Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

CEZOLINE (Cefazolin powder for injection 1GM)

2. Qualitative and quantitative composition

Each vial Contains: Cefazolin sodium..... Equivalent to 1000mg Cefazolin

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for Injection

Description: A white to off-white, crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Cefazolin for Injection is indicated in the treatment of the following infections due to susceptible organisms:

Respiratory Tract Infections: Due to S. pneumoniae, S. aureus (including beta- lactamase-producing strains) and S. pyogenes.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available.

Urinary Tract Infections: Due to E. coli, P. mirabilis.
Skin And Skin Structure Infections: Due to S. aureus (including beta-lactamase- producing strains), S. pyogenes, and other strains of streptococci.

Biliary Tract Infections: Due to E. coli, various strains of streptococci, P. mirabilis, and S. aureus.

Bone And Joint Infections: Due to S. aureus.

Genital Infections: (i.e., prostatitis, epididymitis) due to E. coli, P. mirabilis.

Septicemia: Due to S. pneumoniae, S. aureus (including beta-lactamase-producing strains), P. mirabilis, E. coli.

Endocarditis: Due to S. aureus (including beta-lactamase-producing strains) and S. pyogenes.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefazolin.

Perioperative Prophylaxis: The prophylactic administration of cefazolin preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

The perioperative use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of cefazolin should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted.

4.2 Posology and method of administration

Adults:

Moderate-to-Severe Infections - 0.5-1 g IV q6-8hr

Mild Infections With Gram-Positive Cocci- 250-500 mg IV q8hr

Mild-to-Moderate Cholecystitis - 1-2 g IV q8hr for 4-7 days

Uncomplicated Urinary Tract Infection -1 g IV q12hr

Preparation for Surgery:

Prophylaxis against infection
Preoperatively: 1-2 g IV/IM ≤60 minutes before procedure (may be repeated in 2-5 hours intraoperatively)

Postoperatively: 0.5-1 g IV q6-8hr for 24 hours

Surgical infection

- Cardiac procedures, hysterectomy, oral or pharyngeal procedures, craniotomy, joint replacement, thoracic procedures, arterial procedures, amputation, traumatic wounds; high-risk esophageal, gastroduodenal, or biliary tract procedures: 1-2 g IV
- Colorectal procedures: 1-2 g IV plus metronidazole 0.5 g IV
- High-risk cesarean section, 2nd trimester abortion: 1 g IV
- Ophthalmic procedures: 100 mg subconjunctivally

Endocarditis

- 1 g IV/IM 30-60 minutes before procedure
- American Heart Association (AHA) guidelines: Endocarditis prophylaxis recommended only for high-risk patients

Bacterial Keratitis (Off-label)

1 drop instilled into affected eye(s) q1-2hr; typically alternated every other hour with antibiotic providing gram-negative coverage (eg, tobramycin)

Extemporaneous compounded fortified cefazolin 50 mg/mL

- Dilute 500 mg parenteral cefazolin powder in sterile water to form 10 mL solution
- Store refrigerated; preparation expires in 7 days

Dosing Modifications

Renal impairment

- CrCl 35-54 mL/min: Give full dose at intervals >8hr
- CrCl 10-35 mL/min: Give therapeutic dose q12hr
- CrCl ≤10 mL/min: Give therapeutic dose q24hr

Hepatic impairment

- Not studied

Dosing Considerations

Susceptible organisms

- Streptococcus pneumoniae, Klebsiella, Haemophilus influenzae, Staphylococcus aureus, group A beta-hemolytic streptococcus, Escherichia coli, Proteus mirabilis, Enterobacter (some strains)

Pediatrics:

Infections With Gram-Positive Cocci

Neonates (<28 days)

- <7 days: 40 mg/kg/day IV/IM divided q12hr
- >7 days, <2 kg: 40 mg/kg/day IV/IM divided q12hr
- >7 days, >2 kg: 60 mg/kg/day IV/IM divided q8hr

Infants & children

- 25-100 mg/kg/day IV/IM divided q6-8hr; not to exceed 6 g/day

Endocarditis

Prophylaxis
50 mg/kg IV/IM ≤30-60 minutes before procedure; not to exceed 1 g
AHA guidelines: Endocarditis prophylaxis recommended only for high-risk patients

Community-Acquired Pneumonia

>3 months and children: 150 mg/kg/day IV/IM divided q8hr (moderate to severe infections, methicillin susceptible S.Aureus preferred

Dosing Considerations

Cefazolin 2 g for Injection is not recommended for use in pediatric patients; to avoid unintentional overdose, 1 g cefazolin for Injection should only be used in pediatric patients who require entire contents of 1 g dose and not any fraction of it
There are no dosing recommendations for pediatric patients for perioperative prophylaxis or for pediatric patients with renal impairment

Method of administration

Intramuscular Administration:
Reconstitute vials with Sterile Water for Injection according to the dilution table above. Shake well until dissolved. Cefazolin for Injection should be injected into a large muscle mass. Pain on injection is infrequent with Cefazolin for Injection.

