Effects on ability to drive and use machines.

Not applicable

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: Macular oedema.

Immune system disorders

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

The reported cases of overdose are those described in the literature after incorrect dilution and non-authorized 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 – Anti-infectives – 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.

CEFUROXIME INJECTION should be used for intracameral application only and should not be used to treat systemic infections 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 “levofloxacin eye drops and without cefuroxime”, 2 patients in group “placebo eye drops and intracameral cefuroxime” and 1 patient in group “levofloxacin 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 ± 209 mg/l (10 patients) 30 seconds and 1027 ± 43 mg/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

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage:

Store below 30°C.

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

6.5 Nature and contents of container

750 mg/10 ml clear glass vial with 20 mm grey bromo butyl rubber plugs and 20 mm green flip off seal.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

PROMED PHARMACEUTICALS LTD

P.O BOX 22953-00100

Nairobi, Kenya

Manufacturing site address:

Makcur Laboratories Pvt Ltd situated at Plot no; 46/4-7, Village -Zak, Tal- Dehgam, Dist; Gadhinagar -382330, Gujarat, India.

8. Marketing authorization number

H2024/CTD10248/22494

9. Date of first registration

8/03/2024

10. Date of revision of the text:
November 2024