1. Name of the Medicinal Product

(a) Product Name : FEXOCLAV ORAL SUSPENSION
(b) Strength : Amoxicillin 200 mg & Clavulanic acid 28.5 mg
(c) Pharmaceutical Dosage Form : powder for oral suspension

2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

Composition:
Each 5ml after Reconstitution contains:
Amoxicillin Trihydrate B.P.
Eq. to Anhydrous Amoxicillin 200 mg
Diluted Potassium Clavulanate B.P.
Eq. to Clavulanic Acid 28.5 mg

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Ingredient	Spec.	Claim	Overages	Qty./5 ml	Functions
Active Ingredient					
Amoxicillin trihydrate Eq. to Anhydrous Amoxicillin	B.P.	200 mg	---	252.50 mg	Penicillin Antibiotic
Diluted Potassium Clavulanate Eq. to Clavulanic Acid	B.P.	28.5 mg	---	37.346 mg	β-Lactamase Inhibitor
Inactive Ingredient					
Colloidal Anhydrous Silica	B.P.	---	---	14.633 mg	Absorbent
Aspartame	B.P.	---	---	17.000 mg	Sweetening Agent
Vanilla powder	U.S.P.	---	---	60.800 mg	Flavoring Agent
Colour Erythrosine Supra	In-house	---	---	0.666 mg	Colouring Agent
Xanthan gum	B.P.	---	---	16.000 mg	Thickening Agent
Hydroxypropylmethylcellulose	B.P.	---	---	134.50 mg	Suspending Agent
Hydrophobic colloidal silicon	B.P.	---	---	66.000 mg	Absorbent
Succinic acid	U.S.P.	---	---	0.860 mg	Acidity Regulator

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.: Off white colour granular powder filled in opaque white pet bottle, on reconstitution with water it forms off white colour thick suspension. The pH of reconstituted suspension is 4.0 to 7.0.

4. Clinical Particulars

4.1 Therapeutic indications:
FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):
• Acute bacterial sinusitis (adequately diagnosed)
• Acute otitis media
• Acute exacerbations of chronic bronchitis (adequately diagnosed)
• Community acquired pneumonia
• Cystitis
• Pyelonephritis
• Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
• Bone and joint infections, in particular osteomyelitis.

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

4.2 Posology and method of administration:
The usual recommended daily dosage of FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) is:

- 25/3.6 mg/kg/day in mild to moderate infections (upper respiratory tract infections, e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections).
- 45/6.4 mg/kg/day for the treatment of more serious infections (upper respiratory tract infections, e.g. otitis media and sinusitis, lower respiratory tract infections, e.g. bronchopneumonia and urinary tract infections).

The table below give guidance for children.

25/3.6 mg/kg/day	2 - 6 years (13 - 21 kg)	200/28.5 mg FEXOCLAV ORAL SUSPENSION b.i.d
	7 - 9 years (22 - 31 kg)	300/42.75 mg FEXOCLAV ORAL SUSPENSION b.i.d.
	10 - 12 years (32 - 40 kg)	400/57 mg (or 2 × 200/28.5 mg) FEXOCLAV ORAL SUSPENSION b.i.d.
45/6.4 mg/kg/day	2 - 6 years (13 - 21 kg)	400/57 mg (or 2 × 200/28.5 mg) FEXOCLAV ORAL SUSPENSION b.i.d.
	7 - 9 years (22 - 31 kg)	2 × 300/42.75 mg FEXOCLAV ORAL SUSPENSION b.i.d
	10 - 12 years (32 - 40 kg)	2 × 400/57 mg FEXOCLAV ORAL SUSPENSION b.i.d.

FEXOCLAV ORAL SUSPENSION is not suitable for patients incapable of using an ordinary drinking straw (e.g. children younger than 2 years). These patients should use other forms of Fexcoclav.

Infants with immature kidney function:
For children with immature renal function FEXOCLAV ORAL SUSPENSION is not recommended.

Elderly
No dose adjustment is considered necessary.

Renal impairment:
For patients with a GFR of >30 ml/min no adjustment in dosage is required. For patients with a GFR of ≤30 ml/min FEXOCLAV ORAL SUSPENSION is not recommended.

Hepatic impairment:
Dose with caution; monitor hepatic function at regular intervals. There is, as yet, insufficient evidence on which to base a dosage recommendation.

Method of administration:
FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) is for oral use.

FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) should be administered with a meal to minimise potential gastrointestinal intolerance.

Shake the bottle before each dose

4.3 Contraindications:
Hypersensitivity to the active substance, to any of the penicillins or to any of the excipients listed in section 6.1.

Safety in pregnancy has not been established. FEXOCLAV ORAL SUSPENSION is contra-indicated in patients with a previous history of amoxicillin and potassium clavulanate associated jaundice/hepatic dysfunction. FEXOCLAV ORAL SUSPENSION is also contraindicated in infectious mononucleosis. Patients with lymphatic leukemia and patients with hyperuricaemia having been treated with allopurinol may also be at an increased risk of developing skin rashes.

