Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Cefoperazone & Sulbactam For Injection

(Brand Name: CEDONEX® 1.5 g Injection)

2. Qualitative and Quantitative Composition

Each combipack contains:
One vial contains:
Cefoperazone Sodium IP (Sterile) equivalent to Cefoperazone …….. 1000 mg.
Sulbactam Sodium USP (Sterile) equivalent to Sulbactam ……. 500 mg.
And
One FFS ampoule contains:
Sterile Water for Injections IP ……..…….. 10 ml.
(For reconstitution)

3. Dosage Form and Strength

Dosage Form: Injection.
Dosage Strength: Cefoperazone 1000 mg and Sulbactam 500 mg per vial.

4. Clinical Particulars

4.1 Therapeutic Indication

CEDONEX Injection is indicated for the treatment of the following infections when caused by susceptible pathogens:

- Respiratory Tract Infections.
- Urinary Tract Infections.
- Peritonitis and Other Intra-abdominal Infections.
- Meningitis.
- Bacterial Septicemia.
- Skin and Skin Structures Infections.
- Bone and Joint Infections.
- Pelvic Inflammatory Disease, Endometritis, Gonorrhea, and Other Infections of the Genital Tract.

4.2Posology and Method of Administration

CEDONEX Injection can be administered by intramuscular (I.M.) or intravenous (I.V.) bolus injection after reconstitution with sterile water for injection. CEDONEX Injection can also be administered by I.V. infusion route after dilution with suitable vehicle.

CEDONEX Injection contains cefoperazone and sulbactam in a ratio of 2:1. As cefoperazone is the main active ingredient, doses are advised in terms of cefoperazone content of the formulation.

Cefoperazone

Adults:

- **Usual recommended dose:** 2 to 4 g per day administered in equally divided doses every 12 hours.
- **Severe infections or infections caused by less sensitive organisms:** 6 to 12 g per day in 2, 3, or 4 divided doses.

Children:

- **Usual recommended dose:** 50 to 100 mg/kg/day in 2 divided doses.
- **Severe infections:** The total daily dose can be increased up to 200 mg/kg/day, given in 2, 3 or 4 divided doses.
- **Newborn infants aged 1-7 days/premature infants having severe infections:** 50 mg per kg every 12 hours.

Or, as prescribed by the Physician.

Sulbactam

Adults and children above 40 kg: The total dose of sulbactam should not exceed 4 g per day.

Children: The maximum daily dose of sulbactam should not exceed 80 mg/kg/day.

Or, as prescribed by the Physician.

If higher dosage of cefoperazone is needed in the treatment of severe infections, consider the maximum recommended daily dose of co-administered sulbactam. In such case, separate dose of cefoperazone injection should be administered.

Directions for Reconstitution and Dilution for Use

Each vial of CEDONEX Injection should be reconstituted with sterile water for injection (supplied separately as a part of combipack). Shake well until powder gets dissolved.

CEDONEX Injection can be administered either by slow I.V. injection over a period of 3 to 4 minutes directly into a vein or by I.V. infusion over a period of at least 30 minutes. For I.V. infusion use, reconstituted solution should be further diluted with a compatible diluent. The reconstituted/diluted solution should be used immediately after preparation. Do not freeze. Unused portion of solution, if any, should be discarded.

Compatible Diluents/Vehicles for I.V. Infusion Use

- 5% or 10% dextrose.

- 0.2% or 0.9% normal saline.
- Lactated Ringer's Injection.

Pharmaceutical Precautions

CEDONEX Injection should not be mixed with other drugs in infusion bottle since compatibility has not been established.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Does not use if reconstituted solution for injection is cloudy or discolored or contains visible particles.

4.3Contraindications

CEDONEX Injection is contraindicated in patients with known hypersensitivity to cefoperazone or to sulbactam or to any components of the formulation, patients with known allergy to the cephalosporin or penicillin class of antibiotics.

4.4Special Warnings and Precautions for Use

Test Dose: Before therapy with CEDONEX Injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to its ingredients. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Hypersensitivity: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam or cephalosporin therapy. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Clostridium Difficile **Associated Diarrhea (CDAD):** Pseudomembranous colitis has been reported with the use of cephalosporin (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad-spectrum antibiotics including CEDONEX Injection may alter normal flora of the colon and may permit overgrowth of clostridia, which may cause antibiotic-associated colitis.

Vitamin K Deficiency: As with other antibiotics, vitamin K deficiency has occurred in a few patients treated with cefoperazone. The mechanism is most probably related to the suppression of gut flora which normally synthesize this vitamin. Those at risk include patients with poor diet, malabsorption states (e.g., cystic fibrosis) and patients on prolonged intravenous alimentation regimens. Prothrombin time should be monitored in these patients, and patients receiving anticoagulant therapy, and exogenous vitamin K administered as indicated.

