Brand Name: OXCLAV 228.5
Generic Name: Amoxicillin & Clavulanate Potassium for Oral Suspension USP 200mg +28.5 mg

1.3.1
Summary Of Product Characteristics (SPC)

1. Product information for health professionals Invented Name of the Medicinal Product

Brand name: OXCLAV 228.5

Generic Name: Amoxicillin & Clavulanate Potassium for Oral Suspension USP 200mg +28.5 mg

Strength

Amoxicillin Trihydrate USP
Equivalent to Amoxicillin… ..... 200 mg
Clavulanate Potassium USP
Equivalent to Clavulanic acid .....28.50 mg

Dosage Form

Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each *5* ml of reconstituted suspension contains:

Amoxicillin Trihydrate USP

Equivalent to Amoxicillin… ..... 200 mg

Clavulanate Potassium USP

Equivalent to Clavulanic acid .....28.50 mg

3. PHARMACEUTICAL FORM

Powder for Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OXCLAV 228.5 should be used in accordance with local official antibiotic prescribing guidelines and local susceptibility data.

OXCLAV 228.5 (228 mg/5 mL), for twice daily oral dosing, is indicated for short term treatment of bacterial infections at the following sites when amoxicillin resistant beta lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered. Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and

bronchopneumonia.

Urinary tract infections e.g. cystitis, urethritis, pyelonephritis.Skin and soft tissue infections e.g. cellulitis, animal bites.

Susceptibility to OXCLAV 228.5 will vary with geography and time (see Pharmacological Properties, Pharmacodynamics for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with OXCLAV 228.5 susceptible beta-lactamase producing organisms may be treated with OXCLAV 228.5 mg/5mL. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology:

Dosage depends on the age, weight and renal function of the patient and the severity of the infection.

Dosages are expressed throughout in terms of amoxicillin/clavulanate content except when doses are stated in terms of an individual component.

- To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of OXCLAV 228.5 Suspension is optimised when taken at the start of a meal.
- Treatment should not exceed 14 days without review. Therapy can be started parenterally and continued with an oral preparation.

OXCLAV 228.5 Suspension bottle presentations for suspension may be supplied with a plastic dosing device. For preparation of the suspensions.

The usual recommended daily dosage 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).

No clinical data are available on doses above 45/6.4 mg/kg/day in children under 2 years.

There are no clinical data for OXCLAV 228.5 suspension 228.5 mg/5 mL to make dosage recommendations for children under 2 months old.

The tables below give dosage guidance for children.

Children 2 years and over

25/3.6 mg/kg/day	2 - 6 years (13 - 21 kg)	5.0 ml **OXCLAV 228.5** suspension 228 mg / 5 ml twice daily or 2.5 ml OXCLAV 228.5 suspension twice daily.
	7 - 12 years (22 - 40 kg)	10.0 ml **OXCLAV 228.5** suspension 228 mg / 5 ml twice daily or 5.0 ml OXCLAV 228.5 suspension twice daily.
45/6.4 mg/kg/day	2 - 6 years (13 - 21 kg)	10.0 ml **OXCLAV 228.5** suspension 228 mg/5 ml twice daily or 5.0 ml OXCLAV 228.5 suspension twice daily.
	7 - 12 years	10.0 ml **OXCLAV 228.5** suspension twice daily.

Children aged 2 months to under 2 years

Children under 2 years should be dosed according to body weight. *Renal Impairment*

No adjustment in dose is required in patients with creatinine clearance greater than 30 mL/min.

OXCLAV 228.5 mg/5 mL are not recommended in patients with a creatinine clearance of less than 30 mL/min.

Hepatic Impairment

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

4.3 CONTRAINDICATIONS

OXCLAV 228.5 is contraindicated in patients with a history of hypersensitivity to beta- lactams, e.g. penicillins and cephalosporins.

OXCLAV 228.5 is contraindicated in patients with a previous history of OXCLAV 228.5-associated jaundice/hepatic dysfunction.

