SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

FIXIME 200 mg FILM COATED TABLETS

FIXIME 400 mg FILM COATED TABLETS

COMPOSITION:

FIXIME Film Coated Tablets 200 mg: Each tablet contains 200 mg cefixime.

FIXIME Film Coated Tablets 400 mg: Each tablet contains 400 mg cefixime.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Antimicrobial (Chemotherapeutic) agents – Broad and Medium Spectrum Antibiotics.

PHARMACOLOGICAL ACTION:

Cefixime is an orally active third generation cephalosporin antibiotic which has *in-vitro* bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms including *Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Klebsiella species, Haemophilus influenza* (beta-lactamase positive and negative), *Moraxella (Branhamella) catarrhalis* (beta-lactamase positive and negative). **Cefixime** is stable in the presence of beta-lactamase enzymes.

The mechanism of action of cefixime is based on inhibition of bacterial cell wall synthesis.

Most strains of enterococci (*Streptococcus faecalis,* group D *Streptococci)* and *Staphylococci* (including coagulase positive and negative strains and methicillin-resistant strains) are resistant to **Cefixime**. In addition, most strains of *Enterobacter and Pseudomonas, Bacteroides fragilis, Listeria monocytogenes and Clostridia* are resistant to **Cefixime.**

INDICATIONS:

FIXIME is indicated for the treatment of infections when caused by susceptible micro-organisms.

Upper respiratory tract infections (infections of the ear, nose and throat); e.g. bacterial pharyngitis, tonsillitis, otitis media, sinusitis, laryngitis.

Lower respiratory tract infections; e.g. bronchitis

Urinary tract infections; e.g. acute cystitis.

Uncomplicated gonorrhoea.

FIXIME is not suitable to treat staphylococcal infections, since staphylococci are resistant.

CONTRA-INDICATIONS:

FIXIME must not be used in patients hypersensitive to cefixime, to other cephalosporins, or to any of the excipients.

WARNINGS:

FIXIME should be given with caution to patients who have shown hypersensitivity to other cephalosporins.

FIXIME should be given with caution to patients allergic to beta-lactam antibiotics such as penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Patients have had severe reactions (including anaphylaxis) to both classes of medicine.

If an allergic effect occurs with **FIXIME**, the medicine should be discontinued and the patient treated with appropriate agents if necessary.

In patients with asthma and allergic diathesis particular caution is recommended.

FIXIME should be administered with caution in patients with markedly impaired renal function (See “Dosage in Renal Impairment”).

Short or prolonged use of **FIXIME** may result in the overgrowth of non-susceptible organisms.

FIXIME has been shown to alter the normal flora of the colon and may permit overgrowth of

Clostridia. Studies indicate a toxin(s) produced by *Clostridium difficile* is the primary cause of antibiotic associated pseudomembraneous colitis.

Severe and persistent diarrhoea requiring medical intervention, may develop. **Fixime** should be discontinued if diarrhoea occurs and corrective treatment has to be started.

In patients with severe gastrointestinal disturbances involving vomiting and diarrhoea treatment with **FIXIME** is not recommended.

Caution is recommended in patients concomitantly treated with diuretics (e.g. furosemide) and/or other potentially nephrotoxic medicinal products (e.g. aminoglycoside antibiotics), especially in patients with underlying medical conditions, where renal ischaemia can be expected (e.g. severe infections, septicaemia). In these patients, impairment of renal function and even acute renal failure, caused by such combinations, may occur. Careful monitoring of renal function is necessary.

Renal impairment

In patients with severely impaired renal function particular caution is recommended. Close monitoring and dose adaptation are recommended.

Neonates

Safety and efficacy have not been established in neonates including preterm neonates. Therefore, the administration of Fixime is not recommended in neonates.

INTERACTIONS

- Potentially nephrotoxic substances such as aminoglycoside antibiotics, colistin, polymyxin, viomycin or potent diuretics may increase the risk of impairment of renal function, when used concomitantly with **FIXIME**

- The calcium-channel blocker nifedipine increases the bioavailability of **FIXIME** film-coated tablets. However, no dose adaptation is recommended.

- Platelet aggregation inhibitors: hypoprothrombineamia induced by large doses of salicylates and/or cephalosporins, and the gastrointestinal ulcerative or haemorrhagic potential of nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, or sulfinpyrazone may increase the risk of haemorrhage.
- Interference with laboratory tests.

- 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 has been reported during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs test may be due to the medicine.

