1.3 Labeling and Packaging

1.3.1 Package Insert/Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

Table of Contents

1. Name of the medicinal product
SANDOX - DS 40 (Cefpodoxime Proxetil for Oral Suspension USP 40mg/5ml)

2. Qualitative and quantitative composition
Label claim:
Each 5ml of the reconstituted suspension contains:
Cefpodoxime Proxetil USP equivalent to anhydrous Cefpodoxime 40mg

Bottle Size:- 50ml & 100ml HDPE bottle

Sl. No:	Raw material	Specification	Quantity / 5 ml (mg)	Quantity / bottle in g (50ml)	Quantity / bottle in g (100ml)	Rationale
1.	Cefpodoxime proxetil (micronized) *	USP	59.440	0.594	1.189	Active ingredient
2.	Sucrose (P.G.SUGAR- #40) **	USP	1443.893	14.439	28.878	Diluent
3.	Sucrose (P.G.SUGAR- #80)	USP	952.000	9.520	19.040	Diluent
4.	Sucralose	USP	3.333	0.033	0.067	Sweetening agent
5.	Aspartame	USP	2.500	0.025	0.050	Sweetening agent
6.	Sodium citrate	USP	1.667	0.017	0.033	Buffering agent
7.	Citric acid (anhydrous)	USP	2.500	0.025	0.050	Buffering agent
8.	Sodium lauryl sulfate	USP	2.000	0.020	0.040	Surfactant
9.	Colloidal silicon dioxide	USP	12.000	0.120	0.240	Glidant
10.	Xanthan gum	USP	5.000	0.050	0.100	Suspending agent
11.	Banana Premium Flavour	IHS	15.000	0.150	0.300	Flavouring agent
12.	Sodium methyl paraben	USP	0.667	0.007	0.013	Preservative

Remarks:
* Calculated based on Assay value of 69.0 % w/w as Cefpodoxime and water content of 2.5 % w/w
** Quantity of Sucrose (PG Sugar) to be adjusted to the final fill weight of 2500.00 mg per 5 ml, based on actual assay and %w/w water content of Cefpodoxime Proxetil.

3. Pharmaceutical form
Dry Powder for Oral Suspension

4. Clinical particulars
4.1 Therapeutic indications
Upper respiratory tract infections caused by organisms sensitive to cefpodoxime, including acute otitis media, sinusitis, tonsillitis and pharyngitis. Cefpodoxime Proxetil for Oral Suspension 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 pneumonia, acute bronchitis and when bacterial super-infection complicates bronchiolitis.
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.

4.2 Posology and method of administration
Adults and 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.
Cefpodoxime Proxetil for Oral suspension should not be used in infants less than 15 days old, as no experience yet exists in this age group.
The product should be taken during meals for optimal absorption.

Renal Impairment: The dosage of Cefpodoxime Proxetil for Oral suspension does not require modification if creatinine clearance exceeds 40 $ml.min^{-1}/1.73m^2$.

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.

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.

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

Instructions for Reconstitution:
The suspension is prepared by adding water to the bottle up to the mark and shaking thoroughly to obtain an evenly dispersed suspension.

4.3 Contraindications
Patients with hypersensitivity to cephalosporin antibiotics.
Patients with phenylketonuria since the product contains aspartame.
Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 penicillin: 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 Cefpodoxime 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.
Cefpodoxime 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. Cefpodoxime 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 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 pseudomembranous 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 Cefpodoxime 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 Cefpodoxime 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.
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.
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
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
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 cefpodoxime, 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
Cefpodoxime proxetil is a beta-lactam antibiotic, a 3rd generation oral cephalosporin. It is the prodrug of cefpodoxime.
Following oral administration, Cefpodoxime 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*)
• *Propionibacterium acnes*
• *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)
• *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
Cefpodoxime 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 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, 2hrs post dose, are between 2.7mg/l (1-6 months) and 2.0mg/l (7 months-2 years).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Sucralose, Aspartame, Sodium Citrate, Citric acid (anhydrous), Sodium Lauryl sulfate, Colloidal silicon dioxide, Xanthan gum, Peppermint flavor, Banana Premium flavor and Sodium Methyl Paraben

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at a temperature below 25°C.

Protect from light. Store reconstituted suspension between 2°-8°C. The reconstituted suspension is stable for 7 days.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Cefpodoxime for Oral Suspension USP 40mg/5ml is available in 50ml / 100ml HDPE bottle packed in a carton along with measuring cup and package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

Sance Laboratories private Limited,
VI/51B, P.B No.2, Kozhuvanal, Pala,
Kottayam– 686573,
Kerala,
India

8. Marketing authorization number(s)

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text