National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. Name of the Medicinal Product

(a) Product Name : FEXOPOZAT 500 TABLET
(b) Strength : 500 mg
(c) Pharmaceutical Dosage Form : Tablet

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 Film Coated Tablet contains:
Cefuroxime Axetil U.S.P.
Eq. to Cefuroxime 500 mg

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

Ingredient	**Spec.**	**Claim**	**Overages**	**Qty./tab**	**Functions**
Active Ingredient					
Cefuroxime Axetil Eq. to Cefuroxime	U.S.P.	500 mg	1.0%	606.00 mg	Active
Inactive Ingredient					
Methyl Paraben Sodium	B.P.	---	---	1.900 mg	Preservative
Sodium Lauryl Sulphate	B.P.	---	---	6.600 mg	Lubricant
Colloidal Silicon Dioxide	B.P.	---	---	6.900 mg	Glidant
Purified Talc	B.P.	---	---	17.00 mg	Lubricant
Microcrystalline Cellulose	B.P.	---	---	99.50 mg	Diluent
Maize Starch	B.P.	---	---	137.80 mg	Diluent
Croscarmellose Sodium	B.P.	---	---	9.400 mg	Disintegrant
Sodium Polystyrene Sulphonate	U.S.P.	---	---	9.900 mg	Taste Masker
Magnesium Stearate	B.P.	---	---	6.290 mg	Lubricant
Crospovidone	B.P.	---	---	19.000 mg	Binder
Sodium Starch Glycolate	B.P.	---	---	29.70 mg	Disintegrant
Hydroxypropylmethyl Cellulose	B.P.	---	---	14.25 mg	Film former
Isopropyl Alcohol	B.P.	---	---	28.00 mg	Solvent
Methylene Chloride	B.P.	---	---	116.66 mg	Solvent
Colour Titanium Dioxide	B.P.	---	---	4.750 mg	Colorant

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.: White colour, oblong biconvex shaped film-coated tablet. One side smooth, other side scored**.**

4. Clinical Particulars

4.1 Therapeutic indications:

FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) is indicated for the treatment of the infections listed below in adults and children from the age of 3 months.

- Acute streptococcal tonsillitis and pharyngitis.
- Acute bacterial sinusitis.
- Acute otitis media.
- Acute exacerbations of chronic bronchitis.
- Cystitis
- Pyelonephritis.
- Uncomplicated skin and soft tissue infections.
- Treatment of early Lyme disease.

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

4.2 Posology and method of administration:

Posology

The usual course of therapy is seven days (may range from five to ten days).

Table 1. Adults and children (≥40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	500 mg daily
Acute otitis media	500 mg daily
Acute exacerbations of chronic bronchitis	500 mg daily
Cystitis	500 mg daily
Pyelonephritis	500 mg daily
Uncomplicated skin and soft tissue infections	500 mg daily
Lyme disease	500 mg twice daily for 14 days (range of 10 to 21 days)

Table 2. Children (<40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	10 mg/kg twice daily to a maximum of 125 mg twice daily
Children aged two years or older with otitis media or, where appropriate, with more severe infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Cystitis	15 mg/kg twice daily to a maximum of 250 mg twice daily

Pyelonephritis	15 mg/kg twice daily to a maximum of 250 mg twice daily for 10 to 14 days
Uncomplicated skin and soft tissue infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Lyme disease	15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10 to 21 days)

There is no experience of using FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) in children under the age of 3 months.

Renal impairment:
The safety and efficacy of FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) in patients with renal failure have not been established.

Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Table 3. Recommended doses for FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) in renal impairment

Creatinine clearance	$T_{1/2}$ (hrs)	Recommended dosage
≥30 mL/min/1.73 m^2	1.4–2.4	no dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 mL/min/1.73 m^2	4.6	standard individual dose given every 24 hours
<10 mL/min/1.73 m^2	16.8	standard individual dose given every 48 hours
Patients on haemodialysis	2–4	a further standard individual dose should be given at the end of each dialysis

Hepatic impairment:
There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Method of administration:
Oral use
FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) should be taken after food for optimum absorption.

