SUMMARY OF PRODUCT CHARACTERISTICS

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.

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

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergy to cephalosporins.

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 galactose intolerance, Lapp lactase deficiency or glucose and galactose malabsorption syndrome (rare hereditary disorders).
- Blood disorders
- As with other beta-lactam antibiotics, neutropenia and, more rarely, agranulocytosis may develop during treatment with cefpodoxime, particularly if given over long periods, in which case blood monitoring should be considered.
- Bullous eruptions
- As with other cephalosporins, cases of bullous eruptions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported. If any skin and/or mucosal disorder occur, patients should contact their doctor immediately and prior to continuing treatment.
- 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.
- Encephalopathy
- Beta-lactams, including cefpodoxime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.

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

Frequencies have been defined as follows: very common (≥ 10%); common (≥ 1% to < 10%); uncommon (≥ 0.1% to < 1%); rare (≥0.01% to < 0.1%); very rare (<0.01%), frequency not known (cannot be estimated from the available data).

- **Blood and lymphatic system disorders**

Uncommon: neutropenia
Rare: thrombocytosis, leucopenia
Not known: agranulocytosis, eosinophilia, thrombocytopenia, hemolytic anemia

- **Ear and labyrinth disorders**

Common: tinnitus

- **Gastrointestinal disorders**

Very common: abdominal pain, diarrhea
Common: nausea, vomiting
Uncommon: enterocolitis
Not known: Hematochezia, pseudomembranous colitis, *clostridium difficile* colitis

- **General disorders and administration site conditions**

Not known: malaise, asthenia

- **Hepatobiliary disorders**

Common: aspartate aminotransferase (ASAT) increased, alanine aminotransferase (ALAT) increased, blood alkaline phosphatase (PAL increased)
Not known: blood bilirubin increased, liver injury, cholestatic liver injury

- **Immune system disorders**

Uncommon: anaphylactic reactions, bronchospasm
Not known: anaphylactic shock, angioedema

- **Infections and infestations**

Not known: superinfection

- **Nervous system disorders**

Very common: headache
Common: dizziness
Not known: paresthesia

Beta-lactams, including cefpodoxime proxetil, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness or movement disorders), particularly in case of overdose or renal impairment.

- **Skin and subcutaneous tissue disorders**

Common: rash, pruritus, urticaria
Not known: purpura, dermatitis bullous, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

- **Renal and urinary disorders**

Rare: slight increase in blood urea and creatinine
Not known: renal function disorders have been observed with antibiotics from the same group as cefpodoxime, particularly when co-prescribed with aminoglycosides and/or potent diuretics.

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.

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.

(Third-generation cephalosporins)

Cefpodoxime proxetil is a semi-synthetic beta-lactam antibiotic, belonging to the class of third-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:

$S \leq 1$ 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:

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

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 microgram/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 microgram/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 microgram/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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core: magnesium stearate, carmellose calcium, hydroxypropylcellulose, sodium lauryl sulfate, lactose

Film coating: 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

[to be filled out subsequently by the Marketing Authorization Holder]

10. DATE OF REVISION OF THE TEXT

[To be filled out subsequently by the Marketing Authorization Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.

Annex II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

A.1. Name and address of the manufacturer(s) of the biological active substance(s)

Not applicable.

A.2. Name and address of the manufacturer(s) responsible for batch release

Sanofi Winthrop Industrie
56 route de Choisy-au-Bac
60205 Compiègne, France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

List I.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

Not applicable.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORIZATION UNDER EXCEPTIONAL CIRCUMSTANCES

Not applicable.

F. QUALITATIVE AND QUANTITATIVE COMPOSITION IN EXCIPIENTS

Magnesium stearate .....2.87 mg

Carmellose calcium .....60.00 mg

Hydroxypropylcellulose.....5.00 mg

Sodium lauryl sulfate .....0.13 mg

Lactose .....21.55 mg

For one 220.00 mg core.

Titanium dioxide ..... 1.40 mg

Talc ..... 1.40 mg

Hypromellose ..... 7.20 mg

For one 230.30 mg film-coated tablet.

ANNEX IIIA

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER PACKAGING OR IMMEDIATE PACKAGING

Outer packaging.

1. NAME OF THE MEDICINAL PRODUCT

Orelox 100 mg film-coated tablets

Cefpodoxime proxetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Cefpodoxime proxetil .....130.45 mg

Equivalent amount of cefpodoxime .....100.00 mg

For one film-coated tablet.

3. LIST OF EXCIPIENTS

Excipient with known effect: lactose

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet.

Box of 10.

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

This medicine must be stored at room temperature.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder

Sanofi Aventis France
82 Avenue Raspail
94250 Gentilly
France

Operator

Sanofi Aventis France
82, avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORIZATION NUMBER(S)

Marketing Authorization No.:

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

List I.

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

Comply with the decision of May 7, 2008 applying Article R. 5121-138 of the French Public Health Code published in the JO (French Official Journal) of May 22, 2008.

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [CIP code]

SN: {number} [serial number]

PICTOGRAM TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Pictogram relative to teratogenic or fetotoxic effects

If applicable, the pictogram mentioned under III of Article R. 5121-139 of the French Public Health Code (teratogenic or fetotoxic effects) must appear, in accordance with the application order stipulated in the same article.

Pictogram relative to effects on the ability to drive

The pictogram mentioned under II of Article R. 5121-139 of the French Public Health Code (effects on ability to drive) must be in accordance with the application order stipulated in the same article.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

NATURE/TYPE BLISTERS / STRIPS

Blisters.

1. NAME OF THE MEDICINAL PRODUCT

Orelox 100 mg film-coated tablets

Cefpodoxime proxetil

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

Sanofi Aventis France

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. OTHER

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SMALL IMMEDIATE PACKAGING UNITS

Not applicable.

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Not applicable.

2. METHOD OF ADMINISTRATION

Not applicable.

3. EXPIRY DATE

Not applicable.

4. BATCH NUMBER

Not applicable.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Not applicable.

6. OTHER

Not applicable.