SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Cefpo 200

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Cefpo tablet contains 260.90mg of cefpodoxime proxetil (equivalent to 200mg cefpodoxime).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Cefpo 200mg tablets are white to off white colored, film coated, rounded, biconvex tablets having “CI 200” on one side and break line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Cefpodoxime proxetil is indicated for the treatment of the following infections when caused by susceptible organisms.
- Acute otitis media
- Sinusitis
- Tonsillitis and pharyngitis

In these indications, cefpodoxime should be reserved for recurrent or chronic infections, or for infections where the causative organism is known or suspected to be resistant to commonly used antibiotics or in case the commonly used antibiotic cannot be used for any reason.
- Acute bronchitis
- Bacterial pneumonia

Cefpodoxime is not the preferred antibiotic for the treatment of staphylococcal pneumonia and should not be used in the treatment of atypical pneumonia caused by organisms such as Legionella, Mycoplasma and Chlamydia.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Adults and adolescents with normal renal function:
Sinusitis: 200mg twice daily.
Tonsillitis and pharyngitis: 100mg twice daily
Acute bronchitis, exacerbation of chronic bronchitis and bacterial pneumonia: 100-200 mg twice daily, dependent on the severity of the infection.
Elderly:
It is not necessary to modify the dose in elderly patients with normal renal function.
Children:
Cefpodoxime proxetil Powder tablets are not recommended for children.
Renal Impairment:

The dose of cefpodoxime does not require modification if creatinine clearance exceeds 40ml/min. Below this value, pharmacokinetic studies indicate an increase in plasma elimination half-life. Therefore, the dose should be adjusted appropriately.

CREATININE CLEARANCE (ML/MIN)	
39 – 10	4 mg/kg should be administered once every 24 hours.
< 10	4 mg/kg should be administered once every 48 hours.
Haemodialysis Patients	4 mg/kg should be administered after each dialysis session.

NOTE: [1] The unit dose is either 100mg or 200mg, depending on the type of infection as stated above.

Hepatic Impairment:
The dose does not require modification in cases of hepatic impairment
Duration
The duration of therapy depends on the patient, the indication and the causative pathogen(s).
Method of Administration
For oral administration. The tablets should be taken with food for optimum absorption.

4.3 Contraindications

Hypersensitivity to cefpodoxime, to any of the cephalosporins or to any of the tablet excipients.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.
Phenylketonuria since the product contains aspartame.

4.4 Special warnings and precautions for use

Before therapy with cefpodoxime is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to cefpodoxime, cephalosporins, penicillins, or other beta-lactam drugs.
Cefpodoxime is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin.
It is also contraindicated in patients who have had a previous immediate and /or any severe hypersensitivity reaction to any penicillin or to any other betalactam drug.
Cefpodoxime should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug.
In cases of severe renal insufficiency it may be necessary to reduce the dosage regimen dependent on the creatinine clearance (see section 4.2).
Antibiotic associated diarrhoea, colitis and pseudomembranous colitis have been reported with the use of cefpodoxime. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Cefpodoxime should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted Cefpodoxime should always be used with caution in patients with a history of gastrointestinal disease, particularly colitis.
As with all beta-lactam antibiotics, neutropenia, and more rarely agranulocytosis may develop, particularly during extended treatment. For cases of treatment lasting longer than

10 days, the blood count should be monitored and treatment discontinued if neutropenia is found.
Cephalosporins may be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug. This can produce a positive Coomb's test and very rarely, haemolytic anaemia. Cross-reactivity may occur with penicillin for this reaction.
Changes in renal function have been observed with cephalosporin antibiotics, particularly when given concurrently with potentially nephrotoxic drugs such as aminoglycosides and/or potent diuretics. In such cases, renal function should be monitored.
As with other antibiotics, the prolonged use of cefpodoxime proxetil may result in the overgrowth of non-susceptible organisms.
The product should not be used in infants less than 15 days old as no clinical trial data in this age group yet exists.
This medicinal product contains 1.8 g of sucrose per 5 ml and is unsuitable in fructose intolerance, glucose-galactose malabsorption syndrome or sucrase-isomaltase deficiency.
This medicinal product contains aspartame and is therefore unsuitable for patients with phenylketonuria (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction
Studies have shown that bioavailability is decreased by approximately 30% when cefpodoxime is administered with drugs which neutralise gastric pH or inhibit acid secretions. Therefore, such drugs as antacids of the mineral type and H2 blockers such as ranitidine, which can cause an increase in gastric pH, should be taken 2 to 3 hours after cefpodoxime administration.
A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

4.6 Pregnancy and lactation
Studies carried out in several animal species have not shown any teratogenic or fetotoxic effects. However, the safety of cefpodoxime proxetil in pregnancy has not been established and, as with all drugs, it should be administered with caution during the early months of pregnancy.
Cefpodoxime is excreted in human milk. Mothers should stop breastfeeding during treatment with cefpodoxime.

