# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Cefixime 200 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 223.81 mg Cefixime trihydrate equivalent to 200 mg Cefixime (anhydrous)

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

White, circular, biconvex film-coated tablets debossed with 'C' on one side and plain surface on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms (see sections 4.4 and 5.1):

Acute exacerbations of chronic bronchitis
Community-acquired Pneumonia
Lower urinary tract infections
Pyelonephritis

In the treatment of:
Otitis media
Sinusitis
Pharyngitis

The use of cefixime should be reserved for infections in which the causative organism is known or suspected to be resistant to other commonly used antibacterial agents or when treatment failure with other commonly used antibacterial agents may carry significant risk.

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

## 4.2 Posology and method of administration

*Adults*
The recommended dose for adults is 200-400 mg daily according to the severity of infection,taken as a single dose (400 mg may also be taken as two divided doses) (see section 5.1).

*Elderly patients*
Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment (See above and section 4.4).

*Adolescents ≥ 12 years of age*
Adolescents ≥ 12 years of agemay be given the same dose as recommended for adults.

*Children from 6 months to 11 years of age*
It is recommended that children from 6 months to 11 years of age be given cefixime as an oral suspension because 200 mg cannot be adequately dosed for this age group. The recommended dosage for children in this age group is 8 mg / kg body weight / day administered as a single dose or in two divided doses.

*Children less than 6 months of age*
The safety and efficacy of cefixime has not been established in children less than 6 months of age.

*Renal insufficiency*
Cefixime may be administered in the presence of impaired renal function in adult patients. Normal dose and schedule may be given in adult patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency: the use of cefixime in these patient-groups is not recommended.

**Method of administration**
Cefixime tablets are for oral administration only. Cefixime tablets should be taken with a sufficient amount of water. Cefixime may be taken with or without food (see section 5.2).

**Duration of treatment**
The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

## 4.3 Contraindications

Hypersensitivity to cefixime, other cephalosporin antibiotics or to any of the excipients.

Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

## 4.4 Special warnings and precautions for use

Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins.

Patients have had severe reactions (including anaphylaxis) to both classes of drugs. Special care is indicated in patients who have experienced any allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If severe hypersensitivity reactions or anaphylactic reactions occur after administration of cefixime, the use of cefixime should be discontinued immediately and appropriate emergency measures should be initiated.

*Renal insufficiency*
Cefixime should be administered with caution in adult patients with creatinine clearance < 20 ml / min (see sections 4.2 and 5.2). There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency: the use of cefixime in these patient-groups is not recommended.

Prolonged use of cefixime may result in the overgrowth of non-susceptible organisms.

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins including cefixime); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics.

In patients who develop severe diarrhoea during or after use of cefixime, the risk of life threatening pseudo-membranous colitis should be taken into account (see section 4.8). The use of cefixime should be discontinued and appropriate treatment measures should be established. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded. The use of medicinal products inhibiting the intestinal peristalsis is contra-indicated.

## 4.5 Interaction with other medicinal products and other forms of interactions

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.

A false positive direct Coombs' test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs' test may be due to the drug.

In common with other cephalosporins, increases in prothrombin time have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy:*
For cefixime, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Cefixime should not be used in pregnant mothers unless considered essential by the physician.

*Lactation:*
It is unknown whether cefixime is excreted in human breast milk. Animal studies have shown excretion of cefixime in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with cefixime should be made taking into account the benefit of breast-feeding to the child and the benefit of cefixime therapy to the woman. However, until further clinical experience is available, cefixime should not be prescribed to breast-feeding mothers.

## 4.7 Effects on ability to drive and use machines

Cefixime has no known influence on the ability to drive and use machines. However, side effects may occur (See also section 4.8), which may influence the ability to drive and use machines.

## 4.8 Undesirable effects

In this section, the following convention has been used for the classification of undesirable effects in terms of frequency:

Common: ≥1/100 to <1/10,
Uncommon: ≥1/1,000 to <1/100,
Rare: ≥1/10,000 to <1/1,000 and
Very rare: <1/10,000

| **MedDRA System Organ Class** | **Adverse Drug Reaction** | **Frequency** |
|---|---|---|
| Infections and infestations | Superinfection bacterial, superinfection fungal | Rare |
| | Antibiotic-associated colitis (see section 4.4) | Very rare |
| Blood and lymphatic system disorders | Eosinophilia | Rare |
| | Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia | Very rare |
| Immune system disorders | Hypersensitivity | Rare |
| | Anaphylactic shock, serum sickness | Very rare |
| Metabolism and nutrition disorders | Anorexia | Rare |
| Nervous system disorders | Headache | Uncommon |
| | Vertigo | Rare |
| | Psychomotor hyperactivity | Very rare |
| Gastrointestinal disorders | Diarrhoea | Common |
| | Abdominal pain, nausea, vomiting | Uncommon |
| | Flatulence | Rare |
| Hepatobiliary disorders | Hepatitis, cholestatic jaundice | Very rare |
| Skin and subcutaneous tissue disorders | Rash | Uncommon |
| | Angioneurotic oedema, pruritus | Rare |
| | Stevens-Johnson syndrome, toxic epidermal necrolysis | Very rare |

| | | |
|---|---|---|
| Renal and urinary disorders | Interstitial nephritis | Very rare |
| General disorders and administration site conditions | Mucosal inflammation, pyrexia | Rare |
| Investigations | Hepatic enzyme increased (transaminase, alkaline phosphatase) | Uncommon |
| | Blood urea increased | Rare |
| | Blood creatinine increased | Very rare |

