SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Tricef 400 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of cefixime.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
White film-coated tablets, oblong, and debossed with "Bial" and "TF/400" on opposite sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tricef is indicated for the treatment of the following infections caused by susceptible agents (see section 4.4 and 5.1):
- Acute otitis media
- Upper respiratory tract infections (pharyngitis, tonsillitis, acute sinusitis)
- Lower respiratory tract infections (acute exacerbations of chronic bronchitis, community acquired pneumonia);
- Urinary tract infections (acute cystitis, uncomplicated acute pyelonephritis);
- Uretritis and uncomplicated gonococcal cervicitis.

Consideration should be given to national and/or local guidelines on the appropriate use of antibiotics.

4.2 Posology and method of administration

The usual recommended posology is as follows:
- *Adults and children older than 12 years* (or weighing more than 30 kg): 400 mg in a single daily dose. For the uncomplicated urinary tract infections a dose of 200 mg per day is effective.
- *Elderly*: The same dose as recommended for adults, unless there is a severe renal impairment (see ahead).
- *Patients with renal impairment*: The medicine may be administered to patients with impaired renal function. Doses indicated above may be given in patients with creatinine clearance of 20 mL/min or above. In patients whose creatinine clearance is less than 20 mL/min, it is recommended not to exceed a daily dose of 200 mg. This dose should also not be exceeded in patients undergoing chronic peritoneal dialysis or hemodialysis, since cefixime is slowly removed from circulation by dialysis.

In patients with impaired liver function, there is an increase on time required for reaching the maximum serum concentration of cefixime, however this does not require changes of posology in these patients.

Tricef tablet formulation is not intended for pediatric use.

Concomitant administration with food may increase the time required to reach the Cmax not interfering with AUC24 or T1/2β, effect with no clinical relevance.

4.3 Contraindications

Hypersensitivity to the active substance and, in general, to beta-lactam antibiotics or to any of the excipients mentioned in section 6.1.

4.4 Special warnings and precautions for use

Tricef should be used with caution during pregnancy and lactation, the contraindications related to hypersensitivity to cefixime or its excipients should be respected, and also the dose reduction in renal impaired patients should be observed.

Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of cross-allergy between penicillins and cephalosporins, as severe reactions (including anaphylaxis) to both classes have been observed (see section 4.3).

Cases of severe skin reactions with cefixime, as toxic epidermal necrolysis, Stevens-Johnson syndrome or rash with eosinophilia and systemic symptoms (DRESS) were reported. If a severe adverse skin reaction occurs, the use of cefixime should be immediately discontinued and appropriate therapeutic measures should be triggered.

Like other cephalosporins, cefixime may also lead to acute renal impairment, including interstitial nephritis. When acute renal impairment occurs, cefixime should be discontinued and appropriate therapeutic measures should be adopted.

Tricef should be used with caution particularly in the presence of severe renal impairment (see section 5.2).

Prolonged use of cefixime may cause overgrowth of non-sensitive agents. The treatment with broad spectrum antibiotics alters the normal flora of the colon and can lead to the colonization by *Clostridium* strains. Studies indicate that the toxin produced by *Clostridium difficile* is the major cause of antibiotic associated diarrhea. The pseudomembranous colitis is associated with the use of broad spectrum antibiotics (macrolides, semi-synthetic penicillins, lincosamides and cephalosporins including cefixime). It is important to consider this diagnosis in patients who develop diarrhea associated with antibiotic use.

Some patients with severe diarrhea due to pseudomembranous colitis, developed during or after the use of cefixime, have been at risk of life, thus it should be considered (see section 4.8). In case of suspicion, the use of cefixime should be discontinued and appropriate treatment measures should be initiated. Digestive endoscopic procedures, such as sigmoidoscopy or bacteriological might be necessary. Treatment measures include fluids, electrolytes and protein supplements. If colitis does

not ameliorate after drug discontinuation or if symptoms get worse, treatment with oral vancomycin is indicated. This is the antibiotic of choice in pseudomembranous colitis by *C. difficile*. Other causes of colitis should be excluded. The use of drugs that inhibit intestinal peristalsis is contraindicated.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids do not interfere with the absorption of cefixime. The tubular reabsorption inhibitors such as probenecid may hinder the urinary excretion of cefixime by increasing the values of Cmax and AUC24.
The salicylates and other nonsteroidal anti-inflammatories can displace cefixime from of its plasma protein binding, thereby increasing the concentration of free fraction.

In common with most cephalosporins, increases in prothrombin times have been noted in a few patients. Thus, caution is recommended in the administration of cefixime in patients undergoing anticoagulant treatment and adjustment of frequency of monitoring of the International Normalized Ratio (INR).

