SCHEDULING STATUS

S4

1. **NAME OF MEDICINE:**

   EXSEF 400 FILM COATED TABLET

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   Each film coated tablet contains Cefixime Trihydrate equivalent to Cefixime 400 mg

   For the full list of excipients, see **section 6.1**

   Sugar free

3. **PHARMACEUTICAL FORM**

   Film-coated tablets.

   White, to off white, film coated, oblong shaped tablets, with a deep score line on each side, debossed with “A” and “10” on one side and plain on other side.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic Indications

EXSEF 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 gonorrhea.

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

4.2 Posology and method of administration

Posology

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 **EXSEF** 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

Paediatric population

EXSEF is not recommended in children < 12 years.

Method of administration

For oral administration.

Absorption of **EXSEF** 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.

4.3 Contraindications

EXSEF must not be used in patients hypersensitive to cefixime, to other cephalosporins, or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship

Encephalopathy

Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.

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.

EXSEF should be given with caution to patients who have shown hypersensitivity to other drugs.

Hypersensitivity to penicillins

As with other cephalosporins, cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins.

Patients have had severe reactions (including anaphylaxis) to both classes of medicines. If an allergic effect occurs with **EXSEF**, the drug should be discontinued, and the patient treated with appropriate agents if necessary.

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

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.

Renal impairment

EXSEF should be administered with caution in patients with markedly impaired renal function (See section 4.2).

Paediatric

Safety of cefixime in premature or newborn infants has not been established

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment.

Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the medicine has been discontinued, or if the symptoms are severe, oral vancomycin is the medicine of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

4.5 Interaction with other medicines and other forms of interaction

Anticoagulants

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.

Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin potassium. Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

Other forms of interaction

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 recognised that a positive Coombs test may be due to the medicine.

Use with probenecid:

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.

Other nephrotic medicines:

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 **EXSEF**,

- The calcium-channel blocker nifedipine increases the bioavailability of **EXSEF**, **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.

Laboratory investigations

Changes in renal and liver functions tests have been observed (see section 4.8)

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established

Breast feeding

Safety in lactation has not been established

Fertility

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 foetus.

Effects on ability to drive and use machines

EXSEF may have an effect on the ability of patients to drive or operate complex machines

4.8 Undesirable effects

Infections and infestations:

Frequent: Oral candidiasis (sore mouth or tongue), vaginal candidiasis (vaginal itching and discharge), pseudomembranous colitis

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

Blood and Lymphatic System disorders:

Less frequent: Eosinophilia, 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

Immune System disorders:

Less frequent: Hypersensitivity reactions of varying degrees such as flush, palpitations, dyspnoea, hypotension, bronchospasm, angioedema, anaphylactic shock, serum sickness-like reactions, drug rash with eosinophilia and systemic symptoms (DRESS), urticaria, arthralgia.

Nervous system disorders:

Less frequent: Headache dizziness, transient hyperactivity, an increased tendency to seizures cannot be excluded

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea

Gastrointestinal disorders.

Frequent: Diarrhoea, loose stools

*Less frequent: N*ausea, abdominal pain, dyspepsia, vomiting, flatulence, pseudomembranous colitis, lack of appetite, antibiotic associated inflammation of the large intestine.

Hepato-biliary disorders:

Less frequent: Reversible elevation in hepatic enzymes (transaminases, alkaline phosphatase) in serum, hepatitis, cholestatic jaundice

Skin and subcutaneous tissue disorders:

Less frequent: Rashes, erythema, exanthema, pruritus, mucosal inflammation. toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema exudativum multiforme.

Renal and Urinary disorders:

Less Frequent: Transient elevation in urea concentrations, elevation of serum creatinine, interstitial nephritis.

Investigations:

Less frequent: Positive Coombs' test, Changes in liver and renal function tests have been observed.

4.7 Overdose

There is a risk of encephalopathy in cases of administration of beta-lactam antibiotics, including cefixime, particularly in case of overdose or renal impairment. 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.
Cefixime is not removed from the circulation in significant quantities by dialysis.
No specific antidote exists. General supportive measures are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

***Class of medicine*:** Antimicrobial (Chemotherapeutic) agents – Broad and Medium Spectrum Antibiotics; A 20.1.1

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.

5.2 Pharmacokinetic properties

The absolute oral bioavailability of cefixime is in the range of 22-54%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.
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.
The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5

days. Mean C_{max} and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.
Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.

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.

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). No data are available on secretion of cefixime in human breast milk. Placetal transfer of cefixime was small in pregnant rats dosed with labelled cefixime

5.3 Pre-Clinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the professional information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate, starch pregelatinised, cellulose, microcrystalline, magnesium stearate, hypromellose, titanium dioxide, macrogol, triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special Precautions for storage

Store at or below 25 °C in the original pack away from light and moisture.

6.5 Nature and contents of container

1’s - PVC/ Aclar or PVC/PVdC clear film and foil blister pack containing 1 tablet in a blister. The blister is packed in a printed carton

5’s - PVC/ Aclar or PVC/PVdC clear film and foil blister pack containing 5 tablets per blister strip. Blister strips are packed in a printed carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT