1.3 Product Information

1.3.1 Summary of product characterization

1. Name of the Medicinal Product

(a) Product Name : Fexopozat Injection (Cefuroxime for Injection U.S.P.)
(b) Strength : 750 mg
(c) Pharmaceutical Dosage Form : Dry Powder Injection

2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

Each vial contains:
Cefuroxime sodium U.S.P.
Eq. to Cefuroxime 750 mg

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Sr. No.	Components (INN)	Reference	Label Claim	Qty./vial	Active/ Inactive
1	Cefuroxime Sodium (Sterile) Eq. to Cefuroxime	U.S.P.	750 mg	810.0 mg	Active

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.: Amber colour glass vial contains white crystalline powder for Injection.

4. Clinical Particulars

4.1 Therapeutic Indications:

Cefuroxime for injection is indicated for the treatment of infections listed below in adults and children, including neonates (from birth):

- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis
- Complicated urinary tract infections, including pyelonephritis
- Soft-tissue infections: cellulitis, erysipelas and wound infections
- Intra-abdominal infections
- Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section)

In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered with additional appropriate antibacterial agents.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration:

Posology

Adults and children ≥ 40 kg

Indication	Dosage
Community acquired pneumonia and acute exacerbations of chronic bronchitis	750 mg every 8 hours (intravenously or intramuscularly)
Soft-tissue infections: cellulitis, erysipelas and wound infections.	
Intra-abdominal infections	
Complicated urinary tract infections, including pyelonephritis	1.5 g every 8 hours (intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)
Surgical prophylaxis for gastrointestinal, gynaecological surgery (including caesarean section) and orthopaedic operations	1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.
Surgical prophylaxis for cardiovascular and oesophageal operations	1.5 g with induction of anaesthesia followed by 750 mg (intramuscularly) every 8 hours for a further 24 hours.

Children < 40 kg

	Infants and toddlers > 3 weeks and children < 40 kg	Infants (birth to 3 weeks)
Community acquired pneumonia	30 to 100 mg/kg/day (intravenously) given as 3 or 4 divided doses; a dose of 60 mg/kg/day is appropriate for most infections	30 to 100 mg/kg/day (intravenously) given as 2 or 3 divided doses
Complicated urinary tract infections, including pyelonephritis		
Soft-tissue infections: cellulitis, erysipelas and wound infections		
Intra-abdominal infections		

Renal impairment

Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of Cefuroxime should be reduced to compensate for its slower excretion.

Recommended doses for Cefuroxime in renal impairment

Creatinine clearance	$T_{1/2}$ (hrs)	Dose mg
> 20 mL/min/1.73 m^2	1.7–2.6	It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily).
10-20 mL/min/1.73 m^2	4.3–6.5	750 mg twice daily
< 10 mL/min/1.73 m^2	14.8–22.3	750 mg once daily

Patients on haemodialysis	3.75	A further 750 mg dose should be given intravenously or intramuscularly at the end of each dialysis; in addition to parenteral use, cefuroxime sodium can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).
Patients in renal failure on continuous arteriovenous haemodialysis (CAVH) or high-flux haemofiltration (HF) in intensive therapy units	7.9–12.6 (CAVH) 1.6 (HF)	750 mg twice daily; for low-flux haemofiltration follow the dosage recommended under impaired renal function.

Hepatic impairment
Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction this is not expected to effect the pharmacokinetics of cefuroxime.

Method of Administration
Cefuroxime should be administered by intravenous injection over a period of 3 to 5 minutes directly into a vein or via a drip tube or infusion over 30 to 60 minutes, or by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 750 mg should be injected at one site. For doses greater than 1.5 g intravenous administration should be used.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with known hypersensitivity to cephalosporin antibiotics.
- History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warning and precautions for use:

Hypersensitivity reactions
As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta lactam agent. Caution should be used if cefuroxime is given to patients with a history of non severe hypersensitivity to other beta-lactam agents.

