SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEFEYE 50 mg powder for solution for intracameral injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Active substance:
Cefuroxime sodium.....52.6 mg (equivalent to 50 mg cefuroxime)
When reconstituted as directed, 10.52 mg of cefuroxime sodium is obtained, equivalent to 10 mg of cefuroxime per mL.

Excipient(s):
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for intracameral injection
White to yellowish powder
A colorless to yellowish solution, free of particles, when reconstituted with the solvent listed on the label.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the antibiotic prophylaxis of post-operative endophthalmitis after cataract surgery (see Section 5.1).

4.2 Posology and method of administration

For intraocular (intracameral) injection. One vial for single-use only.

Posology/frequency and duration of administration:
Adults:
The recommended dose is 0.1 mL of reconstituted solution (see Section 6.6), i.e. 1 mg of cefuroxime.
DO NOT INJECT MORE THAN THE RECOMMENDED DOSE (see Section 4.9).

Method of administration:
CEFEYE must be administered after reconstitution by intraocular injection into the anterior chamber of the eye (intracameral use) by an ophthalmic surgeon under the recommended aseptic conditions of cataract surgery. Only sodium chloride 9 mg/mL (0.9%) solution for injection must be used when reconstituting CEFEYE.

After reconstitution, CEFEYE 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.

Additional information on special populations:
Renal/Hepatic impairment:
Considering the low dose of CEFEYE and the expected negligible systemic exposure to cefuroxime, no dose adjustment is necessary.

Pediatric population:
The optimal dose and safety of CEFEYE have not been studied in the pediatric population.

Elderly:
No dose adjustment is necessary.

4.3 Contraindications

CEFEYE should not be used in patients with hypersensitivity to cefuroxime or to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

Treatment with CEFEYE 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 colonization 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), CEFEYE 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.

4.5 Interactions 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.

Additional information on special populations:
Pediatric population:
No interaction studies have been conducted.

Elderly:
No interaction studies have been conducted.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category: B

Women of childbearing potential/Birth control (Contraception)
The effect of CEFEYE on childbearing potential and contraception is unknown.

Pregnancy
There are no available clinical data on exposure to cefuroxime during pregnancy. Animal studies have not shown any direct or indirect harmful effects on pregnancy/embryonic/fetal development/delivery and postnatal development (see Section 5.3).
Caution should be exercised when prescribing to pregnant women.

There are limited amount of data from the use of cefuroxime in pregnant women. Animal studies do not show any harmful effects on embryonal and fetal development (see Section 5.3). Cefuroxime reaches the embryo/fetus via the placenta. No effects during pregnancy are anticipated, since systemic exposure to cefuroxime is negligible. Caution should be exercised when prescribing CEFEYE to pregnant women.

Breast-feeding
Cefuroxime is expected to be excreted in human milk in very small quantities. Undesirable effects at therapeutic doses are not expected after CEFEYE use. CEFEYE 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

Temporary blurred vision or other visual disturbances may affect the ability to drive and use machines. If blurred vision occurs after administration, the patient should wait until the blurred vision clears before driving or operating machinery.

4.8 Undesirable effects

The following adverse reactions have been reported in the literature when cefuroxime is administered as an intracameral (intraocular) injection.

Undesirable effects are listed with the following frequencies:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000

to <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from available data).

Immune system disorders:
Very rare: Anaphylactic reaction

Eye disorders:
Unknown: Macular edema

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reaction via the national reporting system.

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.

Accidental high-dose (3 times the recommended dose) intracameral cefuroxime was administered to 6 patients after incorrect dilution due to a 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 edema. Six weeks after surgery, mean visual acuity reached 20/25. Macular optic coherence tomography profile returned to normal. However, a 30% reduction in scotopic electroretinography was observed in all patients.

Administration of incorrectly diluted cefuroxime (10-100mg per eye) to 16 patients resulted in ocular toxicity including corneal edema 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

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.

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

- Hydrolysis of beta-lactamases. Cefuroxime can be efficiently hydrolyzed by certain extended-spectrum beta-lactamases (ESBLs) and by the chromosomally encoded (AmpC) enzyme, which can be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- Reduced affinity of penicillin-binding proteins for cefuroxime
- Outer membrane permeability, 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). CEFEYE should be used for intracameral administration 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.

Clinical experience
An academic prospective, randomized, partially masked, multicenter cataract surgery study was conducted in 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

General properties
Absorption:
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.

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

Distribution:
No information is available.

Biotransformation:
No information is available.

Elimination:
No information is available.

Linearity/non-linearity:
No data are available on linearity/non-linearity.

Pharmacokinetic/pharmacodynamic relationships:
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index that correlates with *in vivo* efficacy has been shown to be the percentage of the dosing interval (T%) defined as the unbound concentration remaining above the minimum inhibitory concentration (MIC) of cefuroxime for certain target species (T%>MIC).
After intracameral injection of 1 mg cefuroxime, cefuroxime levels in the ocular fluid were above the MIC for several important species for 4-5 hours after surgery.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures in excess of the maximum human exposure, indicating no relevance to clinical use.

Intravitreal injection of 1 mg cefuroxime in albino rabbits resulted in aqueous and vitreous levels of 19-35 mg/L and 600-780 mg/L, respectively, 30 minutes after injection. The levels decreased to 1.9 – 7.3 and 190 – 260 mg/L in these two structures, respectively, after 6 hours. There was no increase in the intraocular pressure during the first 3 days. Histopathological examinations 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

24 months

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

6.4 Special precautions for storage

Store at room temperature below 25°C away from light in the outer carton.

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

6.5 Nature and contents of container

Primary packaging is an 8 mL clear (Type I) glass vial, closed with a gray rubber stopper and sealed with a blue flip-off cap. An outer carton contains 1, 10 or 20 vials together with the package insert. Boxes of 1 vial contain 1 needle tip, and boxes of 10 and 20 vials contain 10 and 20 needle tips in a separate clear plastic package.

6.6 Special precautions for disposal and other handling

CEFEYE must be administered by intracameral injection by an ophthalmic surgeon under the recommended aseptic conditions of cataract surgery.

VIAL IS FOR SINGLE USE ONLY.
USE ONE VIAL FOR ONE PATIENT. Affix the vial label to the patient's chart.

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

1. Remove the 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 sterile needle vertically into the center of the vial stopper, holding the vial in an upright position. 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 a 5 micron filter (acrylic copolymer membrane on non-woven nylon) onto a 1ml sterile syringe. Then push this 1 ml syringe vertically into the center of the vial stopper, keeping the vial in an upright position.
6. Aseptically withdraw at least 0.1 mL 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 0.1 mL mark on the syringe. The syringe is ready for injection.

The reconstituted solution should be inspected visually and should only be used if it is a colorless to

yellowish solution free from particles. It has a pH and osmolality close to physiological values (pH about 7.3 and osmolality about 335 mosmol/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 disposal requirements.
Discard used needles in a sharps container.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – Istanbul/TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

2020/33

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorization: 21.02.2020
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT

06.07.2021