Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

KADFIX 400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KADFIX 400 mg capsules:

Each capsule contains 400 mg of cefixime (as a trihydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

KADFIX 400 mg capsules:
Blue and yellow capsules, with KADFIX marked on the cap and 400 marked on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of acute and chronic infections of different severity caused by cefixime-sensitive pathogens and which can be treated orally:

- upper and lower respiratory tract infections
- infections of the ear, nose and throat area, e.g. middle ear infection (otitis media), sinusitis, infections of the tonsils and the pharynx (tonsillitis, pharyngitis, laryngitis)
- infections of the kidney and the urinary tract
- bile duct infections
- acute, uncomplicated gonorrhoea in the cervix, urethra and rectum in adults

The generally recognised recommendations on the appropriate use of antimicrobial substances must be taken into account when using *Mirafix*.

4.2 Posology and method of administration

Posology
In the case of conventional bacterial infectious disease, the duration of treatment depends on the course of the disease. Normally a treatment period of 5-10 days is sufficient.

In the treatment of infections with β-haemolysing streptococcal infections, a minimum duration of 10 days is recommended for caution, in order to prevent late complications (rheumatic fever, glomerulonephritis).

In cases of uncomplicated urinary tract infections in women, a treatment period of 1-3 days is often sufficient.

In the case of acute, uncomplicated gonorrhoea, a single administration of 2 capsules of *KADFIX 200 mg* or 1 capsule of *KADFIX 400 mg* (corresponding to 400 mg of cefixime) is generally sufficient. The success of the treatment of a gonococcal infection should be checked by means of a culture check 3-4 days after the end of treatment.

Adults and adolescents over the age of 12:
Unless otherwise prescribed, adults and adolescents aged 12 years and over receive 1 x 400 mg daily in a single dose (corresponding to 1 x 1 capsule of *KADFIX 400 mg)*

Children and adolescents aged under 12 years:
A liquid oral formulation with the active substance cefixime is recommended for children under 12 years of age or under 50 kg body weight and patients with swallowing disorders.

Elderly patients:
It is generally not necessary to adjust the dose for elderly patients.

Method of administration
The capsules should be swallowed with plenty of fluid.
Taking the capsule with meals does not affect resorption. The medicinal product may be taken before or as well together with a meal.

4.3 Contraindications

- Hypersensitivity to the active substance, to other cephalosporins or to any of the excipients listed in section 6.1
- Known hypersensitivity reactions of an immediate nature or severe hypersensitivity reactions, anaphylaxis in response to penicillins or other beta-lactam antibiotics.

4.4 Special warnings and precautions for use

Until more clinical experience is available, cefixime should not be given to premature infants, newborn infants or breast-feeding mothers.

Particular caution is advised before using cefixime in patients with any hypersensitivity to penicillin or other beta-lactam antibiotics, as there may be a parallel allergy (see section 4.3). Cefixime should also be used with particular caution in patients with a high likelihood of allergic reactions of another type (e.g. hay fever or bronchial asthma), as in these cases, the risk of severe hypersensitivity reactions is increased.

Hypersensitivity reactions of all degrees of severity may occur after taking cefixime. In case of severe, acute hypersensitivity reactions up to anaphylactic shock (see section 4.8), cefixime therapy must be discontinued immediately and appropriate emergency measures must be initiated.

Treatment with cefixime should be avoided in patients with vomiting and diarrhoea, because adequate absorption is not guaranteed (parenteral therapy with a suitable antibiotic is recommended).

During or after therapy, antibiotic-associated intestinal inflammation (e.g. pseudomembranous colitis) may occur with severe, persistent diarrhoea, which sometimes contains blood. In such a case, cefixime should be discontinued immediately and a pathogen and appropriate therapy should be performed. Antiperistaltic medicinal products are contraindicated (see section 4.8).

Proven infections caused by staphylococci should not be treated with cefixime since staphylococci are resistant.

In cases of severe renal impairment (creatinine clearance <10 mL/min/1.73 m^2), cefixime should be used with particular caution (see section 4.2).