- Probenecid: decreases renal tubular secretions in increased and prolonged cephalosporin serum concentrations, prolonged elimination half-life, and increased risk of toxicity; however, cefixime and probenecid might be used concurrently in the treatment of infections, such as sexually transmitted diseases (STDs) or other infections, in which high and/or prolonged antibiotic serum and tissue concentrations are required.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Absorption of **FIXIME** is not significantly modified by the presence of food. The usual course of treatment is 5 -14 days. The film-coated tablet has to be taken with plenty of liquid either before or during a meal.

Adults and Children over 12 years:

The recommended adult dosage is 200 – 400 mg daily given either as a single dose or in two divided doses.

In **lower respiratory tract infections**, 400 mg daily is recommended.

For **upper respiratory tract infections** and **uncomplicated urinary tract infections**, 200 mg once daily is usually effective.

For **uncomplicated infections of the lower urinary tract**, in general, treatment over 1 to 3 days is sufficient.

For **sinusitis** the therapeutic dosage must be administered for 10 to 14 days.

Treatment of Uncomplicated Gonorrhoea:

The recommended dosage is 400 mg as a single oral dose.

The Elderly: Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed, and dosage should be adjusted in severe renal impairment. (See "Dosage in Renal Impairment").

Dosage in Renal Impairment: Patients with impaired renal function may require a reduction in dose of **FIXIME** as follows:

Creatinine Clearance (ml/min)/ml/sec)	**Dose**
> 60/1.00	200 mg every 12 hours; 400 mg once daily.
21 – 60/0.35 – 1.00 or haemodialysis patients	75 % of standard dosing at standard dosing interval.
< 20/0.33 or chronic ambulatory peritoneal dialysis (CAPD) patients	50 % of standard dosage at standard dosing intervals.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The following definitions apply to the frequency terminology used hereafter:

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)

Immune system Disorders:

Rare: Hypersensitivity reactions of varying degrees such as flush, palpitations, dyspnoea, hypotension, bronchospasm, angioneurotic oedema.

Very rare: Anaphylactic shock, serum sickness-like reactions.

Skin and subcutaneous tissue Disorders:

Uncommon: Rashes, erythema, exanthema.

Rare: Pruritus, mucosal inflammation.

Very rare: Toxic Epidermal Necrolysis, Stevens-Johnson syndrome, Erythema exudativum multiforme.

Renal and urinary Disorders:

Rare: Transient elevation in urea concentrations.

Very rare: Elevation is serum creatinine, interstitial nephritis.

Caution is recommended in patients concomitantly treated with diuretics and/or other potentially nephrotoxic medicinal products, especially in patients with underlying medical conditions, where renal ischaemia can be expected. In these patients, impairment of renal function and even acute renal failure, caused by such combinations, may occur. Careful monitoring of renal function is necessary.

Infections and Infestations:

Rare: Superinfections with resistant bacteria or fungi after long-term and repeated administration.

Common: Oral candidiasis (sore mouth or tongue), Vaginal candidiasis (vaginal itching and discharge)

Nervous System Disorders:

Uncommon: Headache

Rare: Dizziness

Very rare: Transient hyperactivity.

An increased tendency to seizures cannot be excluded.

Gastro-intestinal Disorders:

Common: Loose stools, diarrhoea

Uncommon: Disturbances in the form of abdominal pain, indigestion, nausea and vomiting

Rare: Lack of appetite, flatulence

Very rare: Antibiotic-associated inflammation of the large intestine, pseudomembranous colitis.

General Disorders and administration site conditions:

Rare: Drug fever

Blood and Lymphatic System Disorders:

Rare: Eosinophilia.

Very rare: Leukopenia, agranulocytosis, pancytopenia, thrombocytopenia and further changes in the blood count. These adverse reactions return usually to normal spontaneously after the end of therapy.

Coagulation disorders, haemolytic anaemia.

Hepatobiliary Disorders:

Uncommon: Reversible elevation in hepatic enzymes (transaminases, alkaline phosphatase) in serum

Very rare: Hepatitis, cholestatic jaundice.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No specific antidote exists. **FIXIME** is not removed from the circulation in significant quantities by dialysis. Treatment is symptomatic and supportive.

IDENTIFICATION:

Tablets 200 mg: White, convex, rectangular film-coated tablets with rounded corners and beveled edges and with a divided breakline on each side and EM 72 impressed on the one side.

Tablets 400 mg: White, convex, rectangular film-coated tablets with rounded corners and beveled edges and with a divided breakline on each side impressed on the one side.

PRESENTATION:

Tablets 200 mg and 400 mg. Blister packs containing 1, 3, 5 and 10 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in the original pack or in containers which prevent access of light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

FIXIME Film-coated tablets 200 mg: W/20.1.1/255

FIXIME Film-coated tablets 400 mg: W/20.1.1/256

NAME AND BUSINESS ADDRESS OF APPLICANT:

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