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

Tambac 100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Cefpodoxime proxetil USP equivalent to cefpodoxime 100 mg.

3. PHARMACEUTICAL FORM

Tablet for oral use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftopix is a bactericidal cephalosporin antibiotic active against a wide range of Gram-negative and Gram-positive organisms. It is indicated for the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity.

UPPER RESPIRATORY TRACT INFECTIONS caused by organisms sensitive to cefpodoxime, including sinusitis.

In tonsillitis and pharyngitis, Ceftopix 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.

LOWER RESPIRATORY TRACT INFECTIONS caused by organisms sensitive to cefpodoxime, including acute bronchitis, relapses or exacerbations of chronic bronchitis and bacterial pneumonia.

UPPER AND LOWER URINARY TRACT INFECTIONS caused by organisms sensitive to cefpodoxime including cystitis and acute pyelonephritis.

SKIN AND SOFT TISSUE INFECTIONS caused by organisms sensitive to cefpodoxime such as abscesses, cellulitis, infected wounds, furuncles, folliculitis, paronychia, carbuncles and ulcers.

GONORRHOEA - uncomplicated gonococcal urethritis.

4.2 Posology and method of administration

Route of administration: oral.

ADULTS:

Adults with normal renal function:

UPPER RESPIRATORY TRACT INFECTIONS: For upper respiratory tract infections caused by organisms sensitive to cefpodoxime, including sinusitis. In tonsillitis and pharyngitis, Ceftopix 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. Sinusitis: 200mg twice daily. Other upper respiratory tract infections: 100mg twice daily.

LOWER RESPIRATORY TRACT INFECTIONS: For lower respiratory tract infections caused by organisms sensitive to cefpodoxime, including acute bronchitis, relapses or exacerbations of chronic bronchitis and bacterial pneumonia: 100-200 mg twice daily, dependent on the severity of the infection.

URINARY TRACT INFECTIONS:

Uncomplicated lower urinary tract infections: 100mg should be taken twice daily.
Uncomplicated upper urinary tract infections: 200mg should be taken twice daily.
Uncomplicated gonococcal urethritis: 200mg should be taken as a single dose.

SKIN AND SOFT TISSUE INFECTIONS: 200mg should be taken twice daily.
Tablets should be taken during meals for optimum absorption.

ELDERLY:

It is not necessary to modify the dose in elderly patients with normal renal function.

CHILDREN:

Ceftopix Paediatric is available to treat infants (over 15 days old) and children. Please refer to the separate Summary of Product Characteristics for details.

HEPATIC IMPAIRMENT:

The dosage does not require modification in cases of hepatic impairment.

RENAL IMPAIRMENT:

The dosage of Ceftopix does not require modification if creatinine clearance exceeds 40 ml/min.

Below this value, pharmacokinetic studies indicate an increase in plasma elimination half-life and the maximum plasma concentrations, and hence the dosage should be adjusted appropriately.

CREATININE CLEARANCE (ML/MIN)	
39 – 10	Unit dose[1] administered as a single dose every 24 hours (i.e half of the usual adult dose).
< 10	Unit dose[1] administered as a single dose every 48 hours (i.e quarter of the usual adult dose).
Haemodialysis Patients	Unit dose[1] administered after each dialysis session.

NOTE:

1. The unit dose is either 100mg or 200mg, depending on the type of infection.

4.3 Contraindications

Hypersensitivity to cephalosporin antibiotics

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).

4.4 Special warnings and precautions for use

Preliminary enquiry about allergy to penicillin is necessary before prescribing cephalosporins since cross allergy to penicillins occurs in 5-10% of cases.

Particular care will be needed in patients sensitive to penicillin: strict medical surveillance is necessary from the very first administration. Where there is doubt, medical assistance should be available at the initial administration, in order to treat any anaphylactic episode.

In patients who are allergic to other cephalosporins, the possibility of cross allergy to Ceftopix should be borne in mind. Ceftopix should not be given to those patients with a previous history of immediate type hypersensitivity to cephalosporins.

Hypersensitivity reactions (anaphylaxis) observed with beta-lactam antibiotics can be serious and occasionally fatal.

The onset of any manifestation of hypersensitivity indicates that treatment should be stopped.

Ceftopix 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.

In cases of severe renal insufficiency it may be necessary to reduce the dosage regimen dependent on the creatinine clearance.

Possible side effects include gastrointestinal disorders such as nausea, vomiting and abdominal pain. Antibiotics should always be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis. Ceftopix may induce diarrhoea, antibiotic associated colitis and pseudomembranous colitis. These side-effects, which may occur more frequently in patients receiving higher doses for prolonged periods, should be considered as potentially serious. The presence of C. difficile should be investigated. In all potential cases of colitis, the treatment should be stopped immediately. The diagnosis should be confirmed by sigmoidoscopy and specific antibiotic therapy (vancomycin) substituted if considered clinically necessary. The administration of products, which cause faecal stasis, must be avoided. Although any antibiotic may cause pseudomembranous colitis, the risk may be higher with broad-spectrum drugs, such as the cephalosporins.

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, blood count should therefore 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 antibiotics of the same class, 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. With oral antibiotics the normal colonic flora may be altered, allowing overgrowth by clostridia with consequent pseudomembranous colitis. Repeated evaluation of the patient is essential and if superinfection occurs during therapy, appropriate measures should be taken.

4.5 Interaction with other medicinal products and other forms of Interaction

No clinically significant drug interactions have been reported during the course of clinical studies.

As with other cephalosporins, isolated cases showing development of a positive Coombs' test have been reported (see Precautions).

Studies have shown that bioavailability is decreased by approximately 30% when Ceftopix 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 cause an increase in gastric pH, should be taken 2 to 3 hours after Ceftopix administration.

The bioavailability increases if the product is administered during meals.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

4.6 Pregnancy and lactation

Pregnancy

For cefpodoxime proxetil no clinical data on exposed pregnancies are available. In rat, cefpodoxime proxetil reaches the embryo/fetus via the placenta. Animal data reveal no undesirable effects on reproduction (see section 5.3 preclinical data). As a precautionary measure, Cefpodoxime should only be used during pregnancy after benefit / risk assessment by the doctor in charge, especially during the first trimester.

Breast-feeding

Cefpodoxime is excreted in maternal milk. Diarrhoea and fungus infections of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued during treatment with Cefpodoxime. The possibility of sensitisation should be borne in mind.

Fertility

No untoward effects on fertility or reproduction were noted when 100 mg/kg/day or less (2 times the human dose based on mg/m2sup) was administered orally to rats.

4.7 Effects on ability to drive and use machines

Attention should be drawn to the risk of dizzy sensations.

4.8 Undesirable effects

The following adverse reactions have been reported (organised by organ system). The following frequencies are defined in the evaluation of side effects:
very common (more than 1 in 10 people);
common (up to 1 in 10 people);
uncommon (up to 1 in 100 people);
rare (up to 1 in 1,000 people);
very rare (up to 1 in 10,000 people),
not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon:
Haemolytic anaemia.
Very rare:
In some cases, blood disorders (thrombocytosis, thrombocytopenia, leukopenia, neutropenia, agranulocytosis, eosinophilia, decreased haemoglobin values) were observed. These very rare changes are reversible upon discontinuation of therapy.

Diseases of the nervous system
Uncommon:
Headache, tinnitus, paresthesias and dizziness were observed.

Gastrointestinal disorders
Common:
Stomach upset, nausea, vomiting, loss of appetite, bloating or diarrhoea. Bloody diarrhoea may occur as a symptom of enterocolitis.
Rare:
If severe or persistent diarrhoea during or after therapy thought to be Pseudomembranous enterocolitis (rare in children), diagnosis should be confirmed. In these rare cases, cephalosporins should be discontinued immediately and appropriate therapy initiated. Peristalsis agents are contraindicated.
Very rare:
Single cases of acute pancreatitis have been reported.

Renal and urinary disorders
Very rare:
Single cases of acute renal failure have been reported.

Hypersensitivity reactions
Common:
Allergic reactions have been observed, mostly in the form of skin lesions with or without itching (erythema, rash, urticaria, purpura).
Very rare:
Individual cases of bullous skin reactions (erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome) have been reported. The mediciation should be discontinued if such symptoms occur.
Hypersensitivity reactions of any severity (e.g. angioedema, bronchospasm to life threatening shock) have been observed. Severe acute hypersensitivity reactions may require appropriate emergency measures. With hypersensitivity to other beta-lactam antibiotics, cross reactions with cefpodoxime proxetil may occur (see Section 4.3 Contraindications).
General disorders and administration site

Uncommon:
Asthenia, fatigue and discomfort (malaise).
Hepato-biliary disorders
Very rare:
Single cases of acute hepatitis have been reported.

