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

AQUIXIM SUSPENSION

(Cefixime for Oral Suspension USP)

1.3.1.2 Strength

Cefixime (As Trihydrate) USP
Eq. to Anhydrous Cefixime……..100 mg

1.3.1.3 Dosage Form

Oral solid dosage form (Powder for Suspension)

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of reconstituted suspension contains:
Cefixime (As Trihydrate) USP
Eq. to Anhydrous Cefixime……..100 mg
Excipients …….q.s.
Approved colour used.

1.3.1.5 PHARMACEUTICAL FORM

Oral Suspension

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1Therapeutic indications

Cefixime is indicated for oral treatment of the following bacterial infections when caused by susceptible organisms. Acute exacerbations of chronic bronchitis - Community – acquired pneumonia - ENT infections (e.g. otitis media, sinusitis, tonsillitis, pharyngitis, laryngitis) - Uncomplicated lower urinary tract infections including gonococcal urethritis - Uncomplicated pyelonephritis The use of cefixime should be reserved for infections in which the causative organism is known or suspected to be resistant to other commonly used antibacterial agents or when treatment failure may carry significant risk. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults and adolescents: 1 x 400 mg (= 20 ml of the reconstituted suspension) per day, as a once-a-day dose or 2 x 200 mg (= 10 ml) with an interval of 12 hours. Children from 6 months to 11 years of age: 8 mg cefixime/kg bodyweight per day: either as a once-a-day dose or twice daily 4 mg/kg bodyweight with an interval of 12 hours. Children less than 6 months of age the safety and efficacy of cefixime has not been established in children less than 6 months of age. Dosage recommendations for syringe (10 ml, marked at each half ml) and spoon (5 ml with 1.25, 2.5 ml graduation) are given in the table below, as the medicinal product [nationally completed name] 100 mg/5 ml granules for oral suspension will be either provided with syringe or spoon. 1 ml reconstituted suspension contains 20 mg cefixime:

		SYRINGE	**SPOON**
Body weight (kg)	**Daily dosage (mg)**	**Daily dosage (ml)**	**Daily dosage (measuring spoons)**
2,5	20	1	1 x ½ (or 2 x ¼)
5	40	2	
6	48	2,5	
7,5	60	3	1 x 1 (or 2 x ½)
10	80	4	
12,5	100	5	
15	120	6	1 x 2 (or 2 x 1)
17,5	140	7	
20	160	8	
22,5	180	9	
25	200	10	
27,5	220	11	1 x 3 (or 2 x 1 ½)
30	240	12	
37,5	300	15	
> 37,5	400	20	1 x 4 (or 2 x 2)

It is recommended that adolescents and adults without complaints in swallowing take Cefixime capsules or tablets. The duration of treatment is dependent on the course of the infection. Generally, the duration of treatment with antibiotics is 7-10 days. It should be noted that streptococcal infections require a minimum therapy of 10 days in order to avoid secondary illnesses (rheumatic fever, glomerulonephritis) 1-3 days' treatment is often sufficient for uncomplicated pyelonephritis in women. A once-only dose of 400 mg cefixime is generally sufficient for gonococcal infections. Patients with impaired renal function: Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances 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 peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min/1.73 m2. There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended. Older people: Older 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”). The ready-to-use suspension is to be taken undiluted either prior or with meal. For the preparation of the ready-to-use suspension the bottle with the granules is first vigorously shaken, then fresh drinking water is added up to the filling mark and the suspension is immediately vigorously shaken again. After allowing the suspension to stand for a short time water is added up to the marked level of filling once more and it is again vigorously shaken. The white to light-yellow suspension is now ready for use. The bottle should be shaken vigorously before every administration. For the exact administration of the dosage a 5 ml measuring spoon (with 1.25- and 2.5-ml graduation) or 10 ml syringe with adapter is included in the package to aid correct dosing. After preparation of the ready-to-use suspension Cefixime 100 mg / 5 ml granules for oral suspension should be used within 2 weeks

1.3.1.6.3 CONTRAINDICATIONS

Cefixime is contraindicated in cases of hypersensitivity to cefixime, to any other cephalosporin antibiotics, or a known immediate and severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic or to one of the excipients of the medicinal product. Cefixime is contraindicated in preterm and term newborn infants (0-27 days).

