SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefixime FrostPharma 20 mg/ ml granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of reconstituted oral suspension contains cefixime trihydrate corresponding to 20 mg of cefixime.

Excipient(s) with known effect
Sucrose 503.8 mg/ ml
Sodium benzoate (E 211) 0.5 mg/ ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension

Almost white to pale yellow granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefixime FrostPharma is indicated for the treatment of the following infections in children above 6 months, adolescents and adults only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections and when antibacterial susceptibility is confirmed (see section 4.4 and 5.1.):

- Acute bacterial sinusitis
- Acute otitis media
- Pharyngo-tonsillitis
- Acute bacterial exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Uncomplicated urinary tract infection
- Acute pyelonephritis

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

4.2 Posology and method of administration

Posology

Adults and adolescents (from 12 years)
400 mg once daily (=20 ml of the reconstituted suspension) as a single dose or 200 mg twice daily (=10 ml of the reconstituted suspension) every 12 hours.

Elderly
Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed, and dosage should be adjusted in patients with creatinine clearance below 20 ml/min (See dosage in “Renal impairment” and section 4.4.).

Children under 12 years
Cefixime 8 mg / kg body weight / day (maximum 400 mg/day), either as a single dose or in two equal divided doses.
The dosing recommendations are given in the following table:

Body weight	**Daily dose (ml) Once daily**	**Daily dose (ml) Twice daily**	Daily dose (mg)
6.0 kg-9 kg (for infants above 6 months)	1 x 2.5 ml	2 x 1.25 ml	50 mg
10.0 kg	4 ml	2 x 2 ml	80 mg
12.5 kg	5 ml	2 x 2.5 ml	100 mg
15.0 kg	6 ml	2 x 3 ml	120 mg
17.5 kg	7 ml	2 x 3.5 ml	140 mg
20.0 kg	8 ml	2 x 4 ml	160 mg
22.5 kg	9 ml	2 x 4.5 ml	180 mg
25.0 kg	10 ml	2 x 5 ml	200 mg
27.5 kg	11 ml	2 x 5.5 ml	220 mg
30.0 kg	12 ml	2 x 6 ml	240 mg
32.5 kg	13 ml	2 x 6.5 ml	260 mg
35.0 kg	14 ml	2 x 7 ml	280 mg
37.5 kg	15 ml	2 x 7.5 ml	300 mg
40.0 kg	16 ml	2 x 8 ml	320mg
42.5 kg	17 ml	2 x 8,5 ml	340 mg
45.0 kg	18 ml	2 x 9 ml	360 mg
47,5 kg	19 ml	2 x 9.5 ml	380 mg
50.0 kg	20 ml	2 x 10 ml	400 mg

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

Renal impairment
Cefixime may be administered in the presence of impaired renal function.

Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients with a creatinine clearance less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The same dose regimen is applied to those patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis.

In children under 12 years with a creatinine clearance less than 20 ml/min, a dose of 4 mg cefixime/kg body weight should be given only once daily (maximum 200 mg/day).

Duration of treatment
The usual course of treatment is 7-10 days. This may be continued for up to 14 days according to the severity of the infection.
For acute uncomplicated cystitis in women, the treatment period is 3 days.

<u>Method of administration</u>

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Cefixime FrostPharma is for oral administration only. The reconstituted suspension should be administered undiluted and can be given with or without food (see section 5.2).

A plastic pipette (5 ml) is provided with the bottle to aid correct dosing.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any cephalosporin antibacterial medicinal product.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins, monobactams or carbapenems).

4.4 Special warnings and precautions for use

The selection of cefixime to treat an individual patient should take into account the appropriateness of using a third-generation oral cephalosporin agent considering in particular the nature of the infection and the risk of bacterial resistance.

Hypersensitivity reactions
Hypersensitivity has been reported with cefixime (see section 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibacterial medicinal products may also be hypersensitive to cefixime. Before initiating therapy, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics (see section 4.3).

If a severe allergic reaction occurs, treatment with cefixime must be discontinued immediately and adequate emergency measures must be initiated.

Pseudomembranous colitis
Treatment with cefixime at the recommended (400 mg) dose can significantly alter the normal flora of the colon and lead to overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. In patients who develop severe persistent diarrhoea during or after use of cefixime, the risk of life-threatening pseudomembranous colitis should be taken into account. The use of cefixime should be discontinued and appropriate treatment measures should be established.

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

Severe cutaneous adverse reactions
Severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) or bullous skin reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome) have been reported in patients treated with cefixime (see section 4.8). If such reactions occur, cefixime should be immediately stopped and appropriate therapy and/or measures should be taken.

Administration with other medicinal products
Renal function is to be monitored under a combination therapy with cefixime preparations and aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics (e.g. furosemide) because of the probability of additional renal impairment. This applies particularly for patients with already restricted renal function (see section 4.5).

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

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

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

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

Cefixime FrostPharma contains 0.5 g of sucrose per ml reconstituted suspension. This should be taken into account by patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains 0.5 mg sodium benzoate (E 211) per ml reconstituted suspension. Sodium benzoate (E211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

This medicine contains less than 1 mmol sodium (23 mg) per ml reconstituted suspension, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant intake with potentially nephrotoxic substances (such as aminoglycoside antibiotics, colistin, polymyxin and viomycin) and strong-acting diuretics (e.g. ethacrynic acid or furosemide) induce an increased risk of impairment of renal function (see section 4.4).