Laboratory tests
Uncommon:
Elevation of liver enzymes (transaminases, alkaline phosphate) and/or bilirubin as a sign of liver cell damage (cholestatic) as a sign of liver cell damage.
Very rare:
In some cases, an increase of uremic substance (creatinine and urea) in serum
Infections and infestations
Proliferation of non-susceptible organisms, especially with prolonged use

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to pharmacovigilance@cadilapharma.co.in

4.9 Overdose
In the event of overdosage with Ceftopix, supportive and symptomatic therapy is indicated.
In cases of overdosage, 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

Pharmacotherapeutic group:
Third generation cephalosporins
ATC code: J01DD13

Cefpodoxime proxetil is a beta-lactam antibiotic, a third generation oral cephalosporin. It is the prodrug of cefpodoxime.

Mechanism of action
Like other beta-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
- impermeability of the outer membrane of the cell wall of gram-negative bacteria to cefpodoxime thereby restricting access of cefpodoxime to penicillin-binding proteins
- the presence of drug efflux pumps that extrude cefpodoxime from bacteria

Breakpoints:

The following limits (MIC breakpoints) are proposed to distinguish sensitive from resistant organisms: Sensitive ≤ 1 mg/l, resistant > 4 mg/l.

Susceptibility (antibiotic spectrum)

The prevalence of acquired resistance may vary geographically and with species over time, therefore, particularly when treating severe infections, local information on resistance is desirable. The use of cefpodoxime proxetil should be based on the local prevalence of resistance and expert advice should be sought when appears questionable for at least some types of infections. Especially in serious infections or treatment failure with a microbiological diagnosis with detection of the pathogen and its susceptibility to cefpodoxime proxetil is desirable.

The following table shows the sensitivity of each category of relevant species compared with cefpodoxime proxetil.

Prevalence of acquired resistance in Germany, based on data from the last 5 years of national resistance monitoring projects and studies (December 2010):

Category 1

Commonly susceptible species

Aerobes, Gram-positive microorganisms:

Staphylococcus aureus (methicillin sensitive)

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobes, Gram negative microorganisms:

Haemophilus influenzae

Neisseria gonorrhoeae

Proteus mirabilis

Category 2

Species for which acquired resistance may be a problem

Aerobic, Gram-positive microorganisms:

Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Streptococcus pneumonia (Penicillin-intermediate)

Aerobic, Gram-negative microorganisms:

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Serratia marcescens
Moraxella catarrhalis

Category 3

Inherently resistant species

Aerobic, Gram-positive microorganisms:

Enterococcus spp
Staphylococcus aureus(Methicillin resistant)
Streptococcus pneumonia (Penicillin resistant)

Aerobic, Gram-negative microorganisms:

Morganella morganii
Pseudomonas aeruginosa

Other microorganisms

Chlamydia spp
Chlamydophila spp
Legionella pneumophila
Mycoplasma spp

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

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.

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 is similar.

Studies in healthy volunteers show medium 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.

Metabolism

Cefpodoxime proxetil is a prodrug of cefpodoxime. Essentially the entire drug that is absorbed is deesterified, pre-systemically in the small intestine to its active form. Cefpodoxime itself does not undergo any significant metabolism and is excreted unchanged, largely in the urine.

Elimination

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 5 mg/kg dose in 4-12 year olds produced a maximum concentration similar to that in adults given a 200 mg dose.

In patients below 2 years receiving repeated doses of 5 mg/kg 12 hourly, the average plasma concentrations, 2 hours post dose, are between 2.7 mg/L (1-6 months) and 2.0 mg/L (7 months-2 years).

In patients between 1 month and 12 years receiving repeated doses of 5 mg/kg 12 hourly, the residual plasma concentrations at steady state are between 0.2-0.3 mg/L (1 month-2 years) and 0.1 mg/L (2-12 years).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Avicel RC 591 USP, Sodium Lauryl Sulphate BP, Hydroxy Propyl Cellulose LH-11 NF, Colloidal Silicone Dioxide USNF, Magnesium Stearate BP, Opadry 03B50857 Blue In House, Isopropyl Alcohol BP and Methylene Chloride BP

6.2 Incompatibilities

None reported during clinical studies.

6.3 Shelf-life

24 months.

6.4 Special precautions for storage

Store below 30°C. Protect from light

6.5 Nature and contents of container

Tambac 100 tablets are supplied in strip packs of 10 tablets. One such strip will be placed in a carton along with pack insert for packs of 1 x 10's tablets.

6.6 Instructions for use and handling

None.

7. MARKETING AUTHORISATION HOLDER

Cadila Pharmaceuticals Limited,
1389, Trasad, Road, Dholka – 382 225,
District: Ahmedabad, Gujarat State,
INDIA

8. MARKETING AUTHORISATION NUMBER(S)

B4 - 6175

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2016

10. DATE OF REVISION OF THE TEXT

10 June 2019