4.4 Special warning and precautions for use:
Before initiating therapy with FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml), careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, FEXOCLAV ORAL SUSPENSION

(Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) discontinuation and contra-indicates any subsequent administration of amoxicillin.

FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated

colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of Clavulanic acid in FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) contains aspartame, sorbitol, glucose, benzyl alcohol and sodium.

This medicinal product contains aspartame. Aspartame is a source of phenylalanine. This medicinal product should be used with caution in patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interactions:

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international

normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate: Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid: Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil: In patients receiving mycophenolate mofetil, reduction in pre- dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Pregnancy and Lactation:

Pregnancy

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).

Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use 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 (see section 4.8).

4.8 Undesirable effects:

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The following terminologies have been used in order to classify the occurrence of undesirable effects:

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)

Infections and infestations:
Common: Mucocutaneous candiosis
Not known: Overgrowth of non-susceptible organisms

Blood and lymphatic system disorders:
Rare: Reversible leucopenia (including neutropenia) and Thrombocytopenia.
Not known: Reversible agranulocytosis, Haemolytic anaemia, Prolongation of bleeding time and prothrombin time.

Immune system disorders:
Not known: Angioneurotic oedema, Anaphylaxis, Serum sickness-like syndrome and Hypersensitivity vasculitis.

Nervous system disorders:
Uncommon: Dizziness, Headache.
Not known: Reversible hyperactivity, Convulsions, Aeseptic meningitis.

Gastrointestinal disorders:
Very common: Diarrhoea.
Common: Nausea, Vomiting, Indigestion.
Not known: Antibiotic-associated colitis, Black hairy tongue.

Hepatobiliary disorders:
Uncommon: Rises in AST and/or ALT.
Not known: Hepatitis, Cholestatic jaundice.

Skin and subcutaneous tissue disorders:
Uncommon: Skin rash, Pruritus, Urticaria.
Rare: Erythema multiforme.
Not known: Stevens-Johnson syndrome,Toxic epidermal necrolysis, Bullous exfoliative-dermatitis.

Renal and urinary disorders:
Not known: Intestinal nephritis, Crystalluria.

4.9 Overdose
Symptoms of overdose: Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4)

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained(see section 4.4).

Treatment of intoxication: Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties: General Pharmacodynamic Effect

Pharmacotherapeutic group: Antibacterials for systemic use; betalactam antibacterials, penicillins; Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

• Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant

Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus [2]	≤ 2	-	> 2
Coagulase-negative staphylococci [2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

1 The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.
2 The reported values are Oxacillin concentrations.
3 Breakpoint values in the table are based on Ampicillin breakpoints.
4 The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
5 Breakpoint values in the table are based on Benzylpenicillin breakpoints.

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
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus (*methicillin-susceptible)£ Coagulase-negative staphylococci (methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other beta-haemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative micro-organisms *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic Properties:

Absorption and bioavailability

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets given twice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose	Cmax	Tmax *	AUC (0-24h)	T 1/2
	(mg)	(µg/ml)	(h)	(µg.h/ml)	(h)
Amoxicillin					

AMX/CA 875/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6). Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Metabolism
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Fexoclav Oral Suspension (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical Safety Data:
Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) or its components.

6.0 Pharmaceutical Particulars

6.1 List of excipients:

Sr. No.	Name of the Materials	Specification
1	Colloidal Silicon Dioxide	B.P.
2	Aspartame	B.P.
3	Vanilla Powder	U.S.P.
4	Xanthan Gum	B.P.
5	Hydroxypropylmethylcellulose	B.P.
6	Colour Erythrosine Supra	In-House

7	Hydrophobic Colloidal Anhydrous Silica	B.P.
8	Succinic Acid	U.S.P.

6.2 Incompatibilities:
Not applicable.

6.3 Shelf life:
The shelf of unconstituted FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml) from the date of manufactur is 30 Months.

The reconstituted suspension is stable for 7 days when stored at 2 – 8 °C.

6.4 Special precautions for storage:
Do not store above 30°C.

For storage conditions after reconstitution of the FEXOCLAV ORAL SUSPENSION (Amoxicillin and Potassium Clavulanate for Oral Suspension B.P. 228.5 mg/5 ml), see section 6.3

6.5 Nature and contents of container:
Off white colour granular powder filled in 100ml HDPE opaque white pet bottles along with dosing cup.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Constitution/Administration instructions
The bottle should be shaken vigorously before the medication is taken.

The reconstituted suspension when refrigerated between 2 and 8°C can be kept for up to 7 days.

7.0 Applicant/Manufacturer

Name : **ZEE LABORATORIES LIMITED**

Address : **Behind 47, Industrial Area, Paonta Sahib-173025 (INDIA)**

Phone : **08032587764**

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E-mail : **fexonapharmltd@yahoo.com**