1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product

1.1 Product Name

CEFIXIME AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION 50MG + 31.25MG

1.2 Strength

50MG + 31.25MG

1.3 Pharmaceutical Dosage Form

Solid Oral Dosage Form, Powder for oral suspension

2. Quality and Quantitative Composition

2.1 Quantitative Declaration

Each 5ml of reconstituted Suspension Contains:

Cefixime BP (As trihydrate) eq.to

Anhydrous Cefixime…….……....50 mg

Clavulanate Potassium BP eq.to

Anhydrous Clavulanic Acid ……31.25mg

Excipients…….…...q.s.

Approved colors and flavour used.

2.2 Quantitative Declaration

Qualitative-Quantitative formula:

Qty of Cefixime Trihydrate is Approx. 1119.19mg and Clavulanate Potassium with Syloid Base is Approx. 744.53 mg equivalent to Cefixime 50mg and potassium clavulanate 31.25mg

Batch Size: 5000 Bottles

Sr. No	Ingredients	Grade	Rationale	Label Claim	Quantity Bottle (mg)	Quantity/ Batch (Kg)
DRY MIXING						
1.	Cefixime Trihydrate (Plain)*****	BP	API	1000 mg	1119.19	5.60
2.	Clavulanate Potassium With Syloid Base *	BP	API	625mg	744.53	3.72
3.	Mannitol $	BP	Sweetener	-----	7938.60	39.69
4.	Xanthan Gum	BP	Thickener	-----	112.00	0.56
5.	Sodium Benzoate	BP	Preservative	-----	186.67	0.93
6.	Colloidal anhydrous silica (Aerosil)	BP	Glidant	-----	466.67	2.33
7.	Sodium Citrate Anhydrous	BP	Buffering	-----	210.00	1.05
8.	Orange Fresh DM 6024 Dry Flavour	IHS	Flavoring agent	-----	81.67	0.41

9.	Citric Acid Anhydrous	BP	Preservative		56.00	0.28
10.	Aspartame	BP	Sweetener		81.67	0.41
11.	Colour Sunset Yellow Supra	IHS	Coloring agent		3.00	0.02
				Mixed Blend Weight	**11000.00**	**55.00**

NOTE:

1. * Mentioned quantity is considering Assay (on as is basis) as 100%, Potency correction to be done while dispensing considering the actual assay on as is basis.
2. $ Mannitol to be compensate after potency correction of Cefixime Trihydrate (Plain) and clavulanate potassium with Syloid base.

EQUIVALENCY:

API quantity calculation as per molecular weight

Molecular weight of Cefixime Trihydrate = 507.500 g/mol

Molecular weight of Cefixime = 453.452 g/mol

Dose of Cefixime = 1000 mg

453.452 g/mol Cefixime = 1000 mg

507.500 g/mol Cefixime Trihydrate = $\frac{1000 \text{ X } 507.500}{453.452}$

= **1119.19 mg** of Cefixime Trihydrate required.

API quantity calculation as per molecular weight

Molecular weight of clavulanate Potassium = 237.250 g/mol

Molecular weight of Clavulanic acid = 199.160 g/mol

Dose of clavulanate Potassium = 625.00 mg

199.160 g/mol Clavulanic acid = 375.00 mg

= 237.250 g/mol clavulanate Potassium = $\frac{625.000 \text{ X } 237.250}{199.160}$

= **744.53 mg** of Potassium clavulanate required.

BP- British Pharmacopoeia, Current version

IHS - In-house specification

Pack Size: 01 x 01's HDPE Bottle

Further details provided under 3.2.P.7 Container-closure system.

3. **Pharmaceutical Form:** White to off white, orange flavored granular free flowing powder, after reconstitution, yellow coloured homogeneous suspension having orange flavored.

4. Clinical Particulars

4.1 Therapeutic indications

Cefixime with potassium Clavulanate is indicated for the treatment of the following infections in adults and children:

• Upper respiratory tract Infection

• Low respiratory tract infection

• Urinary tract infection

4.2 Posology and Method of Administration

Absorption of Cefixime is not significantly modified by the presence of food. The usual course of treatment is 7 days.

This may be continued for up to 14 days if required.

Adults and Children over 10 Years: The recommended adult dosage is 200-400 mg daily according to the severity of infection, given either as a single dose or in two divided doses.

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").

Children (Use Paediatric Oral Suspension): The recommended dosage for children is 8 mg/kg/day administered as a single dose or in two divided doses. As a general guide for prescribing in children the following daily doses in terms of volume of Paediatric Oral Suspension are suggested:

6 months up to 1 year:	3.75 ml daily
Children 1-4 years:	5 ml daily
Children 5-10 years:	10 ml 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 infection). The safety and efficacy of cefixime has not been established in children less than 6 months.

Dosage In Renal Impairment: Cefixime with potassium Clavulanate oral suspension 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.

4.3 Contraindications

• Hypersensitivity to the active substances, to any of the Cephalosporin or to any of the excipients.

• History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin, carbapenem or monobactam).

4.4 Special Warnings and Precautions for Use

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 with potassium Clavulanate Oral suspension 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 crossallergenicity between the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with Cefixime with potassium Clavulanate oral suspension, the drug should be discontinued and the patient treated with appropriate agents if necessary.

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 readministration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated haemolytic anaemia has also been reported.

Renal failure acute

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

Cefixime with potassium Clavulanate Oral Suspension should be administered with caution in patients with markedly impaired renal function.

Paediatric use

Safety of cefixime in premature or newborn infant 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 drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by C. difficile. Other causes of colitis should be excluded.

4.5 Interaction with Other Drugs, Other Forms of Interactions

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 suspension, 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.

4.6 Fertility, pregnancy and lactation

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 fetus 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 sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine. There are no adequate and well-controlled studies in pregnant women. Cefixime should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.

4.7 Effects on ability to drive and operate machine

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

The following adverse reaction (Preferred term# or equivalent) will be considered listed:

Blood and lymphatic system disorders:	Eosinophilia Hypereosinophilia Agranulocytosis Leucopenia Neutropenia Granulocytopenia Haemolytic anaemia Thrombocytopenia Thrombocytosis
Gastrointestinal disorders:	Abdominal pain Diarrhoea* Dyspepsia Nausea Vomiting Flatulence
Hepatobiliary disorders:	Jaundice
Infections and infestations:	Pseudomembranous colitis Vaginitis
Investigations:	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased
Nervous system disorders:	Dizziness Headache Cases of convulsions have been reported with cephalosporins including cefixime (frequency not known)**

	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 (frequency not known)**
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Renal and urinary disorders:	Acute renal failure with tubulointerstitial nephritis.
Immune system disorders:	Anaphylactic reaction Angio-oedema Serum sickness-like reaction
Skin and subcutaneous tissue disorders:	Drug rash with eosinophilia and systemic symptoms (DRESS) Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Urticaria Rash Pruritus Acute generalised exanthematous pustulosis (AGEP)
General disorders and administrative site conditions:	Drug Fever Arthralgia Pyrexia Face oedema Genital pruritus

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use.

*Diarrhoea has been more commonly associated with higher doses. Some cases of moderate to severe diarrhoea have been reported; this has occasionally warranted cessation of therapy. Cefixime should be discontinued if marked diarrhoea occurs.

**Cannot be estimated from available data

Reporting of suspected adverse reactions

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.

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

Pharmacotherapeutic group: third generation cephalosporin, ATC code: J01DD08

Cefixime is an oral third generation cephalosporin which has marked in vitro bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.

Clinical efficacy has been demonstrated in infections caused by commonly occurring pathogens including *Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Klebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative), *Branhamella catarrhalis* (beta-lactamase positive and negative) and *Enterobacter* species. It is highly stable in the presence of beta-lactamase enzymes.

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 *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 – 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. Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

5.3 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.

6. Pharmaceutical Particulars

6.1 List of excipients

Mannitol
Xanthan Gum
Sodium Benzoate
Colloidal Silicon Dioxide (Aerosil)
Sodium Citrate Anhydrous
Orange Fresh DM 6024 Dry Flavour
Citric Acid Anhydrous
Aspartame
Colour Sunset Yellow Supra

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for Storage

Store protected from moisture below temperature not exceeding 25^0C.

HDPE Bottle: Store in the original package in order to protect from moisture.

6.5 Nature and Contents of Container

- 100 ml of 28mm HDPE round bottle fitted with 28mm screw cap and 28mm Measuring cup.
- Pack 1 HDPE bottle with sticker label on it in 1 carton along with leaflet. Must have 2D barcode overprinting on the carton.
- Pack such cartons in export worthy shipper.

7. Marketing authorization holder

NAME	**:**	**SJS LIFE SCIENCES LIMITED**
ADDRESS	**:**	No. 11 Olu Akrele Street, Ikeja, Lagos, Nigeria.
COUNTRY	**:**	AFRICA
TELEPHONE	**:**	+234 8114441430
E-MAIL	**:**	jkpandey3s@gmail.com

8. Marketing authorization numbers

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text

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