1.3
PRODUCT INFORMATION

1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals

1.3.1.1 Invented Name of the Medicinal Product

Cfxclav 325

(Cefixime 200 mg & Clavulanate potassium 125 mg Tablets)

1.3.1.2 Strength

Cefixime USP…….…..200 mg

Potassium Clavulanate BP……125 mg

1.3.1.3 Dosage Form

Oral Solid Dosage Form (Tablet)

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Cefixime (as Trihydrate) USP

Equivalent to Anhydrous Cefixime ……. 200mg

Diluted Potassium Clavulanate BP

Equivalent to Clavulanic Acid …… 125mg

Excipients……...Q.S.

Color …… Sunset Yellow

1.3.1.5 PHARMACEUTICAL FORM

Tablet

An orange colour, elongated, biconvex film coated Tablets.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1Therapeutic indications

Urinary tract infections

In uncomplicated urinary tract infections, cefixime (200 or 400 mg daily) has been shown to be comparable in efficacy with both sulfamethoxazole and trimethoprim combination (160/800 mg twice daily) and Amoxicillin (250 mg there times daily). All 76 children with urinary infection were cured in a comparative trial of once-daily cefixime (8 $mg.kg^{-1}$) and twice-daily trimethoprim/sulfamethoxazole.

Upper and lower respiratory tract infections

Good results have been obtained with cefixime in the treatment of bacterial pharyngitis and tonsillitis, mainly caused by Streptococcus pyogenes. Results compare favorably with those of Amoxicillin. Cefixime (8 $mg.kg^{-1}$ daily for 10 days) was significantly more effective in the treatment of streptococcal pharyngitis in children in the treatment of streptococcal pharyngitis in children then penicillin V (250 $mg.kg^{-1}$ every 8 h for 10 days) (45/48 versus 36/47). For acute bacterial sinusitis, a once-daily dose of amoxicillin given three times a day (50/53 versus 47/49). In acute pneumonia, acute and chronic bronchitis, and infected bronchiectasis, cefixime has been shown to be at least as effective as amoxicillin and cefaclor in terms of both clinical response and bacteriological clearance. In a double-blind trial, cefixime shower similar efficacy to a twice-daily dose of clarithromycin (97/110 versus 89/103)

Acute otitis media

In several studies of the treatment of children suffering from acute otitis media with effusion, cefixime was found to be as effective as standard doses of cefaclor, amoxicillin, and amoxicillin-clavulanate. Other studies have not found that diarrhea and gastrointestinal symptoms are more common in patients given cefixime than cafaclor (16/58 versus 4/50, 28/134 versus 8/129). Others failed to confirm this. Cefixime was more likely than amoxicillin to cure infections caused by Haemophilus influenzae.

Gonococcal urethritis

Cefixime given as a single 400 mg dose orally was found to be as effective a single intramuscular dose of ceftriaxone in gonococcal urethritis (83/93 versus 92/94) and pharyngitis. A single 800 mg dose was no more effective. Others have confirmed its efficacy but reported adverse effects (often diarrhea) in 10% of the cefixime group. Cefixime is not useful against Chlamydia trachomatis.

Typhoid

Cefixime (10 $mg.kg^{-1}$ per day for 14 days) has been found to have similar efficacy to intravenous ceftriaxone in the treatment of enteric fever caused by Salmonella typhi resistant to sulfamethoxazole and trimethoptim combination, ampicillin, and Chloramphenicol. In each group, 22 of 25 children were cured.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults and Children over 10 Years: One tablet twice daily. The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

1.3.1.6.3 CONTRAINDICATIONS

Cefixime is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

1.3.1.6.4 WARNING AND PRECAUTIONS

Cefixime should not be given to patients who are hypersensitive to it or to other cephalosporins. About 10% of penicillin-sensitive patients may also be allergic to Cephalosporins although the true incidence

is uncertain; great care should be taken if Cefixime is to be given to such patients. Care is also necessary in patients with known histories of allergy.

Cefixime should be given with caution to patients with renal impairment; a dosage reduction may be necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Probenecid: Concomitant administration of probenecid with cefuroxime axetil tablets increases the area under the serum concentration versus time curve by 50%. The peak serum cefuroxime concentration after a 1.5-g single dose is greater when taken with 1 g of probenecid (mean = 14.8 mcg/mL) than without probenecid (mean = 12.2 mcg/mL).

Antacids: Drugs that reduce gastric acidity may result in a lower bioavailability of CEFUROXIME-CLAV compared with that of fasting state and tend to cancel the effect of postprandial absorption.

Oral contraceptives: In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone.

1.3.1.6.6 PREGNANCY AND LACTATION

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Major adverse reactions which may occur are diarrhea/loose motions, nausea/vomiting, transient elevation in AST, ALT, LDH, Eosinophilia.
Other adverse events that may occur are abdominal pain, abdominal cramps, flatulence, indigestion, headache, vaginitis, vulvar itch, rash, hives, itch, dysuria, chills, chest pain, shortness of breath, mouth ulcers, swollen tongue, sleepiness, thirst, anorexia. the patient should not operate machines or drive a vehicle.

1.3.1.6.8 UNDESIRABLE EFFECTS

Early Lyme disease: Two adequate and well-controlled studies were performed in patients with early Lyme disease. In these studies all patients had to present with physician-documented erythema migrans, with or without systemic manifestations of infection. Patients were randomized in a 1:1 ratio to a 20-day course of treatment with cefuroxime axetil 500 mg twice daily or doxycycline 100 mg 3 times daily. Patients were assessed at 1 month posttreatment for success in treating early Lyme disease (Part I) and at 1 year post treatment for success in preventing the progression to the sequelae of late Lyme disease (Part II).

A total of 355 adult patients (181 treated with cefuroxime axetil and 174 treated with doxycycline) were enrolled in the 2 studies. In order to objectively validate the clinical diagnosis of early Lyme disease in these patients, 2 approaches were used: 1) blinded expert reading of photographs, when available, of the pretreatment erythema migrans skin lesion; and 2) serologic confirmation (using enzyme-linked immunosorbent assay [ELISA] and immunoblot assay [“Western” blot]) of the presence of antibodies specific to Borrelia burgdorferi, the etiologic agent of Lyme disease. By these procedures, it was possible to confirm the physician diagnosis of early Lyme disease in 281 (79%) of the 355 study patients. The efficacy data summarized below are specific to this “validated” patient subset, while the safety data summarized below reflect the entire patient population for the 2 studies.

Secondary Bacterial Infections of Acute Bronchitis: Four randomized, controlled clinical studies were performed comparing 5 days versus 10 days of CFXCLAV 325 for the treatment of patients with secondary bacterial infections of acute bronchitis. These studies enrolled a total of 1,253 patients (CAE-

516 n = 360; CAE-517 n = 177; CAEA4001 n = 362; CAEA4002 n = 354). The protocols for CAE-516 and CAE-517 were identical and compared CFXCLAV 325 mg twice daily for 5 days, CFXCLAV 325 mg twice daily for 10 days, and AUGMENTIN® 500 mg 3 times daily for 10 days. These 2 studies were conducted simultaneously. CAEA4001 and CAEA4002 compared CFXCLAV 325 mg twice daily for 5 days, CFXCLAV 325 mg twice daily for 10 days, and CECLOR® 250 mg 3 times daily for 10 days. They were otherwise identical to CAE-516 and CAE-517 and were conducted over the following 2 years. Patients were required to have polymorphonuclear cells present on the Gram stain of their screening sputum specimen, but isolation of a bacterial pathogen from the sputum culture was not required for inclusion.

1.3.1.6.9 OVERDOSE

Seek emergency medical attention

Overdose symptoms may include seizure (black-out or convulsions).

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Combinations of Cephalosporin, incl. beta-lactamase inhibitors.

Cefixime is an orally active, broad-spectrum antibiotic. Cefixime exhibits good in vitro activity (minimum inhibitory concentration for 90% of strains (MIC90 < 1 mg.l) against most of the Enterobacteriaceae, Haemophilus influenzae and Neisseria gonorrhoeae (including □-lactamase producing strains), □-hemolytic streptococci of groups A and B and Streptococcus pneumoniae. However, Staphylococcus aureus is considerably less susceptible, and fecal streptococci, Pseudomonas aeruginosa, most anaerobes, and Chlamydia trachomatis are in susceptible. Against Enterobacteriaceae, its activity is normally superior to that of Cefixime, Cefaclor and Cephalexin, but inferior to that of Ciprofloxacin. It is more active than sulfamethoxazole and Trimethoprim combination against certain species (Providencia stuartii, Proteus vulgaris and Klebsiella spp.) but less active against Escherichia coli, Enterobacter cloacae, and Enterobacter aerogenes. Against H. influenzae and N. gonorrhoeae, Cefixime has been shown to be highly inhibitory to all strains tested. For H. influenzae, this included

strains resistant to ampicillin, cefaclor, cephalexin, chloramphenicol, and sulfamethoxazole and trimethoprim combination.

Clavulanate Potassium

The preferred analytical method for clavulanic acid is high pressure liquid chromatography (HPLC). Where HPLC equipment is not available, a bioassay using agar plates preseeded with a □-lactamase producing strain of Klebsiella aerogenes may be used. The oral absorption of clavulanic acid is 75%.

A peak serum concentration of 5-6 mg clavulanic acid is obtained around 1 h after a 50 mg oral dose. Approximately 30-40 % of this dose can be recovered from the urine 6 h after dosage when taken together with amoxicillin (500 mg), absorption of clavulanic acid (250 mg) is approximately the same, with a serum peak of around 6 mg and a peak amoxicillin level of 10 mg both after 1 h. food does not significantly affect the absorption of clavulanic acid. The urinary recovery is about 27-32 % after a 250 mg dose of clavulanic acid in combination with amoxicillin. The plasma half-life is 0.8 1 h and plasma protein binding is 22-30 %.

Clavulanic acid is distributed throughout body tissues, in concentration similar to those in serum. Penetration of body fluids is more variable, and little crosses the blood-brain barrier into the CSF. Sputum penetration is poor. Very little of the drug is excreted in breast milk.

Oral absorption	75 %
Presystemic metabolism	---
Plasma half-life	
Mean	1 h
Volume of distribution	---
Plasma protein binding	22-30 %

Concentration-effect relationship

The activity of clavulanic acid is dependent upon the drug achieving concentration at the site of action above the minimum inhibitory concentration (MIC) for the particular organism. However, clavulanic acid is not used alone and therefore the MIC that matters is the combination of clavulanic acid plus penicillin derivative. The presence of clavulanic acid in a concentration of 0.5 mg reduces the MIC of amoxicillin for many bacteria. Therefore the MIC of amoxicillin for Staphylococcus aureus is reduced

from 197 mg to 1.1 mg resistant Haemophilus influenzae from 150 mg to 1.1 mg and for Klebsiella aerogenes from 315 mg to 2.5 mg .

When clavulanate is combined with ticarcillin the MIC of Staphylococcus aureus (strain NCTC 11 561) is reduced from 64 mg to 1 mg and the MIC of a ticarcillin-resistant strain of H. influenzae is reduced from 128 mg to 0.25 mg. similarly the MIC of Timentin for Klebsiella pneumoniae is 4 mg (compared with 128 mg for ticarcillin alone), and 2 mg for proteus vulgaris compared with 256 mg for ticarcillin alone (*the concentration for Timentin are expressed as the concentration of ticarcillin in the presence of 2 mg clavulanate.)

Metabolism

Up to 48 % of an intravenous dose and up to 38 % of an oral dose is excreted unchanged in urine. In animal studies, respiratory and urinary excretion of radiolabeled metabolites were the other major routes although the metabolic pathways unknown.

1.3.1.7.2 Pharmacokinetic properties

2.1.1.2 Pharmacokinetics:

Both high performance liquid chromatography (HPLC) with a sensitivity of 0.05 mg.1-1 and microbiological agar diffusion techniques (sensitivity is 0.1 mg.1-1) have been used to assay cefixime concentrations with good agreement between the two methods.

Oral absorption	60-80%
Presystemic metabolism	-
Plasma half-life	
range	2.5-3.8 h
mean	3 h
Volume of distribution	0.1I.kg^{-1}
Plasma protein binding	70%

Cefixime is absorbed slowly after oral administration, the time taken to reach maximum plasma concentrations (Tmax) increasing with increasing dose. It is likely that a significant proportion remains unabsorbed, as a much higher percentage of the drug is excreted renally when administered intravenously rather than orally (64.8% as opposed to 20%).

Cefixime has been shown in one study to have an absolute bio availability of about 50% when compared with an intravenous dose. After a 200 mg oral dose, peak plasma levels of an average of 2.7 mg.1-1 are achieved between 3 and 4 h postdose in fasting volunteers. In non-fasting volunteers, a slight delay in reaching peak plasma concentrations has been noted, without alteration of other pharmacokinetic parameters. Another study showed a 1 h delay in reaching peak plasma concentration, but that peak serum levels, area under the curve

(AUC) and 24 h recovery values were unchanged.

The mean volume of distribution of cefixime is 0.1 1.kg-1. Penetration into tissue fluid is slow (mean Tmax = 6.7h) but peak concentrations similar to those of plasma have been achieved. Lower levels have been found in other tissues, i.e, palatine tonsil, maxillary sinus mucosa sputum and middle ear discharge. Very high concentrations occur in bile. Between 3.5 and 12 h after single oral doses of 100, 200, or 400 mg mean biliary concentrations were 135, 134 and 190 mg.1-1, respectively. The biliary recovery of cefixime in 24 h is 5% of the administered dose, suggesting it is one of the most highly bile-excreted cephalosporins. CSF penetration is poor. After an oral dose of 400 mg to patients with non-inflamed meninges, the CSF level reached 0.17 mg.1-1 compared with serum level of 3.1 mg.1-1. For patients with meningitis, the mean CSF concentration was 0.22 mg.1-1. In normal healthy volunteers cefixime is approximately 70% protein –bound. No biologically active metabolites of cefixime have yet been discovered.

The mean elimination half-life (t ½) of 3 h is somewhat longer than those of earlier oral cephalosporins. Eg. cephalexin, cephradine and cefaclor (< 1 h), and cefadroxil (1.5h). Urinary excretion accounts for between 12 and 34% of an orally administrated dose much less than that of the above-mentioned drugs, which are more than 80% renally excreted. As probenecid appears to make little difference to the rate of excretion, it is likely that elimination occurs mainly via glomerular filtration. The t ½ of cefixime is only significantly prolonged in patients with severely impaired renal function (creatinine clearance < 20ml.min-1), when it is suggested that the dosage be divided for administration over double the normal interval. Old age per se is not an indication for dose adjustment.

Concentration –effects relationship

As with antibiotics, clinically effective plasma and tissue concentrations are related to the minimum concentrations inhibitory against the infecting microorganism. For most susceptible organisms (see clinical pharmacology) a dose of 200 mg given twice daily is adequate; however, for less susceptible organisms, or infections in sites where antibiotic penetration is low, higher dose may be required.

Metabolism

No metabolic pathways have yet been identified Cefixime is mainly excreted unchanged in bile and urine.

Clavulanate potassium

Clavulanic acid has no intrinsic clinical pharmacological effect of its own. It is used in combination to extend the antibacterial spectrum of Amoxicillin. Therefore, an Amoxicillin-Clavulanic acid combination has good activity against penicillinase-producing staphylococci. Clavunanic acid also enhances the susceptibility of Amoxicillin-resistant Haemophilus influenzae, Neisseria gonorrhoeae, Bacteoides fragilis, and many of the Enterobacteriaceae, to Amoxicillin. The sdame activity it shows for the Cefixime combination.

Clavulanic acid also enhances the antimicrobial effect of ticarcillin (as Timentin). Thus, by the addition of clavulanic acid, species of bacteria that are often resistant to ticarcillin become sensitive to Timentin. These include stains of Staphulococichia epidermidis, Escherichia coli, Haemophilus influenzae, Maoraxells catarrhalis, klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Yersinia enterocolitica, and Bacteroides spp.

1.3.1.7.3 Preclinical 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 Summary of Product Characteristics.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Excipients	Specification
Pregelatinized Starch	U.S.P./N.F
Lacto Dc L11 (Lactose)	U.S.P
Microcrystalline Cellulose (102)	U.S.P
Sodium Lauryl Sulfate	U.S.P
Solutab (Cross Carmelose Sodium)	U.S.P
Colloidal Silicon Dioxide	U.S.P
Hydrogenated Castor Oil	U.S.P./N.F
Colloidal Silicon Dioxide	U.S.P
Sodium Lauryl Sulfate	U.S.P
Calcium Stearate	U.S.P
Insta Moist Shield Ic-Ms-2398	IHS
Iso Propyl Alcohol	U.S.P
Methylene Chloride	U.S.P
Tartrazine Yellow Lake	IHS

1.3.1.8.2 Incompatibilities: Not applicable.

1.3.1.8.3 Shelf life:

24 months

1.3.1.8.4 Special precautions for storage:

No special precautions for storage. Store in the original packaging.

1.3.1.8.5 Nature and contents of container:

1 X 6 Tablets 6 X 10 Strips 4 Box Alu-Alu packing along with pack insert.

1.3.1.8.6 Special precautions for disposal and other Special handling:

No special requirements for disposal.

1.3.1.9 Marketed by:

AQUATIX PHARMACEUTICALS LIMITED.

No. 14, Prince Bode Oluwo Street,

Mende, Maryland,

Lagos Nigeria

1.3.1.10 Manufactured by:

CHIROS PHAMA
Vill: Loharon, P.O:
Ghatti, SOLAN-173211
India