Hepatic Dysfunction: Cefoperazone is extensively excreted in bile. The serum half-life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with

hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in bile and only a 2 to 4-fold increase in half-life is seen. Dose modification may be necessary in cases of severe biliary obstruction, severe hepatic disease or in cases of renal dysfunction coexistent with either of those conditions.

In patients with hepatic dysfunction and concomitant renal impairment, cefoperazone serum concentrations should be monitored and dosage adjusted as necessary. In these cases dosage should not exceed 2 g/day of cefoperazone without close monitoring of serum concentrations.

Renal Impairment: Dosage regimens of cefoperazone/sulbactam should be adjusted in patients with a marked decrease in renal function. When high doses of cefoperazone are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly. Patients with creatinine clearances between 15 and 30 ml/min should receive a maximum of 1 g of sulbactam every 12 hours, while patients with creatinine clearances of less than 15 ml/min should receive a maximum of 500 mg of sulbactam every 12 hours.

Gastrointestinal (GI) Diseases: Cefoperazone should be prescribed with caution in individuals with a history of GI diseases, particularly colitis.

Use of Alcohol: A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol was ingested within 72 hours after cefoperazone administration.

Super-infection: As with other antibiotics, overgrowth of non-susceptible organisms may occur during prolonged use of cefoperazone with sulbactam. If super-infection occurs during therapy, appropriate measures should be taken.

General: As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.

4.5Drug Interactions

Aminoglycosides: Concomitant administration of aminoglycosides and cephalosporins may cause nephrotoxicity. Thus, caution should be exercised when these drugs are used concurrently.

Alcohol: A reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol was ingested during and as late as the fifth day after cefoperazone administration. A similar reaction has been reported with certain other cephalosporins and patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of cefoperazone/sulbactam. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

Drug Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility and no teratological findings. Cefoperazone and sulbactam cross the placental barrier. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactating Women

Only small quantities of cefoperazone and sulbactam are excreted in human milk. Although both drugs pass poorly into breast milk of nursing mothers, caution should be exercised when cefoperazone/sulbactam is administered to a nursing mother.

Pediatric Patients

CEDONEX Injection can be administered in pediatric patients. For further details please refer 'Posology and Method of Administration' section.

Geriatric Patients

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.7Effect on Ability to Drive and Use Machines

Clinical experience with cefoperazone and sulbactam combination therapy indicates that it is unlikely to impair a patient's ability to drive or use machinery.

4.8Undesirable Effects

CEDONEX Injection is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment.

Adverse drug reactions with Cefoperazone are:

Hematology: Slight decreases in neutrophils have been reported. As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. A positive direct Coombs test, decreased hemoglobin or hematocrit, transient eosinophilia, thrombocytopenia, and hypo-prothrombinemia have been reported during the treatment with cefoperazone and sulbactam injection.

Gastrointestinal: Diarrhea or loose stools, nausea and vomiting have been reported rarely. **Renal Function Tests:** Transient elevations of the blood, urea, nitrogen (BUN) and serum creatinine have been reported.

Local Reactions: Occasionally, transient pain may occur after I.M. administration. By I.V. infusion some patients may develop phlebitis at the infusion site.

Dermatologic Reactions: As with all penicillins and cephalosporins, hypersensitivity manifested by maculopapular and urticaria has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.
Miscellaneous: Headache, fever, and chills.
Laboratory Abnormalities: Transient elevations of liver function tests, serum glutamic-oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, and bilirubin levels have been noted.

Post-Marketing Experience
In post-marketing experience the following additional undesirable effects have been reported:
General: Anaphylactic reaction (including shock).
Cardiovascular: Hypotension.
Gastrointestinal: Pseudomembranous colitis.
Hematopoietic: Leucopenia.
Skin/Appendages: Pruritus, Stevens Johnson Syndrome.
Urinary: Hematuria.
Vascular: Vasculitis.
Adverse Reactions Reported for Cephalosporin-Class Drugs: Following adverse reactions have been reported for cephalosporin-class antibiotics:
Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, pancytopenia, fixed drug eruption (FDE) and purpura.

4.9Overdose
Limited information is available on the acute toxicity of cefoperazone and sulbactam in humans. Overdose of the drug would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high cerebrospinal fluid (CSF) concentrations of beta-lactam antibiotics may cause neurological effects, including seizures, should be considered. Because cefoperazone and sulbactam are both removed from the circulation by hemodialysis, these procedures may enhance the elimination of the drug from the body if overdose occurs in patients with impaired renal function.

5. Pharmacological Properties
5.1 Mechanism of Action
Cefoperazone
Cefoperazone is a third generation cephalosporin class of beta-lactam antibiotic. Cefoperazone is effective against a wide range of aerobic and anaerobic, gram-positive and gram-negative bacterial pathogens. The bactericidal action of cefoperazone results from the inhibition of bacterial cell wall synthesis.