1.3.1.6.4 WARNING AND PRECAUTIONS

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. Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs. Special care is indicated in patients who have experienced any allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur. If any allergic reaction to cefixime occurs, treatment with cefixime must be discontinued immediately and appropriate emergency measures must be initiated. Particular caution is necessary in patients with allergic diathesis or asthma when using ß-lactam antibiotics, as hypersensitivity is more common in these patients. Particular caution should be exercised when using cefixime in patients with severe renal function disorders (creatinine clearance < 20 ml/min. 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. Pseudomembraneous colitis has been reported with the use of broad-spectrum antibiotics and may range in severity from mild to life threatening. Therefore, it is important to consider its diagnosis in patient who develop serious diarrhea during or after antibiotic use. In case of pseudomembraneous colitis the use of cefixime should be discontinued and appropriate measures should be installed. The use of agents inhibiting the peristaltis is contraindicated. Renal function, hepatic function and blood account should be monitored under long-term therapy with cefixime at high doses. As with any long-term antibiotic therapy, the patient should be monitored for increased growth of nonsensitive bacteria or fungi.

Renal function is to be particularly well monitored under a combination therapy with cefixime preparations and aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics (e.g. furosemide) because of the probability of additional renal impairment up to acute renal failure, in particular in case of secondary diseases correlated with reduced renal perfusion (e.g. severe infections, sepsis). This applies particularly for patients with already restricted renal function. Hypersensitivity to other β-lactam antibiotics may cause cross allergy. Therefore, caution is required in patients who have experienced an anaphylactic reaction to penicillin. Treatment with cefixime should be avoided in patients with severe gastrointestinal disorders, since sufficient absorption cannot be guaranteed. (In such cases a parenteral therapy with a suitable antibiotic is recommended). Note: Proven staphylococcal infections should not be treated with cefixime, since staphylococci are resistant. Warning for patients with diabetes taking Cefixime granules for oral suspension: 5 ml of the ready-to-use suspension of Cefixime granules for oral suspension: contains 2.5 g sucrose (correspond. to 0.21 BE). Influence on laboratory diagnostic 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 drug. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant intake with: Potentially nephrotoxic substances (such as aminoglycoside antibiotics, colistin, polymyxin and viomycin) and strong-acting diuretics (e.g. ethacrynic acid or furosemide) induce an increased risk of impairment of renal function. Nifedipine, a calcium channel blocker, may increase bioavailability of cefixime up to 70 %. Isolated cases have been reported of patients taking cefixime and cumarin anticoagulants concomitantly with prolonged prothrombin times with and without bleeding. In such cases clotting parameters should be monitored.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy: There is insufficient evidence of safety for use during human pregnancy. Animal studies do not reveal a teratogenic effect.

Cefixime passes through the placenta. The risk/benefit of administration of cefixime should be highly critically considered, in particular during the first 3 months of pregnancy. Lactation: No cefixime concentrations could be determined in breast milk. Nevertheless, until further clinical experience is available, cefixime should not be given to nursing mothers or they should use a breast pump for the duration of therapy and dispose of the milk. Fertility: Reproduction studies performed in mice and rats have revealed no evidence of impaired fertility.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cefixime has no or negligible influence on the ability to drive or use machines. However, cefixime may cause side effects influencing the capacity of reaction and the abililty to drive and use machines.

1.3.1.6.8 UNDESIRABLE EFFECTS

Very common (≥1/10)

Common (≥1/100 to<1/10)

Uncommon(≥1/1,000to<1/100)

Rare (≥1/10,000 to < 1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

System Organ Class	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)

Infections and infestations			Prolonged or repeated use may lead to secondary superinfections caused by insusceptible bacteria or fungi.		
Blood and lymphatic system			Eosinophilia	Alteration in blood picture like for	Granulocytopenia
disorders				example leukopenia, agranulocytosis, pancytopenia or thrombocytopenia. Blood clotting impairment, hemolytic anemia.	
Immune system disorders1			Hypersensitivity reactions in all degrees, – such as flush, palpitations dyspnoe, drop	Anaphylactic shock, –Reactions similar to serum disease such as	

			in blood pressure, bronchospasm, angioneurotic oedema. Severe acute hypersensitivity reactions may manifest as: Facial oedema, swollen tongue, swelling of the inner larynx with restriction of airway, racing heart, shortness of breath (respiratory distress), decrease of	anthralgia, arthritis, joint swelling, myalgia, urticaria	
			blood pressure leading to life-threatening shock. Any of these occurrences requires immediate medical		

			treatment.		
Nervous system disorders2		Headache	Dizziness	Transient hyperactivity	Convulsions
Gastrointestinal disorders	Soft stools and diarrhea	Disorders in the form of stomach ache, digestive impairment, nausea, vomiting	Lack of appetite, flatulence	Cases of pseudomembraneous colitis (see section 4.4)	
Hepatobiliary disorders		A reversible increase in liver enzymes (transaminase, alkaline phosphatase) in serum		Hepatitis and cholestatic jaundice	Increase of bilirubin
Skin and subcutaneous tissue disorders		Skin rashes (erythema, exanthema)	Pruritus and inflammation of the mucous membranes	Erythema exsudativum multiforme, Lyell syndrome and Stevens-Johnson syndrom3	DRESS syndrome
Renal and urinary disorders			Transient increase in urea concentrations	Increase in creatinine concentration	Acute renal failure including

				s in serum,	tubulointestinal
			in serum have been observed	interstitial nephritis	nephritis
General disorders and administration site conditions			Mucosal inflammation, pyrexia Drug fever		

