Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Suprax 200 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Cefixime Trihydrate equivalent to cefixime 200 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Off-white to cream, circular, convex, embossed 'ORO' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in the treatment of infections due to micro-organisms sensitive to the antibiotic including pathogens such as *Streptococci pneumoniae* and *pyogenes*, *E.coli*, Proteus, *H. influenza* and *B. catarrhalis* (both beta lactamase positive and negative), Klebsiella and Enterobacter species.

Most Enterococci, Staphylococci, Pseudomonas, Clostridia, *Bacteroides fragilis* and *Listeria monoyctogenes* are resistant to Cefixime.

4.2 Posology and method of administration

Route of administration is oral.

Adults and children of 12 years and over (or more than 50kg body weight):
The usual daily dose is 200-400mg in single or twice daily dosage regimen.
In uncomplicated upper respiratory tract infections or urinary tract infections a daily dose of 200 mg may be sufficient.

Children aged 9 to 12 years:
The usual total daily dose is 300mg (15ml of oral suspension) in single or twice daily regimen.

Children aged 5 to 8 years:
The usual total daily dose is 200 mg (10ml of oral suspension) in single or twice daily dosage regimen.

Children aged 2 to 4 years:
The usual total daily dose is 100 mg (5ml of oral suspension) in single or twice daily dosage regimen.

Children aged 6 months to 2 years:
The usual total daily dose in 8 mg/kg in single or twice daily regimen.

The safety and efficacy of use in infants less than 6 months of age has not been established.

Elderly:
The usual dosage is as for adults with appropriate modifications on the basis of renal impairment.

Patients with Renal Impairment
Dosage does not require modification in patients with a creatinine clearance of 20 ml/minute or greater.

In patients with a creatinine clearance less than 20 ml/minute a dose of 200 mg once daily should not be exceeded. The same dosage regimen is applied to those patients maintained on chronic ambulatory peritoneal dialysis or haemodialysis.

4.3 Contraindications

Cefixime is contraindicated in patients with:
- Hypersensitivity to cefixime or to any of the excipients listed in section 6.1
- Hypersensitivity to any cephalosporin antibacterial agent;
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible (see sections 4.3 and 4.8). If a severe allergic reaction occurs during treatment with cefixime, the medicinal product should be discontinued and appropriate measures taken.

Cefixime is contraindicated in patients with a history of hypersensitivity to any cephalosporin and in patients with severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems) (see section 4.3).

Cefixime should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or other beta-lactam antibacterial agents.

Super-infection:
Prolonged use of an anti-infective may result in overgrowth of non susceptible organisms.

Clostridium difficile associated diarrhoea and colitis
Use of cefixime has been associated with development of Clostridium difficile-associated diarrhoea (CDAD) and pseudomembranous colitis (PMC), during or in the weeks following completion of treatment. If CDAD or PMC occurs or is suspected, Suprax should be stopped immediately and appropriate management should be instituted.

Severe cutaneous adverse reactions (SCARs)
Serious skin reactions including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with cefixime treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of skin hypersensitivity.

Antibiotic resistance
Emergence of resistance to cefixime has not to date been shown to be clinically significant. Nevertheless it is recommended that newer antibiotics such as cefixime should usually be reserved for infections which are recurrent or resistant to other agents.

Vomiting and diarrhoea
Particular care should be exercised in patients with severe gastrointestinal disturbances involving vomiting and diarrhoea. The product should be discontinued if severe diarrhoea develops.

Acute renal failure
Cefixime may cause acute renal failure including tubulointerstitial nephritis. If acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Use with other nephrotoxic medicinal products
Suprax should be used with caution in patients concomitantly receiving other potentially nephrotoxic medicinal products (e.g. aminoglycosides, polymyxin B, colistin or high-dosed loop diuretics). Renal function should be carefully monitored during co-administration especially in patients with pre-existing renal impairment.

Patients requiring additional care
Particular care should be exercised in patients with poor oral nutrition, patients receiving parenteral nutrition, elderly patients or patients in a debilitated state.

Particular care should be exercised in patients with a personal or familial predisposition to allergic reaction such as bronchial asthma, rash or urticaria.

Adverse reactions to drugs are liable to occur more frequently in the elderly patients since they usually have physiological hypofunction. Bleeding tendency due to Vitamin K deficiency may occur in the elderly.

The safety of cefixime in premature or newborn infant has not been established.

Haemolytic anaemia
Drug-induced haemolytic anaemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of haemolytic anaemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated haemolytic anaemia has also been reported.

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

4.5 Interaction with other medicinal products and other forms of interaction

Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin potassium. Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

Other forms of interaction
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 may occur during use of cefixime.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no well-controlled studies with Suprax in pregnant women.
Therefore, Suprax should be used in pregnant women or in women of childbearing potential only if the potential benefit justifies the potential risk to the fetus.

Breast Feeding:
It is not known whether cefixime is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Suprax therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
Nevertheless, breast-feeding (or the medicinal product) should be stopped and ***consult the physician immediately*** in the case of an occurrence of diarrhoea, candidiasis, or rash in the infant.

4.7 Effects on ability to drive and use machines

In the case of side effects such as encephalopathy (which may include convulsions, confusion, impairment of consciousness, movement disorders), the patient should not operate machines or drive a vehicle.

4.8 Undesirable effects

The adverse reactions listed in Table 1 have been observed during clinical studies and/or during marketed use.