Sulbactam

Sulbactam is a beta-lactamase inhibitor drug usually given in combination with beta-lactam antibiotics. Sulbactam inhibit beta-lactamase enzyme produced by certain bacteria to develop resistance to beta-lactam antibiotic (by degradation of bet-lactam ring and thus, making beta-lactam antibiotic ineffective). Sulbactam effectively restores antibacterial efficacy of co-administered beta-lactam antibiotic against beta-lactamase producing strains. Given alone sulbactam has some useful but lesser antibacterial activity. In particular, sulbactam has good inhibitory activity against the clinically important plasmid mediated beta-lactamases most frequently responsible for transferred drug resistance.

Cefoperazone + Sulbactam Combination

Cefoperazone has a high degree of stability against the beta-lactamases, both penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria but, not against chromosomally and plasmid mediated ESBL's (Extended Spectrum Beta-Lactamases) produced by some strains of *Klebsiella, Escherichia coli, Enterobacter spp* and *Serratia spp*.

Sulbactam irreversibly blocks the destruction of beta-lactam ring of cefoperazone by this wide variety of ESBLs and chromosomally mediated beta-lactamases by attaching to these enzymes and acting as a suicide substrate that forms a stable intermediate, rendering the enzyme inactive. Thus, sulbactam restores cefoperazone activity against ESBL producing strains.

The combination of cefoperazone and sulbactam is active against all the organisms sensitive to cefoperazone. In addition combination therapy demonstrates synergistic activity (reduction in minimum inhibitory concentration- MIC compared to only cefoperazone therapy) in a variety of organisms. The presence of sulbactam with cefoperazone may effectively extend the antibiotic spectrum of cefoperazone to include many bacteria normally resistant to it and to other beta-lactam antibiotics.

5.2Pharmacodynamic Properties

CEDONEX Injection is usually active against the following organisms *in vitro* and in clinical infections:

Gram-Positive Aerobes

- *Staphylococcus aureus,*
- *Staphylococcus epidermidis,*
- *Streptococcus pneumoniae,*
- *Streptococcus pyogenes,*
- *Streptococcus agalactiae,*
- *Enterococcus (Streptococcus faecalis, S. faecium and S. durans).*

Gram-Negative Aerobes

- *Escherichia coli,*
- *Klebsiella species,*

- *Enterobacter species,*
- *Citrobacter species,*
- *Haemophilus influenza,*
- *Proteus mirabilis,*
- *Proteus vulgaris,*
- *Morganella morganii,*
- *Providencia stuartii,*
- *Providencia rettgeri,*
- *Serratia marcescens,*
- *Pseudomonas aeruginosa,*
- *Pseudomonas species,*
- *Acinetobacter calcoaceticus* (some strains),
- *Neisseria gonorrhoeae.*

Anaerobic Organisms

- Gram-positive bacilli including *Clostridium, Eubacterium,* and *Lactobacillus species*.
- Gram-negative bacilli including *Bacteroides fragilis*, other *Bacteroides species*, and *Fusobacterium species*.
- Gram-positive and gram-negative cocci including *Peptococcus, Peptostreptococcus,* and *Veillonella species*.

Cefoperazone is also active *in vitro* against a wide variety of other pathogens although the clinical significance is unknown. These organisms include:

- *Salmonella species,*
- *Shigella species,*
- *Serratia liquefaciens,*
- *N. meningitidis,*
- *Bordetella pertussis,*
- *Yersinia enterocolitica,*
- *Clostridium difficile,*
- *Fusobacterium species,*
- *Eubacterium species and*
- Beta-lactamase producing strains of *H. influenzae and N. gonorrhoeae.*

5.3Pharmacokinetic Properties

After intramuscular administration of 1.5 g cefoperazone/sulbactam (cefoperazone 1 g + sulbactam 0.5 g) peak serum concentrations are seen from 15 minutes to 2 hours after administration. The mean serum half-life of cefoperazone is approximately 2.0 hours, independent of the route of administration. Plasma protein binding of cefoperazone varies from 82% to 93%. Both

cefoperazone and sulbactam distribute well into a variety of tissues and fluids, including the bile, gall bladder, skin, appendix, fallopian tubes, ovary, uterus, and others. Cefoperazone is excreted mainly in the bile. Maximum bile concentrations are generally obtained between 1 and 3 hours following drug administration. Following a single I.M. or I.V. dose, the urinary recovery of cefoperazone over a 12-hour period averages 20 to 30%. Approximately 84% of the sulbactam dose is excreted by the kidneys. The mean half-life for sulbactam is about 1 hour.

