Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefodox Paediatric 40mg/5ml Granules for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted each 5ml volume contains 40mg of cefpodoxime, as cefpodoxime proxetil.

Excipients: contains per 5ml:
Aspartame (E951) 20mg
Lactose monohydrate q.s.
Sucrose 601.33mg
Potassium 2.17mg
Sulphites 0.72 micrograms
Glucose 322.2mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension
Pale yellow granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefodox is a bactericidal cephalosporin antibiotic active against *in vitro* a wide range of gram-negative and gram-positive organisms. It is indicated for the treatment of the following infections.

Indications include:
Upper respiratory tract infections caused by organisms sensitive to cefpodoxime, including acute otitis media, sinusitis, tonsillitis and pharyngitis.
Cefodox should be reserved for recurrent or chronic infections.
*Lower respiratory tract infection*s caused by organisms sensitive to cefpodoxime.
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, folliculitis, paronychia, carbuncles, burns and ulcers.

4.2 Posology and method of administration

Route of administration: Oral.

Adults & Elderly:
Not applicable for this product.

Children:
The recommended mean dosage for children is 8mg/kg/day administered in two divided doses at 12 hour intervals.
The following dosage regimen is proposed as a guide to prescribing:

Below 6 months:	8mg/kg/day in 2 divided doses.
6 months-2 years:	5.0 ml twice daily.
3-8 years:	10.0 ml twice daily.

Above 9 years: 12.5ml twice daily or 100mg tablet twice daily.

Cefodox should not be used in infants less than 15 days old, as no experience yet exists in this age group.

A measuring spoon (5ml) is provided with the bottle to aid correct dosing. One measuring spoon (5ml) contains the equivalent of 40 mg cefpodoxime.

The product should be taken during meals for optimal absorption.

Renal Impairment:

The dosage of Cefodox does not require modification if creatinine clearance (CLcr) exceeds 40ml.min^{-1}/1.73m^{2}.

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.

- CLcr 10-39 ml.Min^{-1}/1.73m^{2}=unit dose every 24 hours.
- CLcr <10ml.Min $^{-1}$/1.73m^{2}=unit dose every 48 hours.
- Haemodialysis patients = unit dose after each dialysis session.

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

Instructions for Reconstitution:
Before preparing the suspension the silica gel desiccant contained in a capsule inside the cap must be removed and disposed of. The suspension is prepared by adding water to the bottle up to the calibrated mark and shaking thoroughly to obtain an evenly dispersed suspension.

4.3 Contraindications

Patients with hypersensitivity to cephalosporin antibiotics, or any of the excipients (see section 6.1).

Patients with phenylketonuria since the product contains aspartame.

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.

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.

The product should not be used in infants less than 15 days old as no clinical trial data in this age group yet exists.

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 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.

As with other antibiotics, the prolonged use of cephalosporins 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.

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 penicillins for this reaction.

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

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.

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 antacids of the mineral type and H_2 blockers such as ranitidine, which cause an increase in gastric pH, should be taken 2 or 3 hours after Cefodox administration.

In contrast, drugs that decrease gastric pH such as pentagastrin will increase bioavailability. The clinical consequences remain to be established.

Change in renal function has 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 Warning and Precautions for Use).

The bioavailability increases if the product is administered during meals.
As with other cephalosporins, isolated cases showing development of a positive Coomb's test have been reported. (See Section 4.4. Special Warning and Precautions for Use).

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 Fertility, pregnancy and lactation

Pregnancy
Studies carried out in several animal species have not revealed any teratogenic or 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.

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

Not applicable.

4.8 Undesirable effects

System Organ Class	ADR Term	Frequency
Blood and Lymphatic System Disorders	Eosinophilia	rare
	Thrombocytopenia	rare
	Neutropenia	unknown
	Agranulocytosis	unknown
	Hemolytic anaemia	unknown
Ear and Labyrinth Disorders	Tinnitus	unknown
Gastrointestinal Disorders	Enterocolitis	rare
	Diarrhoea	common
	Nausea	common
	Abdomial pain	uncommon
	Vomiting	uncommon
	Blood in stools	unknown
General Disorders and Administration Site Conditions	Malaise	rare
	Asthenia	uncommon
Hepatobiliary Disorders	Bilirubinemia	rare
	Liver injury	unknown
	Cholestasis	unknown
Immune System Disorder	Shock	unknown
Infections and Infestations	Superinfections	common
	Pseudomembranous colitis	unknown
	Overgrowth of non-susceptible organisms	unknown

Investigations	Increases in liver enzymes	uncommon
	Changes in renal function	rare
Nervous System Disorders	Dizzy sensations	uncommon
	Headache	uncommon
	Paraesthesia	rare
Skin and Subcutaneous Tissue Disorders	Pruritus	uncommon
	Rash	uncommon
	Urticaria	uncommon
	Angioedema	unknown
	Purpura	unknown
	Stevens-Johnson syndrome	unknown
	Toxic epidermal necrolysis	unknown
	Erythema multiforme	unknown
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm	rare

Renal
Slight increases in blood urea and creatinine have been reported.
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).

Other
Occasional cases have been reported of headaches, dizziness, tinnitus, parethesia and asthenia.

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.

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.

The following are resistant to cefpodoxime.

- Enterococci
- Methicillin-resistant Staphylococci (S. Aureus and S. Coagulase (negative))
- 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 (0.6 - 3.1micrograms/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.

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 year 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, 2 hours post dose, are between 2.75 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 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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica
Aspartame (E951)
Banana flavour
Carmellose calcium
Carmellose sodium
Citric acid monohydrate
Hyprolose/hydroxypropylcellulose
Yellow iron oxide (E172)
Lactose monohydrate
Monosodium glutamate
Potassium sorbate (E202)
Sodium chloride
Sorbitan trioleate
Sucrose
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unreconstituted product: 2 years.
Reconstituted suspension: 10 days.

6.4 Special precautions for storage

Bottles: unreconstituted product should be stored below 25°C.

Reconstituted suspension: should be kept refrigerated (2-8°C) for not more than 10 days. Do not freeze.

Any product remaining after use should be discarded.

6.5 Nature and contents of container

Calibrated amber glass bottles containing granules for the preparation of 50ml, or 100ml of suspension.

A plastic spoon is supplied with the bottles.

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

Before preparing the suspension the silica gel desiccant contained in a capsule inside the cap must be removed and disposed of. The suspension is prepared by adding water to the bottle up to the calibrated mark and shaking thoroughly to obtain an evenly dispersed pale yellow suspension.

Shake well before use.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 540/33/1

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