ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Orelox® 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefpodoxime proxetil .....130.45 mg

Equivalent amount of cefpodoxime .....100.00 mg

For one film-coated tablet.

Excipient with known effect: Lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The therapeutic indications of cefpodoxime are based on its antibacterial activity and pharmacokinetic properties.

In adults, they are limited to the treatment of infections due to susceptible bacteria, in particular:

- Documented group A beta-hemolytic streptococcal sore throat.
- Acute sinusitis.
- Acute bronchial suppuration in at-risk patients (particularly alcoholics, smokers, patients over 65 years of age, etc.).
- Exacerbation of chronic obstructive pulmonary disease, particularly in repeat episodes or in at-risk patients.
- Bacterial lung diseases, particularly in at-risk patients.

Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Adults

200 mg or 400 mg to be taken as 2 divided doses, 12 hours apart during meals, i.e.:

- 2 x 200 mg per day, i.e. 2 tablets morning and evening in:
  - acute sinusitis,

In acute maxillary sinusitis, a 5-day treatment has been shown to be effective.

  - acute bronchial suppuration in at-risk patients,
  - exacerbation of chronic obstructive pulmonary disease, particularly in repeat episodes or in at-risk patients,
  - bacterial lung diseases, particularly in at-risk patients,

- 2 x 100 mg per day, i.e. 1 tablet morning and evening in sore throat.

The duration of treatment for sore throat is 5 days.

Elderly

No dose adjustment is required if the elderly subject has normal renal function.

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Patients with kidney failure

No dose adjustment is required if creatinine clearance is over 40 ml/min.

If creatinine clearance is below 40 ml/min, the daily dose should be halved and limited to one single daily dose.

Patients with liver failure

No dose adjustment is required in patients with liver failure.

4.3. Contraindications

- Known allergy to cephalosporin antibiotics.

4.4. Special warnings and precautions for use

Special warnings

- Treatment must be discontinued if any signs of allergy occur.
- Before prescribing cephalosporins, patient history should be investigated, due to the 5-10% occurrence of cross-allergy between penicillins and cephalosporins.
  - Extreme caution should be exercised when administering cephalosporins in penicillin-sensitive patients: strict medical monitoring is necessary as of the first dose.
  - Use of cephalosporins is absolutely contraindicated in patients with a history of immediate allergy to cephalosporins. If in doubt, the physician must absolutely remain with the patient during administration of the first dose, in order to treat any potential anaphylactic events.
- Hypersensitivity reactions (anaphylaxis) observed with these two types of beta-lactam antibiotics can be serious and occasionally fatal.
- The occurrence of an episode of diarrhea may, in exceptional cases, be symptomatic of pseudomembranous colitis, diagnosis of which is based on colonoscopy.
  Although rare with cephalosporins, if this event occurs, treatment must be discontinued immediately and appropriate specific antibiotic therapy (vancomycin) instituted. In this case, administration of drugs promoting fecal stasis must be absolutely avoided.
- This medicinal product contains lactose, and is therefore contraindicated in patients with congenital galactosemia, glucose and galactose malabsorption syndrome or lactase deficiency.
- Beta-lactam antibiotics, including cefpodoxime, predispose patients to encephalopathy (which can include seizure, confusion, consciousness disorders or abnormal movements), particularly if they have had an overdose or if they have impaired renal function.

Precautions for use

- In patients who are allergic to other beta-lactam antibiotics, the possibility of cross-allergy should be taken into account.
- In patients with severe renal failure, it may be necessary to adjust the daily dose based on creatinine clearance (see “At-risk patients” and section 4.2).
- As with other broad-spectrum antibiotics, long-term use of cefpodoxime proxetil may result in overgrowth of non-susceptible organisms, which may require treatment discontinuation.
- *Interactions with laboratory tests*
  Positive Coombs tests have been reported during treatment with cephalosporins.
  A false positive reaction for glucose in the urine may occur with reducing substances, but not when glucose oxidase methods are used.

4.5. Interaction with other medicinal products and other forms of interaction

- Food:

A study has shown that regardless of the type of food, the bioavailability of cefpodoxime increases when the medicinal product is administered during meals.

- Gastric pH changes:

Increased gastric pH: H2 antagonists (ranitidine) and antacids (aluminum hydroxide, sodium bicarbonate) lead to reduced bioavailability.

Conversely, reduced gastric pH (pentagastrin) induces an increase in bioavailability.

The clinical implications of these effects have yet to be determined.