Intravenous Administration:
Direct (bolus) injection: Following reconstitution according to the above table, further dilute vials with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion**:** Dilute reconstituted Cefazolin for Injection in 50 to 100 mL of 1 of the following solutions:

- Sodium Chloride Injection, USP
- 5% or 10% Dextrose Injection, USP
- 5% Dextrose in Lactated Ringer's Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Invert Sugar 5% or 10% in Sterile Water for Injection

- Ringer's Injection, USP
- 5% Sodium Bicarbonate Injection, USP

4.3 Contraindications

Cefazolin for Injection Is Contraindicated In Patients With Known Allergy To The Cephalosporin Group Of Antibiotics.

4.4 Special warnings and precautions for use

Endocarditis prophylaxis recommended only for high-risk patients, per AHA guidelines.

Prolonged treatment, hepatic or renal disease, or nutritional deficiency may be associated with increased international normalized ratio (INR).

Use with caution in patients with seizure disorder (high levels are associated with increased risk of seizures); seizures may occur, particularly in patients with renal impairment when dosage is not reduced appropriately; dose must be adjusted in severe renal insufficiency (high doses may cause CNS toxicity); discontinue if seizures occur or make appropriate dosage adjustments in patients with renal impairment; continue anticonvulsant therapy in patients with known seizure disorders.

Prescribing cefazolin injection in absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases risk of development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of cefazolin injection may result in overgrowth of nonsusceptible microorganisms; repeated evaluation of the patient's condition is essential; should superinfection occur during therapy, appropriate measures should be taken. Therapy may result in a false-positive reaction with glucose in urine when using glucose tests based on Benedict’s copper reduction reaction that determine amount of reducing substances like glucose in urine; it is recommended that glucose tests based on enzymatic glucose oxidase be used.

Hypersensitivity reactions, including anaphylaxis, reported with administration of dextrose-containing products; these reactions have been reported in patients receiving high concentrations of dextrose (i.e. 50% dextrose); reactions have been reported when corn-derived

dextrose solutions were administered to patients with or without a history of hypersensitivity to corn products.

As with other dextrose-containing solutions, cefazolin injection should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

Cefazolin for Injection, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

As with other dextrose-containing solutions, Cefazolin for Injection should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Antibiotic associated diarrhea

- Clostridioides difficile-associated diarrhea (CDAD) reported with use; may range in severity from mild diarrhea to fatal colitis; treatment with antibacterial agents alters normal flora of colon leading to overgrowth of C. difficile
- C. difficile produces toxins A and B, which contribute to development of CDAD; hypertoxin-producing isolates of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy
- CDAD must be considered in all patients who present with diarrhea following antibacterial drug use; careful medical history is necessary since CDAD has been reported to occur over two months after administration of antibacterial agents
- If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued; appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C. difficile, and surgical evaluation instituted as clinically indicated

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Drug/Laboratory Test Interactions

A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix®.

Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Category B on teratogenic effects:

Available data from published prospective cohort studies, case series and case reports over several decades with cephalosporin use, including cefazolin, in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes; drug crosses the placenta

Animal data

- Animal reproduction studies with rats, mice and rabbits administered cefazolin during organogenesis at doses 1 to 3 times maximum recommended human dose (MRHD) did not demonstrate adverse developmental outcomes; in rats subcutaneously administered cefazolin prior to delivery and throughout lactation, there were no adverse effects on offspring at a dose approximately 2 times the MRHD

On labor and delivery; When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus

Lactation

Data from published literature report that cefazolin is present in human milk, but not expected to accumulate in a breastfed infant; there are no data on effects of drug on breastfed child or on milk production

Developmental and health benefits of breastfeeding should be considered along with mother's clinical need for therapy and any

potential adverse effects on breastfed child from drug or from the mother's underlying condition

Fertility

In animal studies, no effect on fertility was observed.

4.7 Effects on ability to drive and use machines.

Cefazolin does not affect the ability to drive or operate machinery.

4.8 Undesirable effects

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia. Hepatic: Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Rare instances of phlebitis have been reported at site of injection. Some induration has occurred.

Other Reactions: Genital and anal pruritus (including vulvar pruritus, genital moniliasis, and vaginitis).

Postmarketing Reports

Immune system disorders: Serum sickness-like reaction
Renal and urinary disorders: Acute tubulointerstitial nephritis
Skin and subcutaneous tissue disorders: Acute generalized exanthematous pustulosis (AGEP)

4.9 Overdose

Accidental overdosage resulting in seizures may occur in patients with renal impairment who receive doses greater than the recommended dosage of cefazolin injection. If seizures associated with accidental

overdosage occur, discontinue cefazolin injection and give supportive treatment.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-bacterial for systemic use**,** first generation cephalosporin**,** ATC code: J01DB04

Mode of Action
Cefazolin 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

Resistance to Cefazolin is primarily through hydrolysis by beta-lactamase.

