Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefodox 100mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cefodox Tablet contains cefpodoxime proxetil equivalent to 100 mg cefpodoxime.

Excipients: each tablet contains 220mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
A biconvex, cylindrical, practically white tablet, 9mm in diameter, with ‘208’ and beneath ‘A’ engraved on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indications include:

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, 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 and relapses or exacerbations of chronic bronchitis, and bacterial pneumonia, including patients at risk or compromised by other underlying illnesses.

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, burns and ulcers.

Gonorrhoea, uncomplicated gonococcal urethritis.

4.2 Posology and method of administration

Adults :
Upper Respiratory Tract Infection
Sinusitis: 200mg twice daily (morning and evening).
Pharyngitis, tonsillitis: 100mg twice daily (morning and evening).
Other upper respiratory tract infections: 100mg twice daily.
Tablets should be taken during meals.

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.

Uncomplicated Lower Urinary Tract Infections
100mg to be taken twice daily.

Uncomplicated Upper Urinary Tract Infections
200mg to be taken twice daily.

Uncomplicated Gonococcal Urethritis
200mg to be taken as a single dose.

Skin and Soft Tissue Infections
200mg to be taken twice daily.
Tablets should be taken during meals with some liquid, for optimum absorption (morning and evening).

***Elderly** :*
In the elderly, provided renal function is normal, it is not necessary to modify the dosage.

***Children** :*
Cefodox Paediatric is available to treat infants (over 15 days old) and children. Please refer to it's separate prescribing information for details.

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 maximum plasma concentrations, and hence the dosage should be adjusted appropriately.

CREATININE CLEARANCE (ML/MIN)	
39-10	UNIT DOSE ADMINISTERED AS A SINGLE DOSE EVERY 24 HOURS (IE HALF OF THE USUAL ADULT DOSE)
<10	UNIT DOSE ADMINISTERED AS A SINGLE DOSE EVERY 48 HOURS (IE QUARTER OF THE USUAL ADULT DOSE)
HAEMODIALYSIS PATIENTS	UNIT DOSE ADMINISTERED AFTER EACH DIALYSIS SESSION

Note [1] : The unit dose is either 100mg or 200mg depending on the type of infection.

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

4.3 Contraindications

Patients with hypersensitivity to cephalosporin antibiotics.

4.4 Special warnings and precautions for use

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

Particular care will be needed in patients sensitive to penicillins : strict medical surveillance is necessary from the very first administration.

As with other antibiotics, the prolonged use of cefpodoxime proxetil may result in overgrowth of non-susceptible organisms. With an oral antibiotic the normal colonic flora may be altered allowing the overgrowth by clostridia with consequent pseudomembranous colitis.

Repeated evaluation of the patient is essential, and if superinfection occurs during therapy, appropriate measurements should be taken.

In patients who are allergic to other cephalosporins, the possibility of cross allergy to Cefodox should be borne in mind. The use of cephalosporins is strictly forbidden in subjects with a previous history of immediate type hypersensitivity to cephalosporins. Where there is any doubt, medical assistance should be available at the first administration, in order to treat any possible anaphylactic reaction.
Hypersensitivity reactions (anaphylaxis) observed with these 2 types of β-lactams may 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 staphyloccocal 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. (See Section 4.2 Posology and method of administration).

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 pseudomembraneous 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 carrying out relevant investigations such as 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 pseudomembraneous colitis, the risk may be higher with broad-spectrum drugs, such as the cephalosporins.

Changes in renal function have been observed with antibiotics of the same class and 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 all beta-lactam antibiotics, neutropenia and more rarely agranulocytosis may develop particularly during extended treatments. 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 antibiotics 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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 mineral antacids and histamine blocking H_2 blockers, which cause an increase in gastric pH, should be taken 2 or 3 hours after Cefodox administration. In contrast, a decrease in gastric pH (pentagastrin) will increase bioavailability.

As with other cephalosporins, isolated cases showing development of a positive Coombs test have been reported (See Section 4.4. Special Warnings and Precautions for Use).

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 (See Section 4.4. Special Warnings and Precautions for Use).

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

The bioavailability increases if the product is administered during meals.

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

Studies carried out in several animal species have not revealed any teratogenic of foetotoxic effects. However, the safety of cefpodoxime proxetil in pregnant women has not been established; it is therefore advisable not to administer the product during pregnancy.

4.6.2 Lactation

Studies have shown that cefpodoxime is excreted in human milk. It is recommended that either breastfeeding should be ceased or treatment should be discontinued.

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 CIOMS frequency rating is used: (very common (>1/10), common (1/10 – 1/100), uncommon (1/100 – 1/1000), rare (1/1000 – 1/10000).

Blood and Lymphatic System Disorders:
Uncommon: Thrombocytosis (usually reversible upon treatment discontinuation).
Rare: Eosinophilia, thrombocytopenia, neutropenia, agranulocytosis, haemolytic anaemia, lymphocytosis, anaemia, leukopenia, leucocytosis.

Ear and Labyrinth Disorders:
Uncommon: Tinnitus.

Gastrointestinal Disorders:
Common: Diarrhoea, nausea, abdominal pain, vomiting, flatulence.
Rare: Enterocolitis, including pseudomembranous colitis, blood in stools, acute pancreatitis.

Renal and Urinary Disorders:
Rare: Acute renal insufficiency.
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 (See Section 4.4. Special Warnings and Precautions for Use).

General Disorders and Administration Site Conditions:
Uncommon: Asthenia, fatigue, malaise.

Hepatobiliary Disorders:
Uncommon: Bilirubinemia, livery injury, cholestasis.
Rare: Acute hepatitis.

Immune System Disorders:
Rare: Hypersensitivity reactions of all severities – e.g. from angioedema and bronchospasm to life-threatening shock.

Infections and Infestations:
Common: Superinfections, overgrowth of non-susceptible organisms.
Superinfection: as with other antibiotics, the use of cefpodoxime proxetil, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Investigations:
Uncommon: Increases in liver enzymes (transaminases, alkaline phosphatases).
Rare: Increase in blood urea and creatinine.

Nervous System Disorders:
Uncommon: Dizzy sensations, headache, paraesthesia.

Skin and Subcutaneous Tissue Disorders:
Uncommon: Pruritus, rash, urticaria, purpura.
Rare: Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme.

Metabolism and Nutrition Disorders:
Common: Appetite loss.

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 via:

IMB Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

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.
No specific antidote exists.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: J01DD01

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 diphtheria*

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 meningitidis*
- *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

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.

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.

Concentration 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 (0.6 - 3.1mg/g), 3-12hrs after an administration of a single 200mg dose. Concentrations of cefpodoxime in the medullary and cortical tissues are 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. gonorrhoea*.

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

Magnesium stearate
Carmellose calcium
Hydroxypropylcellulose
Sodium laurilsulfate
Lactose monohydrate

Coating contains
Titanium dioxide (E171)
Talc
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Cefodox tablets are supplied in PVC/Aluminium blister packs of 2, 10 and 20 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/033/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 October 1991

Date of last renewal: 02 August 2010

10 DATE OF REVISION OF THE TEXT

March 2014