SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FIMABUTE 100 (Cefixime for Oral Suspension USP 100mg/5ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of reconstituted suspension contains:

Cefixime As trihydrate USP

Equivalent to anhydrous Cefixime 100mg

3. PHARMACEUTICAL FORM

For oral Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Therapeutic indications Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms.

Acute exacerbations of chronic bronchitis Community-acquired Pneumonia Lower urinary tract infections Pyelonephritis

In the treatment of: Otitis media Sinusitis Pharyngitis

The use of Cefixime should be reserved for infections where the causative organism is known or suspected to be resistant to other commonly used antibiotics, or where treatment failure may carry significant risk.

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

4.2 Posology and method of administration

Adults and children over 10 years of age (body weight is greater than 50 kg) The recommended dose is 200-400 mg daily according to the severity of the infection, given either as a single dose or in two divided doses.

Elderly patients Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe impairment (See dosage for renal impairment and section 4.4).

Children younger than 10 years of age (body weight is lower than 50 kg) – Paediatric Oral Suspension The recommended dosage for children is 8 mg/kg/day administered as a single dose or in two divided doses. The following table describes a range of paediatric dosage according to the weight of the child:

Child’s weight Daily dose Daily dose according to the syringe graduations 5 kg 40 mg 2 ml (once daily) or 1 ml (twice daily) 10 kg 80 mg 4 ml (once daily) or 2 ml (twice daily) 12.5 kg 100 mg 5 ml (once daily) or 2.5 ml (twice daily) 15 kg 120 mg 6 ml (once daily) or 3 ml (twice daily) 17.5 kg 140 mg 7 ml (once daily) or 3.5 ml (twice daily) 20 kg 160 mg 8 ml (once daily) or 4 ml (twice daily) 22.5 kg 180 mg 9 ml (once daily) or 4.5 ml (twice daily) 25 kg 200 mg 10 ml (once daily) or 5 ml (twice daily)

Children weighing more than 50 kg or older than 10 years should be treated with the recommended adult dose (200 -400 mg daily), depending on the severity of the infection.

Children younger than 6 months of age The safety and efficacy of cefixime has not been established in children less than 6 months.

Renal impairment Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearance of 20 ml/ min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearance of less than 20 ml/min.

Method of administration Cefixime powder for oral suspension is for oral administration only. The absorption of cefixime is not significantly affected by the presence of food. Hence it can be administered with or without food.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Duration of treatment The usual course of treatment is 7 days. In severe cases, this can be extended to 14 days.

4.3 Contraindications

Patients with known hypersensitivity to cefixime, other cephalosporin antibiotics or to any of the excipients.

Cefixime is also contraindicated in patients with previous, immediate and/or severe hypersensitivity to penicillin or any beta-lactam antibiotics and preterm and term newborn infants (0-27 days).

4.4 Special warnings and precautions for use

who have shown hypersensitivity to other drugs. Cephalsporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allerginicity between penicillin and cephalsporins.

Patients have had severe reactions (including anaphylaxis) to both classes of drugs. Special care is indicated in patients who have experienced any allergic reaction to penicillins or any beta-lactam antibiotics as cross-reactions may occur (see section 4.3).

If severe hypersensitivity reactions or anaphylactic reactions occur after administration of Cefixime, the medicine should be discontinued immediately and appropriate emergency measures should be initiated.

Prolonged use of cefixime may result in the overgrowth of non-susceptible organisms.

Treatment with a broad spectrum of antibiotics alters the normal flora of the colon and may permit the overgrowth of Clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause for antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalsporins). It is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics.

In patients who develop severe diarrhoea during or after use of cefixime, the risk of life threatening pseudo-membranous colitis should be taken into account (see section 4.8). The use of cefixime should be discontinued and appropriate treatment measures should be established. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolyte and protein supplementation. If the colitis does not improve after the drug has been discontinued or if the symptoms are severe, oral vancomycin is the drug of choice for antibioticassociatedpseudomembreanous colitis produced by C. Difficile. Other causes of

colitis should be excluded. The use of medicinal products inhibiting the intestinal peristalsis is contra-indicated.

Cefixime contains sucrose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

Use of Nifedipine, a calcium channel blocker, may increase bioavailability of Cefiximeupto70%.

Renal insufficiency Cefixime should be administered with caution in adult patients with creatinine clearance <20ml/min (see sections 4.2 and 5.2). There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency: the use of cefixime in these patient-groups is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

The administration of cephalsporins may interfere with the results of some laboratory tests.

A false positive reaction for glucose in the urine may occur with the 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 drug.

In common with other cephalsporins, increases in prothrombin times have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

In use with Nifedipine, a calcium channel blocker, may increase bioavailability ofCefiximeupto 70%.

4.6 Pregnancy and lactation

Pregnancy For cefixime, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Cefixime should not be used in pregnant mothers unless considered essential by the physician.

Breast-feeding It is unknown whether cefixime is excreted in human milk and non-clinical studies have shown excretion of cefiximein animalmilk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with cefixime should be made taking into account the benefit of breast-feeding to the child and the

benefit of cefixime therapy to the woman. However, until further clinical experience is available, cefixime should not be prescribed to breast-feeding mothers.

Fertility Animal studies do not indicate any harmful effects with respect to fertility, however, no clinical data are available

4.7 Effects on ability to drive and use machines

Cefixime has no known influence on the ability to drive and use machines. However, side effects may occur (see section 4.8), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Cefixime, like other cephalsporin antibiotics, may be associated with adverse events.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects have been divided in the following categories:

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 Not known: cannot be estimated from the available data

MedDRA System Organ Class

Adverse Reaction Frequency

Superinfection bacterial, superinfection fungal

Rare

Infections and infestations

Antibiotic-associated colitis (see section

Very rare

Eosinophilia Rare

Blood and lymphatic system disorders

Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia

Very rare

Hypersensitivity Rare Immune system disorders Anaphylactic shock, serum sickness Very rare Metabolism and nutrition disorders Anorexia Rare Headache Uncommon Vertigo, dizziness Rare Nervous system disorders Psychomotor hyperactivity Very rare

Diarrhoea Common Abdominal pain, nausea, vomiting Uncommon Flatulence Rare

Gastrointestinal disorders

Cases of pseudomembraneous colitis

Very rare

Hepatobiliary disorders Hepatitis, cholestatic jaundice Very rare Rash Uncommon Angioneurotic oedema, pruritus Rare Skin and subcutaneous disorders Stevens-Johnson Syndrome, toxic epidermal necrolysis, Lyell syndrome Very rare Renal and urinary disorders Interstitial nephritis Very rare General disorders and administration site conditions Mucosal inflammation, pyrexia Rare Hepatic enzyme increased (transaminase, alkaline phosphatase) Uncommon Blood urea increased Rare Investigations Blood creatinine increased Very rare

4.9 Overdose

Adverse reactions seen at dose levels up to 2 g of cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Gastric lavage may be indicated in overdosage. No specific antidote exists. Cefixime is not removed from the circulation in significant quantities by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antibacterial for systemic use, belonging to the class of cephalsporins, ATC code: J01DD08.

Mode of action Cefixime is an antibiotic belonging to the third generation cephalosporin group.

Like other cephalsporins, cefixime exerts antibacterial activity by binding to and inhibiting the action of penicillin-binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

PK/PD Relationship

The time that the plasma concentration of cefixime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in PK/PD studies.

Mechanism of resistance Bacterial resistance to cefixime may be due to one or more of the following mechanisms:

• Hydrolysis by extended-spectrum beta-lactamases and/or by chromosomally-encoded (AmpC) enzymes that may be induced or de-repressed in certain aerobic gram- negative bacterial species

• Reduced affinity of penicillin-binding proteins

• Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins

• 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-lactams and/or antibacterial drugs of other classes.

Breakpoints Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (May 2009) for cefixime are:

Breakpoints (MIC, mg/L) Microorganism Susceptible (≤) Susceptible (≤) Resistant (>) Haemophilusinfluenzae 0.12 mg/L 0.12 mg/L Moraxella catarrhalis 0.5 mg/L 1.0 mg/L Neisseria gonorrhoeae 0.12 mg/L 0.12 mg/L Enterobacteriaceae 1.0 mg/L 1.0 mg/L Enterobacteriaceae: For uncomplicated urinary tract infections only. The breakpoints for Enterobacteriaceae will detect reduced susceptibility mediated by most clinically important beta-lactamases in Enterobacteriaceae. Occassional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production. Non-species related breakpoints Insufficient data

Susceptibility The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections.

As necessary, expert advice should be sought when local prevalence if resistance is such that the utility of the agent in at least some types of infections is questionable.

Category 1: Commonly Susceptible organisms Aerobes, Gram-positive Aerobes, Gram-negative Streptococcus pneumoniae (penicillinsusceptible) Escherichia Coli% Streptococcus pyogenesHaemophilusinfluenzaeKlebsiella species% Morexellacatarrhalis Proteus mirabilis%

Category 2: Organisms for which acquired resistance may be problematic Enterobacter species

Category 3: Resistant organisms Clostridium difficileBacteroidesfragilis Enterococci Pseudomonas species Staphylococcus aureus+ Streptococcus pneumoniae (Penicillin resistant)

% Extended spectrum beta-lactamase (ESBL) producing isolates are always resistant + Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin)

5.2 Pharmacokinetic Properties

The absolute 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 for meals.

Distribution 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.

From in vitro studies, serum or urine concentrations of 1 mg/L 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 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.

Metabolism and elimination 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.

Transfer of 14C-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. Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

Special age groups The pharmacokinetics of cefixime in healthy elderly (aged > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean

Cmax and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population (see section 4.2)

5.3 Preclinical Saftey Data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, in vivo and in vitro studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted. Reproduction studies have been performed in mice and rats at does up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death, which is an expected consequence of the known hypersensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine.

6. Pharmaceutical Particulars

6.1 List of excipients

Aspartame,
Colloidal Silicon Dioxide,
Sucrose, Sucrose,
Sodium Benzoate,
Lactose,
Dry Flavour Strawberry,
Xanthan Gum

6.2 Incompatibility

Not applicable.

6.3 Shelf life

24 months

6.4 Special Precautions for Storage

Store at temperature not exceeding 30^{o}C. Protect from Protect from moisture

6.5 Nature and Contents of Container

20 g Dry Powder of Cefixime filled in White plastic bottle 60 ml making conical packed in a

unit carton.

6.6 Special Precautions for Disposal and Other Handling

Not Applicale

7. MARKETING AUTHORISATION HOLDER

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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

05299/3491/NMR/2017

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10. DATE OF REVISION OF THE TEXT

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