Special INR imbalance issues

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotics. The severity of the infection or inflammation, age and general health status of the patient appear to be risk factors. Under these circumstances, it seems difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly fluoroquinolones, macrolides, cyclines, cotrimoxazole and certain cephalosporins.

4.6. Fertility, pregnancy and lactation

Pregnancy

Due to the expected benefit, use of cefpodoxime can be considered during pregnancy if necessary, despite insufficient data in animals and man.

Breast-feeding

Excretion in breast milk is low, and the amounts ingested by the infant are far lower than therapeutic doses. Consequently, breast-feeding is possible during use of the antibiotic.

However, breast-feeding (or the medicinal product) should be discontinued if diarrhea, candidiasis or skin eruption occurs in the infant.

4.7. Effects on ability to drive and use machines

If adverse effects occur, such as dizziness or encephalopathy (which can include seizure, confusion, consciousness disorders or abnormal movements), (see sections 4.4, 4.8, 4.9), patients should not drive or use machines.

4.8. Undesirable effects

Adverse effects are mainly gastrointestinal disorders:

- diarrhea,
- nausea, vomiting,
- abdominal pain.

There have also been rare cases of the following:

- Gastrointestinal effects: as with other broad-spectrum antibiotics, rare cases of enterocolitis with bloody diarrhea have been reported, as well as rare cases of pseudomembranous colitis.
- Hepatobiliary effects: moderate and transient elevation in ASAT and ALAT transaminase and alkaline phosphatase levels.
- Allergic effects: skin eruptions, pruritus, urticaria, angioedema, anaphylactic shock.
- Cutaneous effects: various types of eruption, localized bullous eruption, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
- Headache.
- Dizziness.
- Beta-lactam antibiotics, including cefpodoxime, predispose patients to encephalopathy (which can include seizure, confusion, consciousness disorders or abnormal movements), particularly if they have had an overdose or if they have impaired renal function.
- Renal effects: mild increase in blood urea and creatinine concentrations.
- Hematological effects: thrombocytosis, thrombocytopenia, leukopenia and hypereosinophilia and, in exceptional cases, agranulocytosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 the French national reporting system, i.e. Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) under "Réseau des Centres Régionaux de Pharmacovigilance" (Network of Regional Pharmacovigilance Centers) - Website: www.ansm.sante.fr.

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4.9. Overdose

Beta-lactam antibiotics, including cefpodoxime, predispose patients to encephalopathy, particularly if they have had an overdose or if they have impaired renal function.

5. PHARMACOLOGICAL PROPRIETES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01DA33.

(J: Anti-infectives)

Cefpodoxime proxetil is a semi-synthetic beta-lactam antibiotic, belonging to the class of 3rd generation oral cephalosporins. It is the prodrug of cefpodoxime.

Orally-administered cefpodoxime proxetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by non-specific esterases into cefpodoxime, a bactericidal antibiotic.

The mechanism of action of cefpodoxime is based on the inhibition of bacterial cell wall synthesis. It is stable in the presence of numerous beta-lactamase enzymes.

SPECTRUM OF ANTIBACTERIAL ACTIVITY

The breakpoints differentiating susceptible strains from intermediate strains, and the latter from resistant strains are as follows:

S f [3] 1 mg/l and R > 2 mg/l.

The prevalence of acquired resistance in certain species can vary geographically and over time. It is therefore useful to have information on the prevalence of local resistance, especially when treating severe infections. These data are only guidelines indicating the probability of susceptibility of a bacterial strain to this antibiotic.

Data on the variability of the prevalence of resistance of a given bacterial species in France are indicated in the table below when available:

[3] Translator's note : Should probably read ≤

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Category	Prevalence of acquired resistance in France (> 10 %) (range)
SUSCEPTIBLE SPECIES	
Gram-positive aerobes	
Corynebacterium diphtheriae	
Streptococcus	
Streptococcus pneumoniae	20 - 60 %
Gram-negative aerobes	
Branhamella catarrhalis	
Citrobacter koseri	
Escherichia coli	
Haemophilus influenza	
Klebsiella	0 - 30 %
Neisseria gonorrhoeae	
Pasteurella	
Proteus mirabilis	
Proteus vulgaris	29 - 38 %
Providencia	
Anaerobes	
Fusobacterium	10 - 20 %
Prevotella	30 - 70 %
Propionibacterium acnes	
INTERMEDIATE SPECIES (intermediate susceptibility *in vitro*)	
Gram-positive aerobes Methicillin-susceptible *staphylococcus*	
RESISTANT SPECIES	
Gram-positive aerobes	
Enterococci	
Listeria monocytogenes	
Methicillin-resistant *staphylococcus* *	
Gram-negative aerobes	
Acinetobacter	
Citrobacter freundii	
Enterobacter	
Morganella morganii	
Pseudomonas	
Serratia	
Anaerobes	
Bacteroides fragilis	
Clostridium	
Peptostreptococcus	

* The prevalence of methicillin resistance is approximately 30% to 50% for all staphylococci, and is mainly found in a hospital setting

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5.2. Pharmacokinetic properties

Absorption

In a tablet containing 100 mg of cefpodoxime proxetil, 40 % to 50 % of its active ingredient, cefpodoxime, is absorbed when administered orally to a fasting patient.

As absorption of the medicinal product is increased when taken with food, it should preferably be taken during meals.

Distribution

- Plasma concentrations:
  - Following oral administration of a single dose of 100 mg, peak plasma concentrations of cefpodoxime (Cmax) are 1 mg/l to 1.2 mg/l. After administration of a 200 mg dose, peak plasma concentrations are 2.2 mg/l to 2.5 mg/l. In both cases (100 mg or 200 mg), they are reached (Tmax) within 2 to 3 hours. Residual concentrations after 12 hours are 0.08 mg/l after administration of 100 mg and 0.18 mg/l after administration of 200 mg.
  - After administration of 100 mg and 200 mg, twice daily for 14.5 days, the plasma pharmacokinetic parameters of cefpodoxime remain unchanged, showing that there is no accumulation of the active substance.
- The volume of distribution of cefpodoxime is 30-35 l in young healthy patients (= 0.43 l/kg).
- Plasma protein binding

Cefpodoxime is approximately 40% bound to plasma proteins, primarily to albumin. This binding is non saturable.

- Humoral and tissue distribution
  - Cefpodoxime is well distributed in the lung parenchyma, bronchial mucosa, pleural fluid, tonsils and interstitial fluid.
  - 4 to 7 hours after a single 100 mg dose, concentrations in the tonsils are 0.24 to 0.1 µg/g (20% to 25% of plasma concentrations).
  - After a single 200 mg dose, cefpodoxime concentrations in the interstitial fluid are 1.5 mg/l to 2.0 mg/l (80% of plasma concentrations).
  - 3 to 12 hours after a single 200 mg dose, cefpodoxime concentrations are 0.6 to 0.2 µg/g in the lung, and 0.6 mg/l to 0.8 mg/l in the pleura.
  - In the bronchial mucosa, between 1 and 4 hours after administration of 200 mg, cefpodoxime concentrations are about 1 µg/g (40% to 45% of plasma concentrations).
  - The concentrations measured are higher than the MICs of susceptible microorganisms.

Metabolism and elimination

- Following absorption of the medicinal product, the main metabolite is cefpodoxime, resulting from hydrolysis of cefpodoxime proxetil.
- Cefpodoxime is poorly metabolized.
- Following absorption of cefpodoxime proxetil, 80% of the cefpodoxime released is excreted unchanged in the urine.
- The mean elimination half-life of cefpodoxime is 2.4 hours.

At-risk patients

- The pharmacokinetic pattern of cefpodoxime is very slightly changed in elderly patients with normal renal function.

However, the minor increase in peak plasma concentrations and elimination half-life does not call for a dose reduction in this population, except in patients with a renal clearance of less than 40 ml/min.

- In patients with renal failure in whom creatinine clearance is less than 40 ml/min, the increase in plasma elimination half-life and peak plasma concentrations makes it necessary to reduce the dose by half and administer it as a single daily dose.
- In patients with liver failure, the minor pharmacokinetic changes observed do not warrant any specific dose adjustment.

5.3. Preclinical safety data

Not applicable.

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6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate, carmellose calcium, hydroxypropylcellulose, sodium lauryl sulfate, lactose, titanium dioxide, talc, hypromellose.

6.2. Incompatibilities

No incompatibilities were observed during clinical studies.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at room temperature.

6.5. Nature and contents of container

10 tablets in (Polyamide/Aluminum/PVC) blisters.

6.6. Special precautions for disposal and other handling

No particular requirements.

7. MARKETING AUTHORIZATION HOLDER

sanofi-aventis France
82, avenue Raspail
94250 Gentilly, France

8. MARKETING AUTHORIZATION NUMBERS

- 34009 333 142 4 8: 10 tablets in (Polyamide/Aluminum/PVC) blisters.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: August 2, 1990.

Date of latest renewal: August 2, 2010.

10. DATE OF REVISION OF THE TEXT

[To be completed by the Marketing Authorization Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.

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