Cephalosporin antibiotics may, in general, be given safely to patients who are hypersensitive to penicillins, although cross-reactions have been reported. Special care is indicated in patients who have experienced an anaphylactic reaction to penicillin.

Concurrent treatment with potent diuretics or aminoglycosides
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides. Renal impairment has been reported during use of these combinations. Renal function should be monitored in the elderly and those with known pre-existing renal impairment.

Overgrowth of non-susceptible microorganisms
Use of cefuroxime may result in the overgrowth of Candida. Prolonged use may also result in the_overgrowth of other non-susceptible microorganisms (e.g. enterococci and Clostridium difficile), which may require interruption of treatment.

Antibacterial agent–associated pseudomembranous colitis has been reported with use of cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime. Discontinuation of therapy with cefuroxime and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Intra-abdominal infections
Due to its spectrum of activity, cefuroxime is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria.

Interference with diagnostic tests
The development of a positive Coombs Test associated with the use of cefuroxime may interfere with cross matching of blood.

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime sodium.

Intracameral use and eye disorders
Cefuroxime is not formulated for intracameral use. Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intracameral use of cefuroxime sodium compounded from vials approved for intravenous/intramuscular administration. These reactions included macular oedema, retinal oedema, retinal detachment, retinal toxicity, visual impairment, visual acuity reduced, vision blurred, corneal opacity and corneal oedema.

Important information about excipients
Cefuroxime powder for solution for injection and infusion contains 40.6 mg sodium per 750mg vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be considered for patients who are on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions:
Cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenicid is not recommended. Concurrent administration of probenecid prolongs the excretion of cefuroxime and produces an elevated peak serum level.

Potential nephrotoxic drugs and loop diuretics
High-dosage treatments with cephalosporins should be carried out with caution on patients who are taking strong-acting diuretics (such as furosemide) or potential nephrotoxic preparations (such as aminoglycoside antibiotics), since impairment of renal function through such combinations cannot be ruled out.

Other Interactions
Determination of blood/plasma glucose levels.
Concomitant use with oral anticoagulants may give rise to increased international normalised ratio.

4.6 Pregnancy and lactation:
Pregnancy
There are limited amounts of data from the use of cefuroxime in pregnant women. Studies in animals have shown no reproductive toxicity. Cefuroxime should be prescribed to pregnant women only if the benefit outweighs the risk. Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother.

Lactation
Cefuroxime is excreted in human milk in small quantities. Adverse reactions at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefuroxime therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machine:
No studies on the effects of cefuroxime on the ability to drive and use machines have been performed. However, based on known adverse reactions, cefuroxime is unlikely to have an effect on the ability to drive and use machines.

4.8 Undesirable Effects:
The most common adverse reactions are neutropenia, eosinophilia, transient rise in liver enzymes or bilirubin, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver and injection site reactions.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare adverse reactions. The frequencies assigned to all other adverse reactions (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for

the classification of frequency: 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 and not known.

System organ class	Common	Uncommon	Not known
Infections and infestations			*Candida* overgrowth, overgrowth of *Clostridium difficile*
Blood and lymphatic system disorders	neutropenia, eosinophilia, decreased haemoglobin concentration	leukopenia, positive Coombs test	thrombocytopenia, haemolytic anaemia
Immune system disorders			drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
Gastrointestinal disorders		gastrointestinal disturbance	pseudomembranous colitis
Hepatobiliary disorders	transient rise in liver enzymes	transient rise in bilirubin	
Skin and subcutaneous tissue disorders		skin rash, urticaria and pruritus	erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome, angioneurotic oedema
Renal and urinary disorders			elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance
General disorders and administration site conditions	injection site reactions which may include pain and thrombophlebitis		
Description of selected adverse reactions Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coombs test (which can interfere with cross matching of blood) and very rarely haemolytic anaemia. Transient rises in serum liver enzymes or bilirubin have been observed which are usually reversible. Pain at the intramuscular injection site is more likely at higher doses. However it is unlikely to be a cause for discontinuation of treatment.			

