SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ORELOX® 100 (tablets)

ORELOX® 200 (tablets)

ORELOX® JUNIOR (granules for oral suspension)

COMPOSITION:

ORELOX 100: Each film-coated tablet contains 130,45 mg of cefpodoxime proxetil equivalent to 100 mg of cefpodoxime.

Contains sugar (lactose monohydrate): 21,55 mg.

Excipients: Carboxymethylcellulose calcium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate.

Film-coating: Hydroxypropyl methyl-cellulose, talc, titanium dioxide.

ORELOX 200: Each film-coated tablet contains 260,90 mg of cefpodoxime proxetil equivalent to 200 mg of cefpodoxime.

Contains sugar (lactose monohydrate): 43,10 mg.

Excipients: Carboxymethylcellulose calcium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate.

Film-coating: Hydroxypropyl methyl-cellulose, talc, titanium dioxide.

ORELOX JUNIOR: Each 5 ml of suspension contains 52,18 mg of cefpodoxime proxetil equivalent to 40 mg of cefpodoxime.

Preservative: Potassium sorbate 0,17 %

Contains sugar: Lactose monohydrate 14,56 mg/5 ml;

Sucrose 601,33 mg/5 ml.

Contains aspartame: 20 mg/5 ml.

Excipients: Anhydrous colloidal silica, aspartame, banana flavour, carboxymethylcellulose calcium, carboxymethylcellulose sodium, citric acid monohydrate, hydroxypropylcellulose, iron oxide yellow, lactose monohydrate, monosodium glutamate, potassium sorbate, sodium chloride, sorbitan trioleate, sucrose, talc.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Cefpodoxime proxetil is a semisynthetic ß-lactam antibiotic belonging to the third generation oral cephalosporin group. Cefpodoxime proxetil is the prodrug of the bactericidal antibiotic cefpodoxime.

Cefpodoxime possesses *in vitro* bactericidal activity against a broad spectrum of Gram-positive and Gram-negative bacteria. *In vitro* sensitivity does not necessarily imply *in*

vivo efficacy. Therefore sensitivity tests must be performed. The mechanism of action is bactericidal through inhibition of bacterial cell wall biosynthesis enhanced by a high affinity for proteins at the cytoplasmic membrane.

The following organisms are not sensitive: Group D streptococci, Methicillin-resistant staphylococci (S. aureus and S. epidermidis), Staphylococcus saprophyticus, Corynebacteria, groups J and K, Listeria monocytogenes, Pseudomonas aeruginosa and Pseudomonas spp., Acinetobacter baumanii, Clostridium difficile, Bacteroides fragilis and related species.

Pharmacokinetic properties:

The bioavailability of cefpodoxime proxetil is increased when the product is administered with meals, or when there is a decrease in gastric pH. An increase in gastric pH results in decreased bioavailability.

Absorption:

After oral administration, cefpodoxime proxetil is absorbed in the gastrointestinal tract and rapidly hydrolysed by non-specific esterases in the gastrointestinal wall to cefpodoxime, the active acid.

Distribution:

In adults:

After oral administration of a single dose of 100 mg of cefpodoxime, the maximum plasma concentration (Cmax) obtained is 1 to 1,2 mg/l and after administration of a

dose of 200 mg of cefpodoxime, the maximum plasma concentration (Cmax) obtained is 2,2 to 2,5 mg/l. In both cases the time (Tmax) taken to reach the maximum concentration is 2 to 3 hours.

Following administration of 100 and 200 mg twice daily for 14,5 days, the pharmacokinetic parameters of cefpodoxime remain unchanged, indicating that there is no accumulation of the active principle.

The binding of cefpodoxime to plasma proteins is about 40 %. This binding is principally to albumin and is of the non-saturable type.

In children:

After oral administration of a single 5 mg/kg dose (200 mg maximum) of cefpodoxime to subjects between 4 and 12 years of age, the maximum plasma concentration (Cmax) is on average 2,6 mg/l. The time taken to reach the maximum concentration (Tmax) is 2 to 4 hours. The average plasma concentrations observed 8 and 12 hours after administration (residual) are 0,39 and 0,08 mg/l respectively.

Diffusion in fluids and tissues:

Cefpodoxime proxetil diffuses well in lung parenchyma, bronchial mucosa, pleural fluid and tonsils.

Metabolism and elimination:

The main metabolite is cefpodoxime, resulting from the hydrolysis of cefpodoxime proxetil.

The elimination half-life of cefpodoxime is 2,4 hours. 80 % of unchanged cefpodoxime is excreted in the urine.

INDICATIONS:

In adults:

Orelox 100 and Orelox 200 are indicated for use in the short-term treatment of upper and lower respiratory tract infections due to susceptible micro-organisms (sensitivity tests must be performed):

- Acute bronchitis due to: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis.*
- Pharyngitis and tonsillitis due to: *Streptococcus pyogenes.*
- Acute exacerbations of chronic bronchitis due to: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis.*
- Bacterial pneumonia and community-acquired bronchopneumonia due to: *Haemophilus influenza*, *Streptococcus pneumoniae*, *Moraxella catarrhalis.*
- Acute sinusitis due to: *Haemophilus influenzae* (non-typeable), *Streptococcus pneumoniae*, Methicillin-sensitive *Staphylococcus aureus*, *Moraxella catarrhalis.*

In children:

Orelox Junior is indicated for use in the short-term treatment of infections due to susceptible micro-organisms:

Upper and lower respiratory tract infections:

- Otitis media due to: *Haemophilus influenzae* (non-typeable), *Streptococcus pneumoniae*, *Moraxella catarrhalis.*
- Tonsillitis and pharyngitis due to: *Streptococcus pyogenes*.
- Pneumonia due to: *Haemophilus influenza*, *Streptococcus pneumoniae*, *Moraxella catarrhalis.*

CONTRAINDICATIONS:

- Known sensitivity to cephalosporin antibiotics (see WARNINGS and SPECIAL PRECAUTIONS).
- Safety of use in pregnancy and lactation has not been established.
- ORELOX JUNIOR must not be given to children with phenylketonuria, since the formulation contains aspartame (20 mg/5ml).
- Children below 1 year of age (see DOSAGE AND DIRECTIONS FOR USE).

WARNINGS and SPECIAL PRECAUTIONS:

Anaphylactic reactions:

Preliminary enquiry as to an allergic diathesis and particularly hypersensitivity of beta-lactam antibiotics should precede treatment with ORELOX.

The use of ORELOX is strictly contraindicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins.

ORELOX should be used with extreme caution in patients sensitive to penicillin and other ß-lactam antibiotics as cross-allergy may develop. Strict medical supervision is required throughout the treatment.

Hypersensitivity reactions (anaphylaxis) observed with ORELOX can be serious and occasionally fatal. Treatment should be stopped immediately, should an allergic reaction occur.

***Clostridium difficile* – associated disease:**

Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment with ORELOX, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. The diagnosis of this possibly fatal condition is confirmed by endoscopy and/or histology. Screening of faeces for this pathogen, and its cytotoxin is the best way to diagnose *Clostridium difficile* associated disease.

If a diagnosis of pseudomembranous colitis is suspected, ORELOX should be stopped immediately and appropriate specific therapy should be started without delay (e.g. vancomycin or metronidazole).

Clostridium difficile-associated disease can be favoured by faecal stasis.

Renal impairment:

Use with care in patients with renal impairment. Changes in renal function have been observed with antibiotics of the same class as ORELOX, particularly when given concurrently with potentially nephrotoxic agents such as aminoglycosides and/or potent diuretics. In such cases, renal function should be monitored.

Positive Coombs' test:

ORELOX may be absorbed onto the surface of red cell membranes and react with antibiotics directed against the medicine. This can produce a positive antiglobulin test and haemolytic anaemia. Cross-reactivity may occur with penicillin for this reaction.

Superinfection:

The use of ORELOX, 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 (see SIDE EFFECTS: Infections and Infestations).

Aspartame:

ORELOX JUNIOR must not be given to children with phenylketonuria, since the formulation contains aspartame (20 mg/5ml) (see CONTRAINDICATIONS).

Lactose/sucrose:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take ORELOX 100 or ORELOX 200, as the tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance, fructose intolerance e.g. galactosemia, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take ORELOX JUNIOR, as it contains lactose and sucrose.