4.4 WARNING AND PRECAUTIONS

Before initiating therapy with OXCLAV 228.5, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

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. If an allergic reaction occurs, OXCLAV 228.5 therapy must be discontinued and appropriate alternative therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required. OXCLAV 228.5 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.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving OXCLAV 228.5 and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Changes in liver function tests have been observed in some patients receiving OXCLAV 228.5. The clinical significance of these changes is uncertain but OXCLAV 228.5 should be used with caution in patients with evidence of hepatic dysfunction. Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment OXCLAV 228.5 mg/5 mL are not recommended. 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 (see Overdose). OXCLAV 228.5 mg/5 mL suspensions contain 12.5 mg aspartame per 5 mL dose and therefore care should be taken in patients with phenylketonuria

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with OXCLAV 228.5 may result in increased and prolonged blood levels of amoxicillin but not of clavulanate. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of OXCLAV 228.5 and allopurinol.

In common with other antibiotics, OXCLAV 228.5 may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. In the literature there are rare 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 OXCLAV 228.5.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid 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.

4.6 PREGNANCY AND LACTATION

Reproduction studies in animals (mice and rats) with orally and parenterally administered OXCLAV 228.5 have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (PROM), it was reported that prophylactic treatment with OXCLAV 228.5 may be associated with an increased risk of necrotising Enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

OXCLAV 228.5 may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant. Effects on Ability to Drive and Use Machines Adverse effects on the ability to drive or operate machinery have not been observed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting. The ADRs derived from clinical studies and post-marketing surveillance with Amoxicillin & Clavulanate, sorted by MedDRA System Organ Class are listed below. 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	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known

Convulsions	Not known
Aeseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known
Tooth discolouration	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
Skin and subcutaneous tissue disorders	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Acute generalised exanthemous pustulosis (AGEP)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

4.9 OVERDOSE

Symptoms and signs 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

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.

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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.

5.2 Pharmacokinetic properties

Absorption

The two components of Amoxicillin and Potassium Clavulanate suspension 228.5 mg/5 ml and 457 mg/5 ml, amoxicillin and clavulanate,are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of Amoxicillin and Potassium Clavulanate 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.

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.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier

<u>Biotransformation</u>

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 amoxicillin & clavulanic 250 mg/125 mg 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.

5.3 Preclinical safety data

Non-clinical 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 discolored tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SR No	Ingredient	Pharmacopeia
1.	Sodium Carboxymethyl Cellulose	USP
2.	Aspartame	USP
3.	Sodium Methyl paraben	USP
4.	Sodium Propyl paraben	USP
5.	Colloidal Silicon dioxide	USP
6.	Trusil Mango	IHS
7.	Citric Acid anhydrous	USP
8.	Sodium Citrate	USP
9.	Sodium Chloride	USP
10.	Sucrose Pharma grade	USP

Brand Name: OXCLAV 228.5
Generic Name: Amoxicillin & Clavulanate Potassium for Oral Suspension USP 200mg +28.5 mg

6.2 Incompatibilities:

None stated.

6.3 Shelf life:

24 Months

6.4 Special precautions for storage:

Store below 30°C and protect from moisture.

6.5 Nature and contents of container:

OXCLAV 228.5 Oral Suspension available as dry powder for reconstitution for 100 ml. One bottle in a carton along with the pack insert.

6.6 Special precautions for disposal and other Special handling:

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketed by:

M/S. AQUATIX PHARMACEUTICALS LTD.
No.7, Sapara Williams Street,
Industrial Estate, Ikeja,
Lagos, Nigeria.

8. Manufactured by:

M/S. BROOKS LABORATORIES LTD.

Village Kishanpura, Nalagarh Road,
Baddi, Tehsil Nalagarh, Distt. Solan,
Himachal Pradesh (174101), India.

9. NAFDAC REGISTRATION NUMBER(S): C4-1143