Summary of Product Characteristics

Cefodox® 100mg and 200mg F/C Tablets

Cefpodoxime proxetil

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1. Name of the medicinal product

Cefodox® 100mg and 200mg F/C Tablets

Cefpodoxime proxetil

2. Qualitative and quantitative composition
   Each Cefodox® tablet contains 100mg OR 200mg of the active ingredient cefpodoxime proxetil

3. Pharmaceutical form

Tablet for oral use.

4. Clinical particulars

4.1 Therapeutic indications

Cefodox®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, Cefodox® 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 infection*s 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, Cefodox® 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:

Cefodox® 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 Cefodox® 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.

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 Cefodox® should be borne in mind. Cefodox® 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.

Cefodox® 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. Cefodox® 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 Coombs' 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.

.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.

Histamine H2-antagonists and antacids reduce the bioavailibility of cefpodoxime. Probenecid reduces the excretion of cephalosporins. Cephlasporins potentially enhance the anticoagulant effect of coumarins and reduce the contraceptive effect of oestrogens.

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 Cefodox® is administered with drugs which neutralise gastric pH or inhibit acid secretions. Therefore, such drugs as antacids of the mineral type and H_2 blockers such as ranitidine, which can cause an increase in gastric pH, should be taken 2 to 3 hours after Cefodox® 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.

Studies carried out in several animal species have not shown any teratogenic or foetotoxic 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. Either breastfeeding or treatment of the mother should be stopped.

4.7 Effects on ability to drive and use machines

Attention should be drawn to the risk of dizzy sensations.

4.8 Undesirable effects

Possible side effects include gastrointestinal disorders such as diarrhoea and rarely antibiotic-associated colitis, including pseudomembranous colitis (see Section 4.4: Special Warnings and Precautions for Use), nausea, vomiting and abdominal pain and rash, urticaria and itching. Changes in renal function have been observed with antibiotics from the same group as Cefpodoxime, particularly when co-prescribed with aminoglycosides and/or potent diuretics.

Occasional cases have been reported of headaches, dizziness, tinnitus, parethesia, asthenia and malaise. Rare cases of allergic reactions include hypersensitivity mucocutaneous reactions, skin rashes and pruritus. Occasional cases of bullous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have also been received. Transient moderate elevations of ASAT, ALAT and alkaline phosphatases and/or bilirubin have been reported. 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.Slight increases in blood urea and creatinine have also been reported. Exceptionally rare are the occurrence of liver damage and of haematological disorders such as reduction in haemoglobin, thrombocytosis, thrombocytopenia, leucopenia and eosinophilia. Haemolytic anaemia has extremely rarely been reported.

As with other β-lactam antibiotics, neutropenia and, more rarely, agranulocytosis may develop during treatment with Cefpodoxime, particularly if given over long periods.

As with other cephalosporins, there have been rare reports of anaphylactic reactions, bronchospasm, purpura and angiodema, serum-sickness-like reactions with rashes, fever and arthralgia.

4.9 Overdose

In the event of overdosage with Cefodox®, 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

Cefodox® (Cefpodoxime proxetil) is a beta-lactam antibiotic, a 3rd generation oral cephalosporin. It is the prodrug of cefpodoxime.

Following oral administration, Cefodox® is taken up by the gastro-intestinal wall where it is rapidly hydrolysed to cefpodoxime, a bactericidal antibiotic, which is then absorbed systemically.

BACTERIOLOGY:

The mechanism of action of cefpodoxime is based on inhibition of bacterial cell wall synthesis. It is stable to numerous beta-lactamases.

Cefpodoxime has been shown to possess *in vitro* bactericidal activity against numerous Gram-positive and Gram-negative bacteria.

It is highly active against the Gram-positive organisms:

Streptococcus pneumoniae

Streptococci of Groups A (*S. pyogenes*), B (*S. agalactiae*), C, F and G

Other streptococci (*S. mitis, S. sanguis* and *S. salivarius*)

Corynebacterium diphtheriae

It is highly active against the Gram-negative organisms:

• *Haemophilus influenzae* (beta-lactamase and non beta-lactamase producing strains)

• *Haemophilus para-influenzae* (beta-lactamase and non beta-lactamase producing strains)

• *Branhamella catarrhalis* (beta-lactamase and non beta-lactamase producing strains)

• *Neisseria meningitides*

• *Neisseria gonorrhoeae*

- *Escherichia coli*
- *Klebsiella* Spp. (*K. pneumoniae*; *K. oxytoca*)
- *Proteus mirabilis*

It is moderately active against meticillin-sensitive staphylococci, penicillinase and non-penicillinase producing strains (*S. aureus* and *S. epidermidis*).

In addition, as with many cephalosporins, the following are resistant to cefpodoxime: enterococci, meticillin-resistant staphylococci *(S. aureus* and *S. epidermidis), Staphylococcus saprophyticus, Pseudomonas aeruginosa and Pseudomonas* Spp.*, Clostridium difficile, Bacteroides fragilis* and related species.

As with all antibiotics, whenever possible, sensitivity should be confirmed by *in vitro* testing.

5.2 Pharmacokinetic properties

Cefodox® 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 100mg of cefpodoxime, 51.5% 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 hrs after dosing. The maximum plasma concentration is 1.2mg/l and 2.5mg/l after doses of 100mg and 200mg respectively. Following administration of 100mg and 200mg 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 hr fractions after a single dose exceed MIC_{90} of common urinary pathogens). Good diffusion of cefpodoxime is also seen into renal tissue, with concentrations above MIC_{90} of the common urinary pathogens, 3-12hrs after an administration of a single 200mg dose (1.6-3.1µG/G). Concentrations of cefpodoxime in the medullary and cortical tissues is similar.

Studies in healthy volunteers show median concentrations of cefpodoxime in the total ejaculate 6-12hrs following administration of a single 200mg dose to be above the MIC_{90} of *N. gonorrhoeae*.

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

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

The product contains Microcrystalline Cellulose, Sodium Lauryl sulfate, Magnesium stearate, Croscarmellose sodium, Sodium starch glycolate, Colloidal silicon dioxide, Opadry OY-L white, Yellow iron oxide.

6.2 Incompatibilities

None reported during clinical studies.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Cefodox® tablets are supplied in blister packs of 10 tablets.

6.6 Special precautions for disposal and other handling.

None.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

Cefodox® 100mg F/C Tablets

145/2001, renewal number 2008/ت ع /230

Cefodox® 200mg F/C Tablets

239/2001, renewal number 97/2009 /ت ع

9. Date of first authorisation/renewal of the authorization

Cefodox® 100mg F/C Tablets

30/9/2001, renewal date 18/12/2008

Cefodox® 200mg F/C Tablets

24/9/2001, renewal date 23/04/2009

10. Date of revision of the text

01/2013