SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefimed 400 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Cefimed 400 mg contains the equivalent of 400 mg cefixime as cefixime trihydrate.

Excipient with known effect: lactose monohydrate.
Each Cefimed 400mg film-coated tablet contains 120.40mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, round, convex film-coated tablet for oral administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cefixime is a 3rd generation cephalosporin antibiotic given orally for the treatment of acute and chronic infections of varying severity caused by bacteria sensitive to cefixime in adolescents and adults aged 12 years and older for the following infections:

- upper respiratory tract infections (e.g. ear, nose and throat infections: otitis media, sinusitis, tonsillitis, pharyngitis, laryngitis),
- lower respiratory tract infections (e.g. pneumonia, acute bronchitis and acute exacerbation of chronic bronchitis),
- infections of the kidney and urinary tract (e.g. cystitis, cystourethritis, uncomplicated pyelonephritis, urethritis, acute gonorrheal urethritis),
- biliary tract infections.

Proven *Staphylococcus* infection should not be treated with cefixime, because *Staphylococcus* is resistant to this medicine.

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

4.2. Posology and method of administration

Posology

The dosage can be adjusted based on the patient's age, body weight, symptoms and kidney function. The preparation is used orally once or twice a day (see section 4.4).

Adults and adolescents 12 years and older

The recommended dose is 400 mg per day. The recommended daily dose should be taken either at once or in two divided doses (in the morning and evening).

Patients with severely impaired kidney function

Patients with significantly reduced kidney function should reduce the dose.
For adults and children 12 years of age and older, if the creatinine clearance is <20 ml/min/1.73 m2, the recommended daily dose is 200 mg once a day.

Elderly

In the case of elderly patients, dose adjustment is usually not necessary.

Paediatric population

Children under 12 years of age

It is recommended to give a liquid form of cefixime to children under 12 years of age.
A suspension cannot be given to premature babies and newborns.

Children and adolescents aged 12 years and older

The recommended dose for this age group is the same as for adults.

Duration of treatment

For common bacterial infections, the duration of treatment depends on the course of the disease. Usually, 5-10 days of treatment is sufficient.

Treatment of beta-haemolytic *Streptococcus* infections should be continued for at least 10 days as a precaution to avoid possible late complications (febris rheumatica, glomerulonephritis).

1-3 days are often enough to treat uncomplicated urinary tract infections in women.

In the case of uncomplicated gonorrhoea, a single dose of 400 mg of cefixime is sufficient. The result of the treatment of gonorrhoeal infection should be checked by culture performed 3-4 days after the treatment.

Method of administration

Oral administration.

The medicine can be taken regardless of food; this does not affect the absorption of the active ingredient.

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Hypersensitivity to penicillins

Cefixime should be given with caution to patients with a history of hypersensitivity to penicillin other beta-lactam antibiotics, as a cross-allergic reaction to cephalosporins may occur.

Like other beta-lactam antibiotics, cefixime can cause allergic reactions. Therefore, the preparation can only be given with extreme caution to patients with a history of allergic symptoms or bronchial asthma. The development of an anaphylactic reaction requires the immediate administration of adrenaline, oxygen and steroids and the provision of an open airway.

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.

Acute renal failure

As with other cephalosporins, cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Epileptic seizure in patients with reduced renal function

Seizures have been reported with several cephalosporins, particularly in patients with reduced renal function whose dose has not been reduced. If a seizure occurs, cefixime should be discontinued and appropriate treatment and/or measures should be instituted.

Renal impairment

Cefixime should be administered with caution in patients with severe renal dysfunction (creatinine clearance <10 ml/min/1.73 m2) (see section 4.2 under Renal Impairment).

Gastrointestinal disorders

Cefixime treatment is not recommended in the case of severe stomach and intestinal disorders accompanied by vomiting and diarrhoea, because adequate absorption of the drug is not ensured (in such a case, it must be given parenterally and appropriate antibiotics).

Antibiotic resistance

Treatment with cefixime may increase the risk of developing drug-resistant microorganisms with or without clinically apparent superinfection.

Superinfection

As with other antibiotics, long-term use of the drug may occasionally cause the proliferation of non-susceptible microorganisms. In the event of superinfection, appropriate treatment must be applied.

Pseudomembranous colitis

In case of severe or persistent diarrhoea, pseudomembranous colitis should be considered! In such a case, the dosage of the product should be discontinued, and the patient should be given appropriate treatment.

Drugs that inhibit peristalsis are contraindicated.

Paediatric use

Safety of cefixime in premature or newborn infant has not been established. Until further clinical experience is gained, Cefimed should not be given to premature infants and newborns.