Nifedipine, a calcium channel blocker, may increase bioavailability of cefixime up to 70 %.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of cefixime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ fetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, Cefixime FrostPharma should not be used in pregnant women unless considered essential by the physician.

Breastfeeding

It is unknown whether cefixime is excreted in human milk. Non-clinical studies have shown excretion of cefixime in animal 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.

Fertility

Reproduction studies performed in mice and rats do not indicate harmful effects with respect to fertility (see section 5.3.).

4.7 Effects on ability to drive and use machines

Cefixime FrostPharma has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

The below specified frequency of side effects are defined as follows:
Very common ≥ 1/10

Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1 000 to < 1/100
Rare ≥ 1/10 000 to < 1/1 000
Very rare < 1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/10,000**	**Not known (cannot be estimated from the available data)**
Infections and infestations			Superinfection bacterial, superinfection fungal	Antibiotic-associated colitis (see section 4.4.)	
Blood and lymphatic system disorders			Eosinophilia	Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia	Thrombocytosis, neutropenia
Immune system disorders			Hypersensitivity	Anaphylactic shock, serum sickness	
Metabolism and nutrition disorders			Anorexia		
Nervous system disorders		Headache	Vertigo	Psychomotor hyperactivity	
Gastrointestinal disorders	Diarrhoea	Abdominal pain, nausea, vomiting	Flatulence		Dyspepsia
Hepatobiliary disorders				Hepatitis, cholestatic jaundice	
Skin and subcutaneous tissue disorders		Rash	Angioneurotic oedema, pruritus	Stevens-Johnson syndrome, toxic epidermal necrolysis	Drug rash with eosinophilia and systemic symptoms (DRESS) (see section 4.4.), erythema multiforme
Renal and urinary disorders				Interstitial nephritis	
General disorders and administration site conditions			Mucosal inflammation, pyrexia		
Investigations		Hepatic enzyme increased (transaminase, alkaline phosphatase)	Blood urea increased	Blood creatinine increased	Direct and indirect positive Coombs tests (see section 4.4)

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 the national reporting system listed in Appendix V.*

4.9 Overdose

There is no experience with cefixime overdose.
Adverse reactions seen at dose levels up to 2 g cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Gastric lavage may be indicated in overdosage. No specific antidote exists. Cefixime is not removed from the circulation in significant quantities by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporins, ATC code: J01DD08

Mechanism 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.

Pharmacokinetic/pharmacodynamic 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 pharmacokinetic/pharmacodynamic 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.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for cefixime and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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: *Streptococcus pyogenes*
Species for which resistance may be a problem
Aerobes, Gram positive: *Streptococcus pneumoniae* Aerobes, Gram negative: *Citrobacter freundii* *Enterobacter cloacae* *Escherichia coli* *Haemophilus influenzae* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Morganella morgani* *Proteus mirabilis* *Serratia marcescens*
Inherently Resistant species
Aerobes, Gram positive: *Enterococci* *Staphylococcus* spp. Aerobes, Gram-negative: *Pseudomonas* species Other micro-organisms: *Chlamydophila* spp. *Legionella pneumophila* *Mycoplasma* spp.

5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of cefixime is in the range of 40-50%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

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 200 mg 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.

Over a dose range of 200 to 2000 mg, there is a less than proportional increase in AUC and C_{max} with increasing dose. Between 200 and 400 mg there was an almost dose-proportional increase in AUC and C_{max} (1.7-fold increase with 2-fold increase in dose).

Distribution

Serum protein binding is well characterised 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.
Cefixime is distributed to target organs/tissues such as tonsils, maxillary sinus mucosal tissue, lung tissue and gallbladder tissue.

From *in vitro* studies, serum or urine concentrations of 1 mcg/ml 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 mcg/ml. Little or no accumulation of cefixime occurs following multiple dosing.

Biotransformation and elimination

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

Special populations

Elderly
The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (18-35) was compared when administering 400 mg doses once daily for 5 days. Mean Cmax 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).

Paediatric Population
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.

Renal Impairment:
Studies in patients with various degrees of renal dysfunction administered single 400 mg 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 4.2.

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)	C_{max} (mg/L)	T_{max} (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

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, *in vivo* and *in vitro* 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 fetus 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.
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). Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Xanthan gum
Sodium benzoate (E 211)
Flavour durarome orange containing:
Flavouring ingredients
Maize maltodextrin
Sucrose
Modified corn starch
Acacia gum (Arabic gum)
Citric acid esters of mono- and diglycerides of fatty acids
Silicon dioxide (E 551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After reconstitution: Store below 25°C for 14 days. Do not freeze.

6.4 Special precautions for storage

Store below 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Brown neutral type III glass bottle, with an aluminium screw cap with a polyethylene sealing.

The bottle is placed in a cardboard box, including a polypropylene measuring cup graduated on 40 ml for reconstitution and a plastic 5 ml pipette for dosing (polystyrene plunger and low-density polyethylene (LDPE) body and protection cap) with a scale from 0.5 ml to 5 ml and graduations on each 0.25ml, imprinted on the plunger.

Pack sizes: 60 ml of oral suspension (reconstituted)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of the suspension:
To reconstitute, use the measuring cup provided in the cardboard box.

- 60 ml oral suspension: Add 40 ml of purified water divided into two portions, shaking after each addition.

The reconstituted suspension is an almost white to pale yellow viscous liquid.

Shake the medicine bottle well before each use.
A graduated plastic pipette is used for measuring the required prescribed amount of suspension. The plastic pipette is included in the package.

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

FrostPharma AB
Berga Backe 2
182 53 Danderyd
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-10-02