Effects on the ability to drive and use machines:

Dizzy sensations may occur, which should be taken into account when driving a vehicle or operating machinery.

INTERACTIONS:

The bioavailability of ORELOX is increased if the product is administered during meals (acid pH).

Histamine H_2 antagonists (such as ranitidine) and antacids reduce the bioavailability of ORELOX.

Probenecid reduces the excretion of ORELOX. ORELOX potentially enhances the anticoagulant effect of warfarin and reduces the contraceptive effect of oestrogens.

Cases showing development of a positive Coombs' test have been reported (see WARNINGS and SPECIAL PRECAUTIONS).

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

PREGNANCY AND LACTATION:

Safety of ORELOX in pregnant women has not been established, it is therefore advisable not to administer ORELOX during pregnancy (see CONTRAINDICATIONS). Since ORELOX is excreted in human breast milk, either breastfeeding or treatment of the mother should be discontinued in mothers who are breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE:

In adults:

Each film-coated tablet contains 100 mg or 200 mg of cefpodoxime. The dosage depends on the condition being treated.

Tonsillitis, pharyngitis and acute bronchitis:

One ORELOX 100 tablet (100 mg) every 12 hours with meals (200 mg/day)

As is the case with all beta-lactam antibiotics in the treatment of beta-haemolytic streptococcal infections, a therapeutic dose has to be administered for at least 10 days.

Acute sinusitis, acute exacerbations of chronic bronchitis, pneumonia:

One ORELOX 200 tablet (200 mg) every 12 hours with meals (400 mg/day)

Elderly patients:

Where renal function is normal, it is not necessary to adjust the dose.

Hepatic insufficiency in adults and children:

No dosage adjustment necessary.

Renal insufficiency in adults and children:

When the creatinine clearance is above 40 ml/min, it is not necessary to adjust the dose. For values below 40 ml/min, the daily dosage regimen should be reduced by half and administered as a single daily dose for values 10 - 39 ml/min, every second day for values below 10 ml/min and after each dialysis session for haemodialysis patients.

In children:

Each 5 ml of suspension contains 40 mg of cefpodoxime.

Preservative: Potassium sorbate 0,17 %.

Contains aspartame 20 mg/5ml.

ORELOX JUNIOR must not be given to children with phenylketonuria, since the formulation contains aspartame (see CONTRAINDICATIONS).

The dosage depends on the weight of the child being treated. The average dose is 8 mg/kg/day administered in two doses at 12 hourly intervals with meals. Shake the bottle before use.

The following table may be used as a dosage guide:

Weight (kg)	**Dose**
Between 10 and 15 kg	5 ml (40 mg) every 12 hours
≥ 15 kg	10 ml (80 mg) every 12 hours

The use of ORELOX JUNIOR in children under one year of age is currently not indicated since insufficient clinical data is available at present (see CONTRAINDICATIONS).

Directions and reconstitution of the suspension:

Remove the screw-cap by simultaneously pushing and turning it. Remove the desiccant plug by pulling the tear-tab, and discard. The indented calibration mark represents the final volume. Half fill the bottle with water and shake vigorously (about 30 seconds). Fill up with water to the calibration mark and shake again to disperse all granules.
A total of 45 ml water is required to make up the 50 ml suspension and a total of 90 ml water is required to make up the 100 ml suspension.

SIDE EFFECTS:

The following side effects have been reported:

Blood and the lymphatic system disorders

Less frequent: reduction of haemoglobin, thrombocytosis, thrombocytopenia, leucopenia, haemolytic anaemia and eosinophilia. Neutropenia and agranulocytosis may occur during treatment with ORELOX.