6. Nonclinical Properties

6.1 Animal Toxicology

Cefoperazone

Long term studies in animals have not been performed to evaluate carcinogenic potential. The maximum duration of cefoperazone animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did cefoperazone show any mutagenic potential at either the chromosomal or subchromosomal level.

Cefoperazone produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg/day (approximately 16 times the average adult human dose) resulted in reduced testicular weight, arrested spermatogenesis, reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg/day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats.

Sulbactam

Relevant data is not available.

7. Description

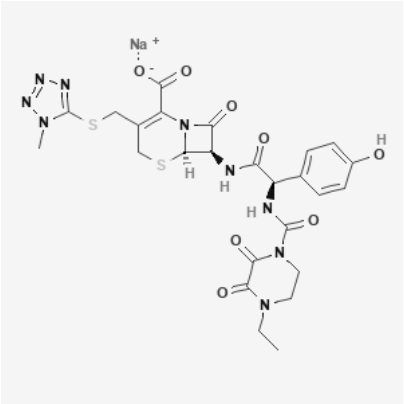
CEDONEX Injection is white to pale yellow crystalline powder filled in 20 ml clear glass vials.

Each vial contains dry powder of 1000 mg of cefoperazone (as a sodium salt) which is a bet-lactam antibiotic plus 500 mg of sulbactam (as a sodium salt) which is a beta-lactamase inhibitor for I.M. or I.V. injection.

Cefoperazone Sodium

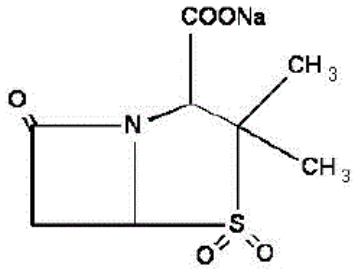
Cefoperazone is a beta-lactam antibacterial agent of third-generation cephalosporin class. Cefoperazone produces bactericidal effect by inhibiting cell wall synthesis. Cefoperazone sodium appears as white to slightly yellowish crystalline powder.

Molecular Weight: 667.7 g/mol.
Molecular Formula: C25H26N9NaO8S2.
Chemical Name: Sodium;(6R,7R)-7-[[(2R)-2-[(4-ethyl-2,3-dioxopiperazine-1-carbonyl)amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[(1-methyltetrazol-5-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.
Structural Formula:



Sulbactam Sodium

Sulbactam is a beta-lactamase inhibitor given in combination with β-lactam antibiotics to inhibit β-lactamase, an enzyme produced by bacteria that destroys antibiotic activity. Sulbactam sodium is a derivative of the basic penicillin nucleus.
Molecular Weight: 255.22 g/mol.
Molecular Formula: C8H10NNaO5S.
Chemical Name: Sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia- 1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4- dio xide.
Structural Formula:



8. Pharmaceutical Particulars

8.1 Incompatibilities

Aminoglycosides: Solutions of cefoperazone/sulbactam and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with an aminoglycoside is intended, this can be accomplished by sequential intermittent I.V. infusion.

Lactated Ringer's Solution: Initial reconstitution with Lactated Ringer's Solution should be avoided since this mixture has been shown to be incompatible. However, it form a compatible mixture in a two-step dilution process involving initial reconstitution with sterile water for injection followed by further dilution with Lactated Ringer's Solution for administration of I.V. infusion.

Lidocaine: Initial reconstitution with 2% lidocaine hydrochloride solution should be avoided since this mixture has been shown to be incompatible. However, a two-step dilution process involving initial reconstitution in sterile water for injection will result in a compatible mixture when further diluted with 2% lidocaine hydrochloride solution.

8.2Shelf-life

Unopened Vial (in powder form): 24 months.

Reconstituted Solution: After reconstitution and/or dilution, to avoid microbiological contamination, the solution should be used immediately. Unused/remaining portion of the solution, if any, should be discarded.

8.3Packaging Information

Combipack of 1 glass vial and one FFS ampoule of 10 ml sterile water for injection in a monocarton.

8.4Storage and Handling Instructions

Store protected from moisture, at a temperature not exceeding 25°C.

Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patient to store medication as advised and not to expose the vial to moisture or direct light.
- When this medicine is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of therapy and increase the likelihood that bacteria will develop antimicrobial resistance.
- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools even as late as two months after the last dose of the antibiotic. If this occurs, instruct patients to contact their physician immediately.
- Instruct patient not to freeze the reconstituted solution and use it immediately after the preparation. Unused portion of solution, if any, should be discarded.

10.Details of Manufacturer

Nitin Lifesciences Ltd.,
Rampur Road, Paonta Sahib, Dist. Sirmour,
Himachal Pradesh – 173 025, India.

11. Details of Permission or License Number with Date

DCG(I) approval date: 12/06/2001.
Manufacturing license No. MB/05/209 dated 08/12/2008.

12. Date of Revision

February 2023.

Marketed by:

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Division of

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