System Organ Class	Preferred Term	Frequency
Infections and infestations:	Pseudomembranous colitis Vaginitis	not known
Blood and lymphatic system class:	Eosinophilia, Agranulocytosis, Leucopenia, Neutropenia, Granulocytopenia, Haemolytic anaemia, Thrombocytopenia, Thrombocytosis, Prolonged PT /Coagulation	not known
Immune System Disorders:	Anaphlactic reaction, Angio-oedema, Serum sickness-like reaction	not known
Nervous System Disorders:	Dizziness, Headache Cases of convulsions have been reported with cephalosporins including cefixime. Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.	not known
Respiratory, thoracic and mediastinal disorders:	Dyspnoea	not known
Gastrointestinal disorders:	Abdominal pain, Diarrhoea, Dyspepsia, Nausea, Vomiting, Anorexia, Flatulence	not known
Hepatobiliary disorders:	Jaundice, Hepatitis	not known
Skin and subcutaneous tissue disorders:	Drug Rash with eosinophilia and systemic symptoms (DRESS), Erythema multiforme, Pruritus, Rash, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Urticaria, Genital pruritus, Acute generalized exanthematous pustulosis (AGEP)	not known
Renal and urinary disorders	Acute renal failure with tubulointerstitial nephritis as an underlying pathological condition	not known
General disorders and administration site conditions:	Pyrexia, Face oedema	not known
Investigations:	Aspartate aminotransferase increased Alanine aminotransferase increased Blood alkaline phosphate increased Blood bilirubin increased Blood urea increased Blood creatinine increased	not known

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 Website: www.hpra.ie

4.9 Overdose

Signs And Symptoms
There is a risk of encephalopathy in cases of administration of beta-lactam antibiotics, including cefixime, particularly in case of overdose or renal impairment.

No specific antidote exists. General supportive measures are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cefixime inhibits the cell wall synthesis of various bacteria.

Cefixime has high affinity for penicillin binding proteins (PBP) 1 (1a, 1b and 1c) and 3 and prevents cross-linking reaction. Cefixime has broad spectrum activity against Gram-positive and Gram-negative bacteria. Sensitivity will vary according to area, and local prescribing guidelines should always be consulted. Where possible microbiological sensitivity tests should guide treatment as resistance can emerge.

Its mechanism of action is bactericidal.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of cefixime to healthy volunteers, peak serum concentrations are generally attained in 3 to 4 hours. After a single oral dose of 50, 100 and 200mg mean peak serum concentrations were 1.02, 1.46 and 2.63 mg/L respectively in 12 healthy volunteers of Western origin and 0.69, 1.13 and 1.95 mg/L respectively in 12 healthy Japanese volunteers.

Paediatric Populations:
Following a single oral dose of 1.5, 3.0 and 6.0 mg/kg of cefixime in Japanese paediatric patients, maximum serum concentrations at around 3 to 4 hours were 1.14, 2.01 and 3.97 mg/L, respectively.

Distribution:
In human plasma, cefixime is approximately 70% protein bound, a value not concentration dependent in the range 0.5 to 30mg/L. Cefixime is distributed to target organs/tissues such as tonsils, maxillary sinus mucosal tissue, lung tissue and gallbladder tissue.

Metabolism & Excretion
No biologically active metabolites of cefixime were identified in plasma or urine following oral administration to healthy volunteers. Around 20% of a 200mg dose of cefixime is recovered unchanged over 24 hours in the urine of healthy volunteers. The elimination half-life is 2-4 hours.

Renal Impairment:
Studies in patients with various degrees of renal dysfunction administered single 400mg oral doses of cefixime indicated that elimination half-life, oral clearance (CL/F), renal clearance and AUC were altered in patients with severe renal dysfunction (creatinine clearance < 20 mL/min) and in those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as compared with healthy subjects. Please also see section 4.4

Table Pharmacokinetic properties (mean values) of cefixime in healthy volunteers and patients with various degrees of renal dysfunction

Study Group	CLCr (mL/min/1.73m^2)	Cmax (mg/L)	Tmax (h)	T1/2$_\beta$ (h)	AUC (mg.h/L)	CL/F (mL/kg/h)	Renal Clearance (mL/kg/h)
Healthy Volunteers	**111**	**4.9**	**4.9**	**3.2**	**40**	**141**	**22**
Renal dysfunction							
Very mild	**71**	**5.8**	**4.0**	**4.7**	**57**	**127**	**22**
Mild	**51**	**7.6**	**4.5**	**7.0**	**90**	**70**	**10**
Moderate	**28**	**7.5**	**3.5**	**7.2**	**100**	**80**	**3.7**
Severe	**9.8**	**9.6**	**6.0**	**11.5#**	**188#**	**41#**	**2.1#**
Hemodialysis	**1.3**	**6.2**	**4.8**	**8.2**	**94**	**73**	**0.4#**
CAPD	**3.0**	**10.2**	**5.0**	**14.9#**	**220#**	**42#**	**0.5#**

Difference statistically significant compared with healthy volunteers
Abbreviations: CLCr = creatinine clearance, T1/2$^\beta$= elimination half life, Cl/F = oral clearance, CAPD = continuous ambulatory peritoneal dialysis
#p <0.05 compared with healthy volunteers

5.3 Preclinical safety data

No relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline Cellulose
Pregelatinised Starch
Calcium Hydrogen Phosphate Dihydrate
Magnesium Stearate

Film coating:
Hypromellose
Macrogol
Titanium Dioxide (171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blister Packs: PVC/aluminium foil laminate blister packs.

Pack sizes: 1, 2, 7, 14.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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