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

### 4.9 Overdose

There is no experience with overdoses with cefixime.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J01DD08

Mode of Action
Cefixime is an antibacterial agent of the cephalosporin class. Like other cephalosporins, cefixime exerts antibacterial activity by binding to and inhibiting the action of penicillin-binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

PK/PD relationship
The time that the plasma concentration of cefixime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in PK/PD studies.

Mechanisms of resistance
Bacterial resistance to cefixime may be due to one or more of the following mechanisms:

- Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or de-repressed in certain aerobic gram-negative bacterial species
- Reduced affinity of penicillin-binding proteins
- Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins
- Drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and / or antibacterial drugs of other classes.

Breakpoints

Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (May 2009) for cefixime are:

- *H.influenzae*: sensitive ≤ 0.12 mg/L, resistant > 0.12 mg/L
- *M.catarrhalis*: sensitive ≤ 0.5 mg/L, resistant > 1.0 mg/L
- *Neisseria gonorrhoeae*: sensitive ≤ 0.12 mg/L, resistant > 0.12 mg/L
- *Enterobacteriaceae*: sensitive ≤ 1.0 mg/L, resistant > 1.0 mg/L (for uncomplicated urinary tract infections only). The breakpoints for Enterobacteriaceae will detect reduced susceptibility mediated by most clinically important beta-lactamases in Enterobacteriaceae. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production.
- Non-species related breakpoints: insufficient data.

**Susceptibility**

The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

| **Commonly susceptible species** |
|---|
| **Aerobes, Gram positive:**<br>*Streptococcus pneumoniae* (Penicillin-susceptible)<br>*Streptococcus pyogenes* |
| **Aerobes, Gram negative:** |

| |
|---|
| *Escherichia coli* [%]<br>*Haemophilus influenzae*<br>*Klebsiella* species [%]<br>*Moraxella catarrhalis*<br>*Proteus mirabilis*[%] |
| **Species for which resistance may be a problem** |
| *Enterobacter* species |
| **Resistant species** |
| *Clostridium difficile*<br>*Bacteroides fragilis*<br>*Enterococci*<br>*Pseudomonas* species<br>*Staphylococcus aureus*[+]<br>*Streptococcus pneumoniae*(Penicillin resistant) |

[%] Extended spectrum beta-lactamase (ESBL) producing isolates are always resistant
[+]Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin)

**5.2 Pharmacokinetic properties**

*Absorption:*
The absolute oral bioavailability of cefixime is in the range of 22-54%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

*Distribution:*
Serum protein binding is well characterized for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations which are not seen following clinical dosing.

From *in vitro* studies, serum or urine concentrations of 1 mg/L or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.

*Metabolism and elimination:*

Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.

Transfer of $^{14}C$-labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5% of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placental transfer of cefixime was small in pregnant rats dosed with labeled cefixime.

*Special age groups:*
The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean $C_{max}$ and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population (see section 4.2).

## 5.3 Preclinical safety data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, *invivo* and *invitro* studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted.

Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death, which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Calcium Hydrogen Phosphate, Anhydrous
Starch, Pregelatinised
Cellulose, Microcrystalline
Silica, Colloidal Anhydrous
Magnesium stearate
Opadry White Y-1-7000

Opadry White Y-1-7000 contains:
Hypromellose (E 464)
Macrogol 400 (E 1520)

Titanium Dioxide (E 171)

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Do not store above 25$^{o}$C
Keep blister in the outer carton.

**6.5 Nature and contents of container**

The product is packed in:

PVC/ PVdC/ Al blister pack: 6s, 7s, 10s - One blister packed in a carton along with a PIL.
12s, 14s, 20s - Two blisters packed in a carton along with a PIL.
30s - Three blisters packed in a carton along with a PIL
40s - Four blisters packed in a carton along with a PIL
100s - Ten blisters packed in a carton along with a PIL

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

Orchid Europe Limited
Building 3
Chiswick Park
566 Chiswick High Road
Chiswick
London
W4 5YA
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA1335/002/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th October 2010
Date of last renewal: 21st November 2014

## 10 DATE OF REVISION OF THE TEXT

November 2018