As with any prolonged antibiotic therapy, the increased growth of non-sensitive bacteria or fungi must be considered.

In long-term therapy with cefixime in high doses, renal and hepatic function and blood count checks are indicated.

If you are combining cefixime with an aminoglycoside antibiotics, polymyxin B, colistin, viomycin or with certain highly dosed loop diuretics such as furosemide, renal function should be monitored very carefully (see section 4.8). This is especially true for patients with renal impairment.

In some cases, the co-administration of cefixime with the calcium channel blocker nifedipine demonstrated that the bioavailability of cefixime capsules increased by 70% (see section 4.5).

In individual cases, prolonged prothrombin times with and without bleeding have been reported in patients who received cefixime and coumarin anticoagulants at the same time. If necessary, a control of the coagulation parameters is indicated (see section 4.5).

Influence on laboratory diagnostics
False-positive reactions can occur in urine glucose determinations with reduction methods. Therefore, with cefixime, the urine sugar should be determined enzymatically.

4.5 Interaction with other medicinal products and other forms of interaction

Cefixime and nifedipine, a calcium channel blocker, increases the bioavailability of cefixime by approximately 70% (see section 4.4).

In individual cases, prolonged prothrombin times with and without bleeding have been reported in patients who received cefixime and coumarin anticoagulants at the same time. A control of the coagulation parameters is indicated (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient clinical data on the administration of cefixime during pregnancy. Animal studies do not indicate teratogenic effects caused by cefixime (see section 5.3). Cefixime can cross the placental barrier. Due to the lack of clinical experience, cefixime should only be used after a careful assessment of the risks and benefits.

Breast-feeding
No cefixime concentrations could be detected in breast milk. Due to the lack of data, it is necessary to decide whether or not breast-feeding can be continued, based on the overall clinical situation on a case-by-case basis.

4.7 Effects on ability to drive and use machines

Based on experience so far, the active substance cefixime generally has no effect on the ability to concentrate and react. However, side effects (see section 4.8) may alter reactivity, and your ability to drive and operate machines may be impaired.

4.8 Undesirable effects

The following definitions of frequencies are used: 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) and not known (frequency cannot be estimated from the available data).

Infections and infestations
Rare: Long-term and repeated use can lead to resistant bacterial or fungal superinfections.

Blood and lymphatic system disorders
Rare: Eosinophilia.
Very rare: Changes in the blood picture, such as leukopenia, agranulocytosis or thrombocytopenia. These side effects revert to normal by themselves at the end of treatment. Blood-clotting disorders, haemolytic anaemia.

Immune system disorders
Rare: Medicinal product fever and hypersensitivity reactions of all severity levels - up to anaphylactic shock and have also been observed following oral administration of cephalosporins, although much less frequently than after intravenous or intramuscular administration. Severe acute hypersensitivity reactions may manifest themselves as: facial oedema, swollen tongue, laryngeal oedema with airway obstruction, tachycardia, respiratory distress (breathlessness), drops in blood pressure to the extent of anaphylactic shock. If these reactions occur, please consult your doctor immediately.
Very rare: Reactions similar to serum sickness.

Nervous system disorders
Uncommon: Headache.
Rare: Dizziness.
Very rare: Temporary hyperactivity.
As with other cephalosporins, an increased tendency to seizures cannot be ruled out.

Gastrointestinal disorders
Common: Soft stools, diarrhoea.
Uncommon: Disorders in the form of abdominal pain, digestive disorders, nausea and vomiting.
Rare: Loss of appetite, bloating.
Very rare: Antibiotic-associated inflammation of the large intestine (e.g. pseudomembranous colitis, see section 4.4).

Hepatobiliary disorders
Uncommon: Reversible increase in liver enzymes (transaminases, alkaline phosphatase) in the serum.
Very rare: Hepatitis and cholestatic jaundice.

Skin and subcutaneous tissue disorders
Uncommon: Skin rashes (erythema, exanthema).
Rare: Itching, mucosal inflammation.
Very rare: Exudative erythema multiforme, Lyell's syndrome.