Severe acute hypersensitivity reactions may manifest as: Facial oedema, swollen tongue, swelling of the inner larynx with restriction of airway, racing heart, shortness of breath (respiratory distress), decrease of blood pressure leading to life-threatening shock. Any of these occurrences requires immediate medical treatment. 2 As with other cephalosporins, a raised tendency to convulsive attacks cannot be ruled out. 3 Lyell syndrome and Stevens-Johnson syndrome may result in life-threatening conditions Reporting of side effects 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 the national reporting system listed in Appendix V*.

1.3.1.6.9 OVERDOSE

Symptoms of intoxication Intoxication in its strictest sense is unknown. Treatment of intoxication Treatment is done by symptomatic measures. No relevant amounts of substance are eliminated by haemodialysis or peritoneal dialysis. There is no specific antidote known.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic Properties

General properties Cefixime is an oral cephalosporin antibiotic similar in structure, bacterial spectrum and ß-lactamase stability to third generation parenteral cephalosporins of the cefotaxime type.

Pharmacotherapeutic group: Third generation cephalosporins. ATC Code: J01DD08 Mode of action Cefixime demonstrates bactericidal action against both Gram-positive and -negative bacteria and has a high level of stability to many clinically relevant beta-lactamases. Cefixime works through an inhibition of the bacterial cell-wall synthesis by blocking of penicillin-binding proteins (PBP3, 1a and 1b). The antibacterial spectrum of cefixime is not however, as broad as that of the parenteral third generation cephalosporins. Antibacterial efficacy of cefixime mainly depends on the time period, in which its level is above the minimum inhibitory concentration (MIC). Mechanisms of resistance • Inactivation of β-lactamases: Cefixime can be hydrolyzed by certain β-lactamases, especially by extended broad-spectrum β-lactamases (ESBL) of e.g. Escherichia coli or Klebsiella pneumoniae or by constitutively expressed AmpC-type β-lactamases of e.g Enterobacter cloacae. Using cefixime for infections, caused by bacteria with inducible AmpC-type β-lactamases and in vitro susceptibility against cefixime, might cause the risk of bacterial mutant selection, which constitutively express AmpC-type β-lactamases, • Reduced affinity of PBPs to cefixime: Acquired resistance of pneumococcus or other streptococcus strains is based on modification of PBPs after mutation. • Reduced outer cell-wall penetration of cefixime in gram-negative bacteria causes insufficient blocking of PBPs. • Active transport of cefixime to the outside of the cell via efflux-pumps. Partial or complete cross-resistance between cefixime and other cephalosporins and penicillins exists. Breakpoints According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST January 2015 v.5.0) for cefixime are: ♣ H.influenzae1 : sensitive ≤ 0.125 mg/L, resistant > 0.125 mg/L. ♣ M.catarrhalis: sensitive ≤ 0.5 mg/L, resistant > 1.0 mg/L ♣ Neisseria gonorrhoeae: sensitive ≤ 0.125 mg/L, resistant > 0.125 mg/L ♣ Enterobacteriaceae: sensitive ≤ 1.0 mg/L, resistant > 1.0 mg/L (for uncomplicated urinary tract infections only). ♣ Non-species related breakpoints: insufficient data. 1 Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint, they should be reported resistant.

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobes, Gram positive
Streptococcus pyogenes
Aerobes, Gram negative
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis [%]
Species for which acquired resistance may be a problem
Aerobes, Gram positive
Streptococcus pneumoniae
Aerobes, Gram negative
Citrobacter freundii [$]
Enterobacter cloacae [$]
Escherichia coli [% &]
Klebsiella oxytoca [%]
Klebsiella pneumoniae [%]
Morganella morganii [$]
Serratia marcescens [$]
Inherently resistant species
Aerobes, Gram positive
Enterococcus spp.
Staphylococcus spp.
Streptococcus pneumoniae (Penicillin-intermediär und –resistent)

Aerobes, Gram negative
Legionella pneumophila
Pseudomonas aeruginosa
Others
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.

$ Natural intermediate susceptibility. % Extended spectrum beta-laktamase (ESBL) producing strains are always resistant. & Resistance rate.

1.3.1.7.2 Pharmacokinetic Properties

After oral administration of 400 mg Cefixime, mean maximum serum concentrations between 2,5 and 4,9 µg/ml were reported 3 – 4 hours after application. After administration of 200 mg Cefixime mean maximum serum concentrations were between 1,49 and 3,25 µg/ml. In children below 12 years a dose of 4 mg/kg bw. Cefixime leads to serum concentrations of 1,8 µg/ml and a dose of 8 mg/kg to serum concentrations of 3,6 µg/ml. The serum protein binding of cefixime is approximately 65%. The elimination half-life is 2 to 4 hours and is not dependent on either the dose or the galenic formulation. Blister fluid showed somewhat higher cefixime concentrations than those measured in serum (on average 133% of the equivalent serum concentration). At 6.7 hours, maximum concentration was achieved later than in serum. Following an oral dose of 200 to 400 mg, 10 - 20% of the substance is excreted unchanged with urine within 24 hours; this is equivalent to 50 – 55% of the resorbed amount of substance. A once-only oral dose of 400 mg cefixime results in urine concentrations that exceed the MHK for relevant bacteria over 24 hours. High concentrations are achieved in the bile. Concentrations were determined for the following tissue and body fluids as follows: tonsils 5 hours after administration of 4 mg/kg b.w. (right on average 0.74 µg/g, left on average 0.53 µg/g); lung tissue 7.8 hours after administration of 200 mg on average 0.99 µg/g, 8 hours after administration of 400 mg 1.76 µg/g: Otorrhea 2 to 3 hours after administration of twice daily 100 mg over several days >1 µg/ml; nasal

sinus mucous membranes 2 to 3 hours after administration of 200 mg 1.2 – 1.4 µg/g; sputum after 100 mg 0.02 to 0.05 µg/ml. There was no evidence of metabolisation of cefixime.

1.3.1.7.3 Preclinical safety data

The investigations on toxicity after repeated application showed substance-related effects in the gastrointestinal system and in the kidneys. Cefixime is, as other cephalosporines, to be classified as potentially nephrotoxic. In three-week old dogs the daily oral administration of 400 mg/kg b.w./d cefixime over 5 weeks led to occasional necrosis of the tubule epithelia of the kidneys. The non-toxic dose was determined at 100 mg/kg b.w./d in this study, which is equivalent to approximately fifteen times the therapeutic dose. In adult dogs histological signs of nephrotoxicity were observed after a 14-day i.v. administration of 1 g/kg b.w./d cefixime (regeneration of renal tubuli after previous necrosis).

In rats, the administration of 1 g/kg b.w./d over one year led to chronic nephropathy with increased renal weight and proteinuria. The only further finding described was enlargement of the caecum which is typical for antibiotics. In rabbits cefixime exerted toxic action even at low doses. This was primarily related to damage to the species-specific gram-positive intestinal flora. For rats and rabbits, a threshold dose was determined of approximately 500 mg/kg b.w./d for toxic action on the proximal renal tubuli after one or only a few parenteral applications. With an effective dose of 12 mg/kg b.w./d the therapeutic spectrum is wide. Studies on three animal species (rat, mouse, rabbit) have shown no evidence of teratogenic properties. An influence on perinatal or postnatal development and fertility in rats has not been observed. Cefixime passes through the placenta. The concentrations in umbilical cord blood were 1 /6 – ½ of the maternal serum concentrations. No cefixime concentrations could be proved in breast milk. Only limited experience is available on use in humans during pregnancy and lactation. Several in-vitro and in-vivo mutagenicity tests have proved negative. Mutagenic action of cefixime in humans can therefore be safely excluded.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Item Name	Specification
Cefixime	U.S.P.
Sucrose	U.S.P.
Sodium Benzoate	U.S.P.
Sunset yellow Supra	I.H.S
Colloidal Silicon Dioxide	U.S.P.
Aspartame	U.S.P.
Orange Flavour	I.H.S
Xanthan Gum	U.S.P.

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:

The reconstituted suspension, when refrigerated between 2 and 8°C can be kept for up to 10 days. Unconstituted Store below 25°C.

1.3.1.8.5 Nature and contents of container:

1 X 100 ml opaque white coloured HDPE bottle in a carton along with pack insert.

1.3.1.8.6 Special precautions for disposal and other Special handling:

No special requirements

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 PHARMA

Vill- Loharan, P.O. Ghatti,

Distt: Solan (H.P) 173 211.