Cefimed contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Effect on laboratory results

During cefixime treatment, the determination of urine sugar using a non-enzymatic method (using Benedict's solution, Fehling's solution or Clinitest tablets) may give a false-positive result. The use of glucose tests based on enzymatic glucose oxidase reactions (e.g., Tes-Tape) is recommended.
The direct Coombs test may give false results during cefixime treatment.

If cefixime is combined with an aminoglycoside antibiotic, polymyxin B, colistin or given together with high doses of loop diuretics (e.g., furosemide), renal function should be carefully monitored, especially in patients with previously impaired renal function.

Cefixime should be used with caution in patients treated with coumarin-type anticoagulants, e.g., treated with warfarin potassium. As cefixime may increase the effect of anticoagulants, prolongation of prothrombin time with or without bleeding may occur.

Nifedipine increased the bioavailability of cefixime in healthy volunteers, but the clinical significance of this has not been demonstrated.

So far, no metabolic interactions between cefixime and other drugs have been observed.

It can be taken simultaneously with mucolytics containing acetylcysteine.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of cefixime during pregnancy has not yet been established. Experimental studies do not indicate a harmful effect on the fetus, however, it can only be given during pregnancy, especially in the first 3 months of pregnancy, after a careful individual consideration of the benefit/risk.

Cefixime crosses the placenta. Umbilical cord blood contains 1/6-1/2 of the maternal serum concentration.

Breast-feeding

It is not known whether cefixime is excreted in human milk. Use during breastfeeding is not recommended. Before using cefixime, a decision should be made whether to discontinue breast-

feeding or to discontinue/abstain from treatment, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

4.7. Effects on ability to drive and use machines

Cefixime is not known to affect the ability to drive or use machines.

4.8. Undesirable effects

Classification of adverse reactions by MedDRA system organ class and frequency. The side effects listed below have been observed during clinical trials and/or post-marketing.

System Organ Classification	*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				Pseudo-membranous colitis	Superinfection with resistant pathogens
Blood and lymphatic system disorders			Eosinophilia	Leukopenia, Agranulocytosis, Pancytopenia, Thrombocytopenia, Coagulopathy	Granulocytopenia, Haemolytic anaemia
Immune system disorders			Hypersensitivity reactions, Anaphylactic shock		Serum sickness-like reactions
Metabolism and nutrition disorders			Loss of appetite		
Nervous system disorders		Headache	Dizziness	Transient hyperactivity, Increased tendency to convulsions	

System Organ Classification	*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)*
Respiratory, thoracic and mediastinal disorders					Dyspnoea
Gastrointestinal disorders	Loose stools, Diarrhoea	Abdominal pain, Nausea, Vomiting	Meteorism		Dyspepsia
Hepatobiliary disorders				Jaundice, Hepatitis, Cholestasis	
Skin and subcutaneous tissue disorders		Skin rashes (exanthema, erythema)	Pruritus	Erythema multiforme, Toxic epidermal necrolysis	Drug-induced rash with eosinophilia and systemic symptoms (DRESS syndrome), Urticaria, Stevens-Johnson syndrome
Renal and urinary disorders					Acute renal failure, including renal failure due to tubulo-interstitial nephritis
General disorders and administration site conditions			Mucosal inflammation		Pyrexia, Facial oedema
Investigations		Reversible increase in serum	Increase in urea nitrogen	Increased serum creatinine	Increase in blood bilirubin

System Organ Classification	*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)*
		liver-derived enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase)			

Gastrointestinal side effects occur more often if the patient takes the daily dose at the same time.

Rarely (>0.01%), in the case of long-term or repeated administration of the drug, superinfection with resistant bacteria or fungi may develop.

Hypersensitivity phenomena

During oral administration of cephalosporins, in addition to allergic skin manifestations, hypersensitivity reactions of varying severity, up to anaphylactic shock, have been observed rarely (> 0.01%), but these are significantly rarer than after parenteral administration.

Manifestations of a severe, acute hypersensitivity reaction may include facial oedema, tongue swelling, laryngeal oedema with narrowing of the airways, palpitations, shortness of breath, and a drop in blood pressure, which may lead to threatening shock. In the event of such phenomena, immediate medical assistance is required.

In some cases, the allergy resulting from sensitization may manifest itself in rare (>0.01%) drug-induced fever, and very rarely (≤ 0.01%) in reactions similar to serum sickness, haemolytic anaemia, and interstitial nephritis.

The very rare changes in the blood count normalized by themselves after the end of the treatment.

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.

4.9. Overdose

Symptoms

Cefixime-related symptoms of poisoning have not yet been reported.

Management

It has no specific antidote. In case of overdose, general supportive interventions are recommended. A significant amount of the active substance cannot be removed from the body by haemo- or peritoneal.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporins, Antibacterials for systemic use, ATC code: J01DD08

Mechanism of action

Its active ingredient is cefixime, which can be administered orally, a 3rd generation cephalosporin antibiotic.