Immune system disorders

less frequent: anaphylactic reactions: e.g. angioedema, bronchospasm, malaise, possibly culminating in shock may occur (see WARNINGS and SPECIAL PRECAUTIONS)

Nervous system disorders

less frequent: headache, dizzy sensations, paraesthesia

Ear and labyrinth disorders

less frequent: tinnitus

Gastrointestinal disorders

frequent: diarrhoea, nausea, vomiting, abdominal pains

less frequent: diarrhoea may sometimes be a symptom of enterocolitis, which may, in some cases, be accompanied by blood in stools. A particular form of enterocolitis than can occur with antibiotics is pseudomembranous colitis (in most cases due to *Clostridium difficile*) (see WARNINGS and SPECIAL PRECAUTIONS)

Hepato-biliary disorders

less frequent: increases in liver enzymes (AST, ALT and alkaline phosphatase), and/or bilirubin

These laboratory abnormalities exceed twice the upper limit of the normal range and elicit a pattern of drug induced hepatitis, usually cholestatic

Skin and subcutaneous tissue disorder

less frequent: cutaneous eruptions, rash, pruritus, urticaria and purpura. Cases of bullous eruptions (erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis) have been reported

Renal and urinary disorders

less frequent: **increase of blood urea and creatinine.**

Changes in renal function have been observed with antibiotics from the same group as ORELOX, particularly when co-prescribed with aminoglycosides and/or potent diuretics (see WARNINGS and SPECIAL PRECAUTIONS)

General disorders and administrative site conditions

less frequent: asthenia

Infections and Infestations

frequent: superinfections, overgrowth of non-susceptible organisms (see WARNINGS and SPECIAL PRECAUTIONS)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment should be symptomatic and supportive.

In cases of overdosage, particularly in patients with renal insufficiency, there is a risk of encephalopathy.

Convulsions have also been reported with very high doses especially in patients with renal impairment.

IDENTIFICATION:

ORELOX 100:

Biconvex, cylindrical practically white tablets, 9 mm in diameter with “208” and beneath “A” engraved on one side. A broken tablet shows a pale yellow core surrounded by a white film-coating.

ORELOX 200:

Biconvex, cylindrical, practically white tablets, 11 mm in diameter with “208” and beneath “C” engraved on one side. A broken tablet shows a pale yellow core surrounded by a white film-coating.

ORELOX JUNIOR:

Pale, yellow granules for reconstitution. The reconstituted suspension is pale yellow in colour and has a banana flavour and odour.

PRESENTATION:

ORELOX 100:

film-coated tablets are available in polyamide/aluminium/polyvinyl chloride/aluminium blister packs, inserted into an outer printed cardboard carton containing 10 tablets (1 strip x 10 tablets).

ORELOX 200:

film-coated tablets are available in polyamide/aluminium/polyvinyl chloride/aluminium blister packs, inserted into an outer printed cardboard carton containing 10 tablets (1 strip x 10 tablets) or 20 tablets (2 strips x 10 tablets).

ORELOX JUNIOR:

is packed into a 75 ml or 150 ml type lll amber glass bottle, fitted with a dehydrating capsule. The closure is a child-proof white opaque plastic screw-cap fitted with a white polyethylene joint and a pilfer proof ring.

The bottle is inserted into an outer printed cardboard carton.

The 75 ml or 150 ml bottles contain granules for reconstitution up to 50 ml or 100 ml of suspension, respectively.

STORAGE INSTRUCTIONS:

ORELOX 100 and ORELOX 200:

Store in a cool, dry place, at or below 25 °C.

Protect from light and humidity.

Keep blister pack in carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

ORELOX JUNIOR:

Before reconstitution: Store in a cool, dry place at or below 25 °C. Protect from light and humidity.

After reconstitution: Use within 10 days. Store in a refrigerator (+2 to +8 °C). Shake before use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ORELOX 100: Z/20.1.1/7

ORELOX 200: A38/20.1.1/0406

ORELOX JUNIOR: 27/20.1.1/0564

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd.

2 Bond Street

Midrand, 1685

South Africa.

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date on the registration certificates (original registration):

ORELOX 100: 9 September 1991

ORELOX 200: 12 June 2009

ORELOX JUNIOR: 10 November 1993

Date of the most recently revised package insert as approved by Council:

To be allocated by council.

NAMIBIA

Scheduling status: NS2

Registration numbers:

ORELOX 100: 04/20.1.1/0379

ORELOX 200: 13/20.1.1/0080

ORELOX JUNIOR: 04/20.1.1/0380

BOTSWANA

Scheduling status: S2

Registration numbers:

ORELOX 100: BOT0700482

ORELOX JUNIOR: BOT0700931