Renal and urinary disorders
Rare: Temporary increased concentrations of urea.

Very rare: Increased concentrations of creatinine in the serum, interstitial nephritis.
High-dose treatments with cephalosporins can lead to impairment of renal function in patients who are receiving diuretics or potentially nephrotoxic substances at the same time (e.g. aminoglycoside antibiotics) (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.

4.9 Overdose

Intoxications in the strict sense are unknown.
No relevant amounts of substance can be eliminated from the body through haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibiotics, 3rd generation cephalosporins, ATC code: J01DD08

Mechanism of action:
The mechanism of action of cefixime is based on an inhibition of the bacterial cell wall synthesis (during the growth phase) by blocking penicillin-binding proteins (PBPs) such as, for example, transpeptidases. This results in a bactericidal effect.

Pharmacodynamic effects:
The effectiveness essentially depends on the duration of the active ingredient level being above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanisms of resistance:
Resistance to cefixime can be based on the following mechanisms:

- Deactivation through beta-lactamases: Cefixime can be hydrolysed by certain beta-lactamases, in particular by extended-spectrum beta-lactamases (ESBLs) which occur, for example, in strains of *Escherichia coli* or *Klebsiella pneumoniae* or through constitutively formed beta- lactamases of the AmpC type which have been identified, for example, in *Enterobacter cloacae*. In the case of infections by bacteria with inducible AmpC beta-lactamase and in-vitro sensitivity to cefixime, there is a risk that during treatment, mutants with constitutive (depressed) AmpC beta-lactamase formation will be selected.
- Reduced affinity of PBPs to cefixime: the acquired resistance in pneumococci and other streptococci is based on modifications of existing PBPs as a result of a mutation.
- Insufficient penetration of cefixime through the external cell wall in Gram-negative bacteria can lead to the PBPs not being sufficiently inhibited.
- Cefixime can be actively transported out of the cell through efflux pumps.

There is a partial or complete cross-resistance of cefixime with other cephalosporins and penicillins.

Limit values:
Cefixime is tested using the usual dilution series. The following minimal inhibitory concentrations for susceptible and resistant germs were determined:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) cut-off values

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae [1)]	≤1 mg/L	>1 mg/L
Haemophilus influenzae	≤0.12 mg/L	>0.12 mg/L
Moraxella catarrhalis	≤0.5 mg/L	>1 mg/L
Neisseria gonorrhoeae	≤0.12 mg/L	>0.12 mg/L

[1)] Only uncomplicated urinary tract information

Prevalence of acquired resistance in Germany:
The prevalence of acquired resistance to an individual species can vary locally over time. This is why local information on the resistance situation is required, in particular in order to treat serious infections adequately. If the effectiveness of cefixime is called into question due to the local resistance situation, treatment advice from experts should be sought. In particular with serious infections or where the treatment fails, a microbiological diagnosis with evidence of the pathogen and its sensitivity to cefixime should be sought.

Prevalence of acquired resistance on the basis of data from the past five years from national resistance monitoring projects and studies (as at January 2015):

Normally susceptible species
Aerobic Gram-positive microorganisms
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis [° %]
Species for which acquired resistance may present a problem for administration
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae
Aerobic Gram-negative microorganisms
Citrobacter freundii [$]
Enterobacter cloacae [$]
Escherichia coli [% &]
Klebsiella oxytoca [%]
Klebsiella pneumoniae [%]
Morganella morganii [$]
Serratia marcescens [$]
Naturally resistant species
Aerobic Gram-positive microorganisms
Enterococcus spp.
Staphylococcus spp.
Streptococcus pneumoniae (intermediate and resistant to penicillin)
Aerobic Gram-negative microorganisms
Legionella pneumophila
Pseudomonas aeruginosa
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.

[°] There were no up-to-date data at the time the table was published. A susceptibility is assumed in the primary literature, standard works and treatment recommendations.

[$] The natural sensitivity of most isolates is in the intermediate range.
[%] Extended-spectrum beta-lactamase (ESBL)-forming strains are always resistant.
[&] In the case of isolates of patients with uncomplicated cystitis, the resistance rate is <10%, otherwise ≥10%.