Cefixime has a bactericidal effect, its mechanism of action is based on the inhibition of bacterial cell wall synthesis. Due to its exceptional resistance to beta-lactamases, many penicillin- and other cephalosporin-resistant bacteria are susceptible to cefixime.

Clinical efficacy

Cefixime has a broad spectrum of activity against Gram-positive and Gram-negative bacteria.

Cefixime is generally effective against the following pathogens:

Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus agalactica
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Escherichia coli
Proteus mirabilis

Proteus spp. (including indole-positive species)
Proteus vulgaris
Klebsiella pneumoniae
Klebsiella oxytoca
Enterobacter spp.
Pasteurella multocida
Providencia spp.
Salmonella spp.
Shigella spp.
Citrobacter amalonaticus
Citrobacter diversus
Serratia marcescens

Cefixime-resistant pathogens:
Pseudomonas spp.
Enterococci
Listeria monocytogenes
Most *Staphylococcus* (both coagulase-positive and coagulase-negative and methicillin-resistant strains)
The majority of anaerobic bacterial strains

5.2. Pharmacokinetic properties

Absorption, distribution and biotransformation
The absolute bioavailability of oral cefixime is in the range of 22-54%. Food does not significantly affect absorption, so cefixime can be taken regardless of food.

Based on data from *in vitro* studies, serum or urine concentrations of 1 μg/ml or higher were already sufficient against commonly occurring pathogens sensitive to cefixime. Peak serum concentrations from doses recommended for adult or pediatric patients typically fall between 1.5 and 3 μg/ml. After multiple doses, little or no accumulation occurs.

The pharmacokinetics of cefixime 400 mg once daily for 5 days were compared in healthy elderly (over 64 years) and young (11 to 35 years) volunteers. The mean Cmax and AUC values were slightly higher in the elderly. The elderly may receive the same dose as the general population.

The binding of cefixime to serum proteins is well defined in both human and animal serum. It binds almost exclusively to the albumin fraction, while the average free fraction is approx. It accounts for 30%. In human serum, the protein binding of cefixime was only very high, and it proved to be concentration-dependent at concentrations not reached in clinical practice.

Elimination

Cefixime is predominantly excreted unchanged in the urine, primarily through the mechanism of glomerular filtration. No metabolites of cefixime were identified in either plasma or urine.

In lactating rats, the amount of 14C-labeled cefixime transferred to the offspring in the mother's milk was small (about 1.5% of the amount of cefixime in the mother's body appeared in the offspring). No data are available on the excretion of cefixime in human milk. Placental transfer of the indicated cefixime was low in pregnant rats.

Impaired kidney function

Studies with a single 400 mg oral dose of cefixime in patients with varying degrees of renal impairment indicated that the elimination half-life, oral clearance (CL/F), renal clearance and AUC indicated severe renal impairment (creatinine clearance < 20 ml/min) or in patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) changes compared to healthy volunteers.

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

	ClCr (ml/min/1.73m2)	Cmax (mg/l)	Tmax (h)	T1/2β (h)	AUC (mg·h/l)	Cl/F (ml/kg/h)	Renal clearance
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
Medium	28	7,5	3,5	7,2	100	80	3.7
Serious	9,8	9,6	6,0	11,5#	188#	41#	2,1#
Haemodialysis	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#

The difference compared to healthy volunteers is statistically significant

Abbreviations: ClCr = creatinine clearance, T1/2β = elimination half-life, Cl/F = oral clearance, CAPD = continuous ambulatory peritoneal dialysis
#p<0.05 compared to healthy volunteers

5.3. Preclinical safety data

Tests conducted on three animal species (rat, mouse, rabbit) showed no teratogenic effect, just as there was no detectable effect on the fertility, peri- and postnatal development of rats.
Several *in vitro* and *in vivo* mutagenicity tests were negative. The mutagenic effect of cefixime on humans can be ruled out with adequate certainty.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Polyvinyl alcohol
Titanium dioxide
Purified talc
Lecithin
Xanthan gum

6.2. Incompatibilities

None stated.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 25^{o}C in the original package, in order to protect from light and moisture.

"Cefimed" 400 mg tablets should be stored in a dry place protected from light at a temperature not exceeding 25^{o}C.

6.5. Nature and contents of container

Cefimed 400 mg film-coated tablets are packed in aluminium foil – polyvinylchloride film blisters. Blisters, with a patient information leaflet are parked in card cartons containing 4, 5, 7, 100, 500 or 1000 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

For oral administration only.

7. MARKETING AUTHORISATION HOLDER

Medochemie Ltd, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

08228/08581/REN/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13/03/2015
Date of latest renewal: 15/12/2022

10. DATE OF REVISION OF THE TEXT

07/2023