The administration of cefixime may reduce the effectiveness of oral contraceptives. It is therefore recommended to take additional non-hormonal contraceptives measures.
False positive results can be observed in the urine glucose determination with cupric reagents, but not by those using glicoxidase. A false positive Coombs test may also be presented as it happens with most of cephalosporins.

4.6 Fertility, pregnancy and lactation

In preclinical trials no differences were detected between the group of animals of control and the group that received the drug, with respect to fertility parameters, namely mating behavior, pregnancy rate, duration of pregnancy or delivery. The transplacental transfer of cefixime was about 1% of the dose administered to pregnant rats. The transfer through breast milk was about 1.5% of the total given to the mother.

Although animal experience does not suggest any kind of toxicity during pregnancy, the harmlessness of cefixime during pregnancy in humans is unclear. Tricef should not be used during pregnancy and lactation unless the doctor considers its use essential.

4.7 Effects on ability to drive and use machines

No effects were observed on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects (according to the results of clinical trials) are listed in order of decreasing seriousness within each frequency class.
The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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

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

MedDRA System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Bacterial superinfection Fungal superinfection Antibiotic-associated colitis (see section 4.4)	Rare Very rare
Blood and lymphatic system disorders	Eosinophilia	Rare
Immune system disorders	Hypersensitivity Anaphylactic shock, rheumatoid arthritis	Rare Very rare
Metabolism and nutrition disorders	Anorexia	Rare
Nervous system disorders	Headache Vertigo Psychomotor hyperactivity	Uncommon Rare Very rare
Gastrointestinal disorders	Diarrhea Abdominal pain, nausea, vomiting Flatulence	Common Uncommon Rare
Hepatobiliary disorders	Hepatitis, jaundice	Rare
Skin and subcutaneous disorders	Rash Rash with eosinophilia and systemic symptoms (DRESS) Erythema multiforme Pruritus Stevens-Johnson Syndrome Toxic epidermal necrolysis Hives	Uncommon Rare Very rare
Renal and urinary disorders	Interstitial nephritis	Very rare
General disorders and administration site conditions	Mucosal inflammation, fever	Rare
Investigations	Hepatic enzyme increased (transaminase, alkaline phosphatase) Bloodurea increased Blood creatinine increased	Uncommon Rare 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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

There is no information about cases of overdose. Doses of 2 g in healthy adults caused moderate gastrointestinal effects as those seen with therapeutic doses.
In case of acute poisoning it is likely to occur diarrhea, vomiting and abdominal pain.
No specific antidote exists. Gastric lavage is indicated (if intake occurred for less than 2 hours) and the patient should be hydrated and, if necessary, electrolytically balanced.
Peritoneal dialysis and hemodialysis do not remove the antibiotic from the circulation in clinical significant quantities.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.2.3 - Anti-infectious drugs. Antibacterials. Cephalosporins. 3rd generation cephalosporins, ATC code: J01D D08 cefixime

Mechanism of action
Cefixime, the only active substance of Tricef, is a bacterial agent belonging to the 3rd generation cephalosporins class.
As a beta-lactam antibiotic, acts by inhibiting bacterial cell wall synthesis. It is therefore a bactericidal antibiotic. Due to the introduction of a carboxymethoxy-imino radical in position 7 of cephemic core, cefixime has a high resistance to inactivation by most of the beta-lactamases produced by gram-positive or gram-negative bacteria. This characteristic translates into a similar activity on susceptible bacteria, whether they are or not beta-lactamases producers.

PK/PD Relationship
The time that the plasma concentration of cefixime exceeds the MIC (minimum inhibitory concentration) of the infecting organism has
been shown to best correlate with efficacy in PK/PD studies.
The best therapeutic response is estimated to occur when T> MIC is at least 40-50% of the interval between doses.

Mechanism of resistance
Bacterial resistance to cefixime may be due to one or more of the following mechanisms:
-Hydrolysis by beta-lactamases, induced or de-repressed in certain aerobic gram-negative bacterial species;
- Reduced affinity of penicillin binding proteins for cefixime;
- Reduction in permeability of the outer membrane of Gram-negative bacteria;
- Expression of membrane 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 beta-lactam antibiotics or to antibiotics of other classes.

Values of critical concentrations (breakpoints)
The breakpoints established for cefixime by EUCAST (European Committee on Antimicrobial Susceptibility Testing) in April 2010, 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 sensitive, resistant > 0.12 mg/L
- *Enterobacteriaceae*: sensitive ≤ 1.0 mg/L, resistant> 1.0 mg/L (for uncomplicated urinary tract infections only). Screening of the production of ESBL (extended spectrum beta-lactamases) may be necessary for infection control, surveillance or epidemiology purposes.