5.2 Pharmacokinetic properties

Absorption:
Cefixime is well resorbed after oral administration and absolute bioavailability is above 40-50%.

Concomitant food intake has no effect on oral resorption.

Distribution:
The serum protein binding of cefixime is 65%.

After a single intravenous application of 200 mg of cefixime, a relative distribution volume of 6.7 litres was determined. At steady state it was 26.8 litres.
Cefixime penetrates well into all the body fluids studied, however the maximum concentration was 6.7 h later than in the serum. After taking 200 mg of cefixime twice daily, cefixime levels of approximately 200 µg/mL were determined in the bile in patients with cholecystectomy. In the urine, mean concentrations of 107 µg/mL were reached 4-6 h after oral administration of 200 mg of cefixime, and 164 µg/mL after taking 400 mg of cefixime. In both the cortex and the medulla, cefixime levels of 5.75 µg/g and 6.38 pg/g could be measured after oral administration of 2 x 200 mg over two days.

After administration of cefixime, subsequent cefixime levels were detected in the following fluids or tissues according to the dose administered:

- Tonsils: 5 h after administration of 4 mg/kg on average 0.6 µg/g.
- Lung tissue: 7.8 h after administration of 200 mg 0.99 µg/g, 8 h after administration of 400 mg 1.76 µg/g.
- Bronchial secretion: 4 h after administration of 400 mg 0.21 µg/mL.
- Otorrhoea: 2-3 h after administration of 100 mg for several days >1 µg/mL.
- Cerebral mucosa: 2-4 h after administration of 200 mg 1.2-1.4 µg/g.
- Sputum: after administration of 100 mg 0.02-0.5 µg/mL.

In clinical studies, peak concentrations of serum in fasting patients were reached between 3-4 hours after administration (200 mg preparation: 1.5-3.3 µg/mL; 400 mg-preparation: 2.5-4.9 µg/mL). When 200 mg is administered twice daily, the maximum serum levels are not different from one single administration, the repeated daily administration of cefixime does not lead to accumulation of serum.

Biotransformation:
No circulating metabolites have been found in clinical trials to provide information on the metabolism of cefixime.

Elimination:
The elimination half-life of cefixime, regardless of the dose administered and the galenic formulation, is 2-4 hours. Excretion is mainly by glomerular filtration and tubular secretion via the kidneys. Approx. 10-20% of the dose taken, corresponding to 50-55% of the absorbed amount, remains unchanged in the urine within 24 hours of oral administration of 200 to 400 mg cefixime. The rate of biliary excretion of cefixime is approximately 10%.

Linearity/non-linearity:
The plasma concentrations of cefixime increase linearly but not proportionally with the dose.

Pharmacokinetic/pharmacodynamic relationships:
In elderly patients, the AUC values (area under the plasma level/time curve) are only slightly higher than in younger patients.

The half-life in children and adolescents is 3.3-3.7 hours, in elderly patients (mean age 68.9 years) it is 3.9-4.2 hours.

5.3 Preclinical safety data

The repeated dose toxicity studies have caused substance-induced effects on the gastrointestinal system and the kidneys. Like other cephalosporins, cefixime is to be assessed as potentially nephrotoxic.

Tests in three animal species (rats, mice, rabbits) show no indication of teratogenic properties. No influences were observed on peri- or postnatal development and fertility in rats.

Several *in vitro* and *in vivo* mutagenicity tests were negative. As there is no evidence of a carcinogenic potential from mutagenicity tests and toxicological long-term studies in rats and cefixime is not generally used over a longer period, no long-term studies were performed on carcinogenicity with cefixime.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate (Ph.Eur)
Highly dispersed silicon dioxide
Lactose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

KADFIX 400 mg capsules:
Folding cardboard box with aluminium PVC/PVDC blister strips with 10 capsules.

6.6 Special precautions for disposal

No special requirements.

7. **MANUFACTURER**-MIRAFLASH NIGERIA LIMITED
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