4.7 Effects on ability to drive and use machines
Dizziness has been reported during treatment with cefpodoxime and may affect patients' ability to drive or operate machinery.

4.8 Undesirable effects
To report any side effect(s):

In this section undesirable effects are defined as follows:
Common: < 10% but ≥ 1%
Uncommon: < 1% but ≥ 0.1%
Rare: < 0.1% but ≥ 0.01% Very rare: < 0.01%

Gastrointestinal disorders
Common: Gastric pressure, nausea, vomiting, abdominal pain, flatulence, diarrhoea.
Bloody diarrhoea can occur as a symptom of enterocolitis.

The possibility of pseudomembranous enterocolitis should be considered if severe or persistent diarrhoea occurs during or after treatment (see 4.4 Special Warnings and Precautions for Use).

Metabolism and nutrition disorders Common: Loss of appetite

Immune system disorders
Hypersensitivity reactions of all degrees of severity have been observed (see 4.4 Special Warnings and Precautions for Use).
Uncommon: Allergic reactions, such as mucocutaneous reactions, skin rashes, urticaria and pruritus.
Very rare: Dermal reactions with blistering (erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome). The medication should be terminated if such symptoms occur. As with other cephalosporins, there have been very rare reports of anaphylactic reactions, bronchospasm, purpura and angioedema.

Renal and urinary disorders
Very rare: Slight increases in blood urea and creatinine

Hepato-biliary disorders
Rare: Transient moderate elevations of ASAT, ALAT and alkaline phosphatase and/or bilirubin. These laboratory abnormalities which may be explained by the infection, may rarely exceed
twice the upper limit of the named range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

Very rare: liver damage

Blood and the lymphatic system disorders
Rare: Haematological disorders, such as reduction in haemoglobin, thrombocytosis, thrombocytopenia, leucopenia and eosinophilia.
Very rare: Haemolytic anaemia

Nervous system disorders
Uncommon: Headaches, paraesthesiae, dizziness. Ear and labyrinth disorders
Uncommon: Tinnitus

Infections and infestations
There can be multiplication of non-sensitive microorganisms (see 4.4 Special Warnings and Precautions for Use).
General disorders and administration site conditions Uncommon: Asthenia or malaise

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorization holder or, where applicable, via the national reporting system https://pv.pharmacyboardkenya.org/

4.9 Overdose

In the event of overdose with Cefpodoxime proxetil, supportive and symptomatic therapy is indicated.
In cases of overdose, particularly in patients with renal insufficiency, encephalopathy may occur. The encephalopathy is usually reversible once cefpodoxime plasma levels have fallen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC classification: J01D D13

Mechanism of action
Like other β-lactam drugs, cefpodoxime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes, namely the penicillin binding proteins. This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanisms of Resistance
Bacterial resistance to cefpodoxime may be due to one or more of the following mechanisms:
- hydrolysis by beta-lactamases. Cefpodoxime 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 cefpodoxime
- outer membrane impermeability, which restricts access of cefpodoxime to penicillin binding proteins in gram-negative organisms
- drug efflux pumps

Breakpoints:
According to the NCCLS (National Committee on Clinical Laboratory Standards) the following breakpoints have been defined for cefpodoxime:
• Enterobacteriaceae and Staphylococcus spp.: ≤ 2 µg/ml susceptible, 4 µg/ml intermediate, ≥ 8
µg/ml resistant
• Haemophilus spp.: ≤ 2 µg/ml susceptible
• Neisseria gonorrhoeae : ≤ 0.5 µg/ml susceptible
• Streptococcus pneumoniae: ≤ 0.5 µg/ml susceptible, 1 µg/ml intermediate, ≥ 2 µg/ml resistant • Other Streptococci that are susceptible to penicillin (MIC90 ≤ 0.12 µg/ml) can be considered susceptible to cefpodoxime.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobes, Gram positive:

Staphylococcus aureus (methicillin susceptible)
Coagulase-negative staphylococci (methicillin-susceptible) Streptococcus agalactiae
Streptococcus pneumoniae Streptococcus pyogenes Aerobes, Gram negative:
Escherichia coli Haemophilus influenzae Klebsiella species Moraxella catarrhalis Neisseria gonorrhoeae Proteus mirabilis Proteus rettgeri Anaerobes:
Peptococcus species Peptostreptococcus species

Species for which resistance may be a problem
Acinetobacter species Citrobacter species Enterobacter species Morganella morganii.
Resistant
Bacteroides fragilis Clostridium difficile Enterococci
Listeria monocytogenes Proteus vulgaris Pseudomonas species Serratia species