The prevalence of acquired resistance may vary geographically and with time. For selected species, local information on resistance is desirable particularly when treating severe infections. Expert advice should be sought when the local prevalence is such that the efficacyof the agent, in some types of infections, is questionable.

Susceptible species
Aerobes, Gram positive *Streptococcus pneumoniae* (penicillin-susceptible) *Streptococcus pyogenes*
Aerobes, Gram negative *Escherichia coli* % *Haemophilus influenzae* *Klebsiella species* % *Moraxella catarrhalis* *Proteus mirabilis* %
Species for which acquired resistance may be a problem *Enterobacter* species
Naturally resistant species *Clostridium difficile* *Bacteroides fragilis* *Enterococci* *Pseudomonas species* *Staphylococcus aureus*+ *Streptococcus pneumoniae* (penicillin-resistant)

% ESLB producing isolates are always resistant
+Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin)

5.2 Pharmacokynetic properties

Absorption

The presence of a vinyl radical in position 3 gives cefixime a satisfactory ability to be orally absorbed. In fact, the oral bioavailability of this antibiotic is about 48-50%. The presence of food does not affect the oral absorption of cefixime. Tmax is slightly wider, however the Cmax and AUC24 are not modified.

Repeated therapeutic doses do not cause accumulation in the body, either in adults or in children.

Distribution

Serum protein binding of cefixime is about 70% and the free fraction diffuses well to various body tissues, except CNS. The antibiotic penetrates well into the maxillary sinuses, middle ear, respiratory tract (including the bronchial secretions), tonsils, prostatic fluid and tissue and other organs.

After a dose of 400 mg, in adults, the concentrations in the tissue of the gallbladder and the bile are approximately 20 and 190 mcg/mL, respectively, 4 to 12 hours after ingestion of the antibiotic. Urinary concentrations are also high.

Biotransformation

Cefixime undergoes moderate metabolization in the body, and is essentially excreted, in active form, mainly by the bile, and in appreciable amount (20 to 30% of the absorbed dose) in urine.

The excretion of cefixime is slow, whereby the T1/2β is quite long (about 4 hours), which ensures a good coverage compared to susceptible bacteria in the 24 hours following a single administration of 400 mg in adults or 8 mg/kg in children.

Elimination

Concentrations in urine and bile are very high, since the elimination takes place through these pathways.

Special Populations

- Children:

There is a longer half-life, a higher AUC24 and an increased urinary excretion in infants when compared with older children, whose pharmacokinetic parameters are comparable to those of adults.

- Elderly patients;

In elderly patients (65-74 years), Cmax and AUC24 have values slightly higher than in young adults (20 to 32 years). However, these differences do not justify a lower dose for the elderly.

- Hepatic impairment:

No change was found in Cmax or AUC24 in cirrhotic patients after administration of 200 mg of cefixime, however the time for Cmax and T1/2β are increased, as well as renal clearance. No metabolites were detected in serum or urine.

- Renal impairment:

Although only 20 to 30% of the absorbed dose is excreted in the urine, Cmax and T½β increase, for a given dose, as renal impairment is more severe. Thus, if these increases are not enough to require a dose reduction, for a creatinine clearance greater than 20 mL/min, the same does not happen when creatinine clearance is 20 mL/min or lower. In these latter circumstances Cmax can double and T½β almost tripling and it is then necessary to reduce the dosage by half (usually to 200 mg/day for adults and 4 mg/kg daily for children).
Hemodialysis and peritoneal dialysis removes from blood only small amounts of cefixime, a fact that has no clinical relevance.

5.3 Preclinical safety data

The studies conducted in rodents and dogs have shown that cefixime is devoid of toxic effects at single or repeated administrations. There were not detected mutagenic or clastogenic properties. The capacity and reproductive behavior of the tested animals was not altered. In rats and mice at cefixime is not teratogenic.
The long-term carcinogenic effect was not assessed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose
Starch pregelatinized
Calcium hydrogen phosphate dihydrate
Magnesium stearate
Liquid paraffin
Hidroxypropylmethylcellulose
Sodium lauryl sulphate and
Titanium dioxide (E171).

6.2 Incompatibilities
Not known.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store at temperature below 25ºC.

6.5 Nature and contents of container
Tricef tablets are conditioned in Alu/Alu blisters and inserted in cardboard box. Packs of 1, 6, 8, 12 film-coated tablets.
Not all packs sizes may be marketed.

6.6 Special precautions for disposal and other handling
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

Bialport - Produtos Farmacêuticos, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

MA1550/00101

9. DATE OF FIRST AUTHORISATION

Date of first authorization: 16th February 2024

10. DATE OF REVISION OF THE TEXT

February 2024