4.3 Contraindications:
Hypersensitivity to the Cefuroxime axetil or to any of the excipients of formulation.

Patients with known hypersensitivity to cephalosporin antibiotics.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of betalactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warning and precautions for use:

Hypersensitivity reactions:
Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics because there is a risk of cross-sensitivity. 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.

Jarisch-Herxheimer reaction:
The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms:
As with other antibiotics, use of cefuroxime axetil 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 difficult), which may require interruption of treatment.

Antibacterial agent–associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including 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 (see section 4.8). 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.

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

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

4.5 Interaction with other medicinal products and other forms of interactions:
Drugs which reduce gastric acidity may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime.

Concomitant use with oral anticoagulants may give rise to increased INR.

4.6 Pregnancy and Lactation:

Pregnancy

There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonic or foetal development, parturition or postnatal development. Cefuroxime axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. Breastfeeding might have to be discontinued due to these effects. The possibility of sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of cefuroxime axetil on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machine:

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8 Undesirable effects:

The most common adverse reactions are Candida overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data (for example from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

Data from large clinical studies were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data were not available. Where incidences have been calculated from clinical trial data, these were based on drug-related (investigator assessed) data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 (cannot be estimated from the available data).

System organ class	Common	Uncommon	Not known
Infections and infestations	Candida overgrowth		Clostridium difficile overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anaemia
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis
Hepatobiliary disorders	transient increases of hepatic enzyme levels		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (see Immune system disorders), angioneurotic oedema
Description of selected adverse reactions Cephalosporins as a class tend to be absorbed onto the surface of red cells 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 have been observed which are usually reversible.			

Paediatric population:
The safety profile for FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) 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 and peritoneal dialysis.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties: General Pharmacodynamic Effect

Pharmacotherapeutic group: antibacterials for systemic use, second-generationce phalosporins, ATC-Code: J01DC02

Mechanism of action
Cefuroxime axetil undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime.

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) by extended-spectrum beta-lactamases (ESBLs), and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacteria 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.

5.2 Pharmacokinetic Properties:
Absorption and bioavailability
After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Optimum absorption occurs when it is administered shortly after a meal.

Following administration of FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) peak serum levels (2.9 μg/mL for a 125 mg dose, 4.4 μg/mL for a 250 mg dose, 7.7 μg/mL for a 500 mg dose and 13.6 μg/mL for a 1000 mg dose) occur approximately 2.4 hours after dosing when taken with food. The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Distribution:
Protein binding has been stated as 33 to 50% depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to 12 healthy volunteers, the apparent volume of distribution was 50 L (CV% = 28%). 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 humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation:

Cefuroxime is not metabolised.

Elimination:
The serum half-life is between 1 and 1.5 hours. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance is in the region of 125 to 148 mL/min/1.73 m^2.

5.3 Preclinical Safety Data:
Non-clinical data reveal no special hazard for humans based on 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.

6.0 Pharmaceutical Particulars

6.1 List of excipients:

Sr. No.	Name of the Materials	Specification
1	Methyl Paraben Sodium	B.P.
2	Sodium Lauryl Sulphate	B.P.
3	Colloidal Silicon Dioxide	B.P.
4	Purified Talc	B.P.
5	Microcrystalline Cellulose	B.P.
6	Maize Starch	B.P.
7	Croscarmellose Sodium	B.P.
8	Sodium Polystyrene Sulphonate	U.S.P.
9	Magnesium Stearate	B.P.
10	Crospovidone	B.P.
11	Sodium Starch Glycolate	B.P.
12	Hydroxypropylmethyl Cellulose	B.P.
13	Isopropyl Alcohol	B.P.
14	Methylene Chloride	B.P.
15	Colour Titanium Dioxide	B.P.

6.2 Incompatibilities:
Not applicable.

6.3 Shelf life:
The shelf of FEXOPOZAT 500 TABLET (Cefuroxime axetil Tablets USP 500 mg) from the date of manufacture is 36 Months.

6.4 Special precautions for storage:

Store protected from light and moisture at a temperature below 30°C. Keep medicine out of reach of children.

6.5 Nature and contents of container:
White colour, oblong biconvex shaped film-coated tablet. One side smooth, other side scored**.** 1×10 Tablets in ALU-ALU Blister pack.

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.

7.0 Applicant/Manufacturer

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