5.2 Pharmacokinetic properties
Cefpodoxime proxetil is taken up in the intestine and is hydrolysed to the active metabolite cefpodoxime. When cefpodoxime proxetil is administered orally to fasting subjects as a tablet corresponding to 100 mg of cefpodoxime, 51.1% is absorbed and absorption is increased by food intake. The volume of distribution is 32.3 l and peak levels of cefpodoxime occur 2 to 3 hours after dosing. The maximum plasma concentration is 1.2 mg/l and 2.5 mg/l after doses of 100 mg and 200 mg respectively. Following administration of 100 mg and 200 mg twice daily over 14.5 days, the plasma pharmacokinetic parameters of cefpodoxime remain unchanged.
Serum protein binding of cefpodoxime, 40% principally to albumin. This binding is non-saturable in type.
Concentrations of cefpodoxime in excess of the minimum inhibitory levels (MIC) for common pathogens can be achieved in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, interstitial fluid and prostate tissue.
Studies in healthy volunteers show median concentrations of cefpodoxime in the total ejaculate 6-12 hours following administration of a single 200 mg dose to be above the MIC90 of N. gonorrhoeae.
As the majority of cefpodoxime is eliminated in the urine, the concentration is high. (Concentrations in 0-4, 4-8, 8-12 hour fractions after a single dose exceed MIC90 of common urinary pathogens). Good diffusion of cefpodoxime is also seen into renal tissue, with concentrations above MIC90 of the common urinary pathogens 3-12 hours after an administration of a single 200 mg dose (1.6-3.1 μg/g). Concentrations of cefpodoxime in the medullary and cortical tissues are similar.

The main route of excretion is renal, 80% is excreted unchanged in the urine with an elimination half-life of approximately 2.4 hours.

Children
In children, studies have shown the maximum plasma concentration occurs approximately 2-4 hours after dosing. A single 5mg/kg dose in 4-12 years olds produced a maximum concentration similar to that in adults given a 200mg dose.
In patients below 2 years receiving repeated doses of 5mg/kg 12 hourly, the average plasma concentrations, 2hrs post dose, are between 2.7mg/1 (1-6 months) and 2.0mg/l (7 months - 2 years).
In patients between 1 month and 12 years receiving repeated doses of 5mg/kg 12 hourly, the residual plasma concentration at steady state are between 0.2 0.3mg/l (1 month - 2 years) and 0.1mg/l (2-12 years).

5.3 Preclinical safety data
Acute Toxicity
The median lethal dose in mice and rats was above 8 g/kg and 4 g/kg bodyweight, respectively. In Fisher rats doses of 1 g/kg body weight and higher influenced stool consistency and weight gain. Single doses of 800 mg/kg body weight were non-toxic in dogs.

Repeat-dose toxicity
Chronic toxicity studies were carried out over 12 months in rats and 6 months in dogs. Maximum daily doses (1000 mg/kg body weight orally in rats and 400 mg/kg orally in dogs) were considerably higher than recommended therapeutic doses (3-8 mg/kg body weight). No mortality was observed in rats receiving 250, 500 or 1000 mg/kg for 12 months. Only at 1000 mg/kg, effects on the GI-tract, softened stools and dilatation of the caecum were observed.
Intestinal side effects, which were more pronounced in Fisher rats, are due to the change in intestinal flora caused by the pronounced antibacterial effect of cefpodoxime. Daily administration of 0, 25, 100, and 400 mg/kg body weight to dogs did not reveal mortality. Unchanged cefpodoxime was detected in faeces.

Reproduction toxicity
Embryotoxicity studies in rats and rabbits have not revealed any signs of teratogenic potential. Cefpodoxime had no adverse effects on fertility and peri-/postnatal toxicity studies in rats. Cefpodoxime or its metabolites cross the placenta and are excreted in breast milk in rats. No experience is available on the use of cefpodoxime during pregnancy and lactation in humans.

Mutagenicity
Extensive mutagenicity testing in different testing models was negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)
Carmellose calcium
Lactose monohydrate
Croscarmellose sodium
Hydroxypropyl cellulose
Sodium lauryl sulphate
Magnesium stearate
Tabcoat TC white
Dichloromethane
Isopropyl alcohol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage

Store below 30°C.
Keep out of the reach and sight of children.
Protect from light and moisture.

6.5 Nature and contents of container
Cartons of 14 (2 x 7) film-coated tablets in Aluminium/Aluminium blisters.

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 Authorisation Holder
Zynova/Oman Pharmaceutical Products .Co. L.L.C.,
Salalah, Sultanate of Oman.

8. Marketing Authorisation Number(S)
H2022/CTD8584/16846

9. Date of First Authorisation/Renewal of the Authorisation
18/04/2023

10. Date of Revision of the Text
18/04/2023