Paediatric population
The safety profile for cefuroxime sodium in children is consistent with the profile in adults.

4.9 Overdose:
Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: antibacterials for systemic use, Second-generation cephalosporins

ATC code: J01DC02

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 by beta-lactamases including (but not limited to) extended-spectrum beta-lactamases (ESBLs), and Amp-C enzymes, 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 efflux pumps.

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime. Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

5.2 Pharmacokinetic Properties:

Absorption

After intramuscular (IM) injection of cefuroxime to normal volunteers, the mean peak serum concentrations ranged from 27 to 35 µg/mL for a 750 mg dose and from 33 to 40 µg/mL for a 1000 mg dose, and were achieved within 30 to 60 minutes after administration. Following intravenous (IV) doses of 750 and 1500 mg, serum concentrations were approximately 50 and 100 µg/mL, respectively, at 15 minutes. AUC and Cmax appear to increase linearly with increase in dose over the single dose range of 250 to 1000 mg following IM and IV administration. There was no evidence of accumulation of cefuroxime in the serum from normal volunteers following repeat intravenous administration of 1500 mg doses every 8 hours.

Distribution

Protein binding has been stated as 33 to 50%, depending on the methodology used. The average volume of distribution ranges from 9.3 to 15.8 L/1.73 m2 following IM or IV administration over the dosage range of 250 to 1000 mg. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation
Cefuroxime is not metabolised.

Elimination
Cefuroxime is excreted by glomerular filtration and tubular secretion. The serum half-life after either intramuscular or intravenous administration is approximately 70 minutes. There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. The majority of the cefuroxime is excreted within the first 6 hours. The average renal clearance ranges from 114 to 170 mL/min/1.73 m2 following IM or IV administration over the dosage range of 250 to 1000 mg.

Special patient populations
Gender
No differences in the pharmacokinetics of cefuroxime were observed between males and females following a single IV bolus injection of 1000 mg of cefuroxime as the sodium salt.

Elderly
Following IM or IV administration, the absorption, distribution and excretion of cefuroxime in elderly patients are similar to younger patients with equivalent renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in cefuroxime dose selection, and it may be useful to monitor renal function.

Paediatrics
The serum half-life of cefuroxime has been shown to be substantially prolonged in neonates according to gestational age. However, in older infants (aged >3 weeks) and in children, the serum half-life of 60 to 90 minutes is similar to that observed in adults.

Renal impairment
Cefuroxime is primarily excreted by the kidneys. As with all such antibiotics, in patients with markedly impaired renal function (i.e. C1cr <20 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by haemodialysis and peritoneal dialysis.

Hepatic impairment
Since cefuroxime is primarily eliminated by the kidney, hepatic dysfunction is not expected to have an effect on the pharmacokinetics of cefuroxime.

PK/PD 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).

5.3 Preclinical Safety Data:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.
Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. Pharmaceutical Particulars

6.1 List of Excipients:
None.

6.2 Incompatibilities:
Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions. The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of Cefuroxime. However, if required, for patients receiving sodium bicarbonate injection by infusion the Cefuroxime solution may be introduced into the tube of the giving set. Cefuroxime should not be mixed in the syringe with aminoglycoside antibiotics.

6.3 Shelf life:
36 Months

6.4 Special precautions for storage:
Store at a temperature not exceeding 30^{O}C. Protect from light & moisture.
Keep medicine out of the reach of children.
Do not refrigerate or freeze.

6.5 Nature and contents of container:
10 ml amber colour glass vial. Such 1 vial with 10 ml WFI ampoule in plastic tray packed in printed carton with pack insert.

6.6 Instructions for use and handling
No special requirement.

7.0 Marketing Authorization Holder

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8.0 Marketing Authorization Numbers
Not applicable

9.0 Date of first authorization/renewal of the authorization
Not applicable

10.0 Date of revision of the text
02/01/2023