Antimicrobial Activity
Gram-Positive Bacteria:
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Methicillin-resistant staphylococci are uniformly resistant to cefazolin.
Gram-Negative Bacteria:
Escherichia coli
Proteus mirabilis

Most isolates of indole positive Proteus (Proteus vulgaris), Enterobacter spp., Morganella morganii, Providencia rettgeri, Serratia spp., and Pseudomonas spp. are resistant to cefazolin.

5.2 Pharmacokinetic properties

Absorption

Intramuscular administration
A 250 mg dose provides serum levels of cefazolin (in mcg/ml) from 15.5 at 30 minutes to 17 at 1 hour, 13 at 2 hours, 5.1 at 4 hours and 2.5 at 6 hours following intramuscular injection. A 500 mg dose provides serum levels of cefazolin (in mcg/ml) from 36.2 at 30 minutes to 36.8 at 1 hour, 37.9 at 2 hours, 15.5 at 4 hours, 6.3 at 6 hours and 3 at 8 hours following intramuscular injection. From an average of two

studies, a 1 g dose provides serum levels of cefazolin (in mcg/ml) from 60.1 at 30 minutes to 63.8 at 1 hour, 54.3 at 2 hours, 29.3 at 4 hours, 13.2 at 6 hours and 7.1 at 8 hours following intramuscular injection. Cefazolin attains peak urine concentrations exceeding 1000 mcg/ml and 4000 mcg/ml following intramuscular doses of 500 mg and 1 g respectively.

Intravenous administration

Clinical pharmacology studies in patients hospitalised with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers. A study giving cefazolin at constant intravenous infusion rates of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg for the next 2 hours (approximately 100 mg) produced a steady serum level at the third hour of approximately 28 mcg/ml in normal volunteers. A single 1 g dose provided average serum levels of cefazolin (in mcg/ml) from 188.4 at 5 minutes to 135.8 at 15 minutes, 106.8 at 30 minutes,73.7 at 1 hour, 45.6 at 2 hours and 16.5 at 4 hours following intravenous injection. The average half-life was 1.4 hours.

Peritoneal dialysis

In patients undergoing peritoneal dialysis at 2 l/hr, mean serum levels of cefazolin were approximately 10 and 30 mcg/ml after 24 hours' instillation of a dialysing solution containing 50 mcg/ml and 150 mcg/ml respectively. Mean peak levels were 29 mcg/ml (range 13 to 44 mcg/ml) with 50 mcg/ml (3 patients), and 72 mcg/ml (range 26 to 142 mcg/ml) with 150 mcg/ml (6 patients).

Distribution

Cefazolin readily crosses an inflamed synovial membrane, and the concentration of the antibiotic achieved in the joint space is comparable to levels measured in the serum. Cefazolin readily diffuses across the placental barrier into the cord blood and amniotic fluid. It is present in very low concentrations in the milk of nursing mothers. When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations well above serum levels occur in the gallbladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic is considerably lower in bile than in the serum.

Biotransformation

Controlled studies in adult normal volunteers receiving cefazolin 1 g four times a day for 10 days, monitoring CBC, AST, ALT, bilirubin,

alkaline phosphatase, BUN, creatinine, and urinalysis indicated no clinically significant changes attributed to cefazolin.

Elimination

Cefazolin is excreted unchanged in the urine primarily by glomerular filtration and, to a lesser degree, by tubular secretion. Following intramuscular injection of 500 mg, 56% to 89% of the administered dose is recovered within 6 hours, and 80% to nearly 100% in 24 hours.

5.3 Preclinical safety data

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Cefazolin for Injection have not been performed.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

If treatment with a combination of another antibiotic with Cefazolin is intended, administration should not occur in the same syringe or in the same infusion solution.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months.

6.4 Special precautions for storage:

Cefazolin sterile powder should be stored below 30 °C and protected from light. Following reconstitution (activation), product must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration.

6.5 Nature and contents of container

White to off white crystalline powder to be filled in 10 ml clear glass vial USP type III having 20 mm Grey butyl rubber stopper and 20 mm flip off seal. Pack Such One Vial in carton with insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing authorization holder and manufacturing site addresses
Marketing authorization holder:
PharmaKen Limited, P.O. Box 95625-80106, Kenya.

Manufacturing site address:
Makcur Laboratories Limited, 46/4-7, Dehgam Road, Zak Village, India.

8. Marketing authorization number
CTD 10489

9. Date of first registration
26/05/2023

10. Date of revision of the text:
15/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable