SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

OBICLAF (AMOXICILLIN & CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP 200MG/28.5 MG)

2. Qualitative and quantitative composition

Composition

Each 5ml reconstituted suspension contains:

Amoxicillin Trihydrate USP	
Eq. to Amoxicillin	200mg
Clavulanate Potassium USP	
Eq. to Clavulanic Acid	28.5mg
Excipients	Q.S.
Colour: Sunset Yellow	

3. Pharmaceutical forms

Oral suspension

White to off white colour powder, after reconstitution turns into orange colour.

4. Clinical Particulars

4.1 Therapeutic Indications

Amoxicillin & Clavulanate Potassium should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data. Amoxicillin & Clavulanate Potassium suspension (228 mg/5 ml and 457mg/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. Dental infections e.g. severe dental abscess with spreading cellulitis. Susceptibility to Amoxicillin & Clavulanate Potassium 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.

4.2 Posology and Method of administration

Posology

Dosage and Administration 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)

The tables below give guidance for children.

Children over 2 years

25/3.6 mg/kg/day	2 - 6 years (13 - 21 kg)	5.0 ml Amoxicillin & Clavulanate Potassium suspension 228 mg/5 ml twice daily ***or*** 2.5 ml Amoxicillin & Clavulanate Potassium suspension 457 mg/5 ml twice daily.
	7 - 12 years (22 - 40 kg)	10.0 ml Amoxicillin & Clavulanate Potassium suspension 228 mg/ 5 ml twice daily ***or*** 5.0 ml Amoxicillin & Clavulanate Potassium suspension 457 mg/5 ml twice daily

45/6.4 mg/kg/day	2 - 6 years (13 - 21 kg)	10.0 ml Amoxicillin & Clavulanate Potassium suspension 228 mg/5 ml twice daily ***or*** 5.0 ml Amoxicillin & Clavulanate Potassium suspension 457 mg/5 ml twice daily
	7 - 12 years	10.0 ml Amoxicillin & Clavulanate Potassium suspension 457 mg/5 ml twice daily.

Children aged 2 months to 2 years

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

There is insufficient experience with Amoxicillin & Clavulanate Potassium suspension 228 mg/5 ml and 457 mg/5 ml to make dosage recommendations for children under 2 months old. Renal Impairment

For children with a GFR of >30 ml/min no adjustment in dosage is required. For children with a GFR of <30 ml/min Amoxicillin & Clavulanate Potassium suspension 228 mg/5 ml and 457 mg/5 ml are not recommended.

Infants with immature kidney function

For infants with immature renal function Amoxicillin & Clavulanate Potassium suspension 228 mg/5 ml and

457 mg/5 ml are 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

Administration

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Amoxicillin & Clavulanate Potassium is optimised when taken at the start of a meal. Duration of therapy should be appropriate to the indication and should not exceed 14 days without review. Therapy can be started parenterally and continued with an oral preparation.

4.3 Contraindications

Amoxicillin & Clavulanate Potassium is contra-indicated in patients with a history of hypersensitivity to betalactams, e.g. penicillins and cephalosporins. Amoxicillin & Clavulanate Potassium is contra-indicated in patients with a previous history of Amoxicillin & Clavulanate Potassium associated jaundice/hepatic dysfunction.

4.4 Special warning and precaution for use

Before initiating therapy with CLAVULIN, 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 (see Contraindications). If an allergic reaction occurs, Amoxicillin & Clavulanate Potassium 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. Amoxicillin & Clavulanate Potassium 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 Amoxicillin & Clavulanate Potassium 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 Amoxicillin & Clavulanate Potassium.

The clinical significance of these changes is uncertain but Amoxicillin & Clavulanate Potassium 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 Amoxicillin & Clavulanate Potassium suspension 228 mg/5 ml and 457 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). Amoxicillin & Clavulanate Potassium 228 mg/5 ml and 457 mg/5ml 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 Amoxicillin & Clavulanate Potassium 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 Amoxicillin & Clavulanate Potassium and allopurinol. In common with other antibiotics, Amoxicillin & Clavulanate Potassium 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 coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of Amoxicillin & Clavulanate Potassium. 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 Fertility, pregnancy and lactation

Reproduction studies in animals (mice and rats) with orally and parenterally administered Amoxicillin & Clavulanate Potassium have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with Amoxicillin & Clavulanate Potassium 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.
Amoxicillin & Clavulanate Potassium may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Data from large clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.
Common: Mucocutaneous candidiasis

Blood and lymphatic system disorders
Rare: Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time

Immune system disorders
Very rare: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders
Uncommon: Dizziness, headache

Very rare: Reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders

Adults:

Very common: Diarrhoea
Common: Nausea, vomiting
Children:
Common: Diarrhoea, nausea, vomiting
All populations:
Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking Amoxicillin & Clavulanate Potassium at the start of a meal.
Uncommon: Indigestion
Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis – see Warnings and Precautions)

Black hairy tongue
Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Hepatobiliary disorders
Uncommon: A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
Very Rare: Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins. 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. 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.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash, pruritus, urticaria Rare Erythema multiforme

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS).

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Renal and urinary disorders

Very rare: Interstitial nephritis, crystalluria *(*see *Overdose)*

4.9 Overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Gastrointestinal symptoms may be treated symptomatically with attention to the water electrolyte balance. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Warnings and Precautions). Amoxicillin & Clavulanate Potassium can be removed from the circulation by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

General properties

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in Amoxicillin & Clavulanate Potassium suspension anticipates this defence mechanism by blocking the β-lactamase enzymes, thus rendering the organisms sensitive to amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body. Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin as Amoxicillin & Clavulanate Potassium it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice. In the list below, organisms are categorised according to their in vitro susceptibility to Amoxicillin & Clavulanate Potassium.

***In vitro* susceptibility of micro-organisms to Amoxicillin & Clavulanate Potassium** Where clinical efficacy of Amoxicillin & Clavulanate Potassium has been demonstrated in clinical trials this is indicated with an asterisk (*). Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to amoxicillin, it can be considered susceptible to Amoxicillin & Clavulanate Potassium.
Commonly susceptible species
Gram-positive aerobes: *Bacillius anthracis Enterococcus faecalis Listeria monocytogenes Nocardia asteroides Streptococcus pyogenes*† Streptococcus agalactiae*†* *Streptococcus* spp. (other β-hemolytic) *† *Staphylococcus aureus* (methicillin susceptible)* *Staphylococcus saprophyticus* (methicillin susceptible) Coagulase negative staphylococcus (methicillin susceptible)
Gram-negative aerobes: *Bordetella pertussis Haemophilus influenzae* Haemophilus parainfluenzae Helicobacter pylori Moraxella catarrhalis* Neisseria gonorrhoeae Pasteurella multocida* *Vibrio cholerae*
Other: *Borrelia burgdorferi* *Leptospira ictterohaemorrhagiae Treponema pallidum*
Gram positive anaerobes: *Clostridium* spp. *Peptococcus niger Peptostreptococcus magnus Peptostreptococcus micros Peptostreptococcus* spp.
Gram-negative anaerobes: *Bacteroides fragilis Bacteroides* spp. *Capnocytophaga* spp. *Eikenella corrodens Fusobacterium nucleatum Fusobacterium* spp. *Porphyromonas* spp. *Prevotella* spp.
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli* Klebsiella oxytoca Klebsiella pneumoniae** *Klebsiella* spp.
Proteus mirabilis Proteus vulgaris Proteus spp. *Salmonella* spp. Shigella spp.
Gram-positive aerobes: *Corynebacterium* spp. *Enterococcus faecium Streptococcus pneumoniae*†* Viridans group streptococcus
Inherently resistant organisms

Gram-negative aerobes: *Acinetobacter* spp. *Citrobacter freundii Enterobacter* spp. *Hafnia alvei* *Legionella pneumophila Morganella morganii Providencia* spp. *Pseudomonas* spp. *Serratia* spp. *Stenotrophomas maltophilia Yersinia enterolitica*
Others: *Chlamydia pneumoniae*
Chlamydia psittaci Chlamydia spp. *Coxiella burnetti* *Mycoplasma* spp.

Infections caused by amoxicillin-susceptible organisms are amenable to *Amoxicillin & Clavulanate Potassium* treatment due to its amoxicillin content. Mixed infections caused by amoxicillin - susceptible organisms in conjunction with *Amoxicillin & Clavulanate Potassium* -susceptible -lactamase producing organisms may therefore be treated with *Amoxicillin & Clavulanate Potassium.*

5.2 Pharmacokinetic Properties

Absorption:
The two components of Amoxicillin & Clavulanate Potassium suspension 228 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 & Clavulanate Potassium is optimised when taken at the start of a meal.

The mean AUC values for amoxicillin are essentially the same following twice a day dosing with the Amoxicillin & Clavulanate Potassium 875/125 mg tablet or three times a day dosing with the Amoxicillin & Clavulanate Potassium 500/125 mg tablet, in adults. No differences between the 875 mg twice daily and 500 mg three times daily dosing regimes are seen when comparing the amoxicillin $T_{1/2}$, or C_{max} after normalisation for the different doses of amoxicillin administered.
Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

The time of dosing of Amoxicillin & Clavulanate Potassium relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the Amoxicillin & Clavulanate Potassium 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and C_{max}, the highest mean values and smallest inter-subject variabilities were achieved by administering Amoxicillin & Clavulanate Potassium at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T1/2 and AUC values for amoxicillin and clavulanate are given below for an 875 mg/125 mg dose of amoxicillin /clavulanic acid administered at the start of a meal.

Mean Pharmacokinetic Parameters:

Drug Administration	Dose (mg)	Cmax (mg/L)	Tmax* (hours)	AUC (mg.h/L)	T1/2 (hours)
CLAVULIN 1g					
Amoxicillin	875 mg	12.4	1.5	29.9	1.36
Clavulanate	125 mg	3.3	1.3	6.88	0.92

Distribution:
The pharmacokinetics of the two components of Amoxicillin & Clavulanate Potassium are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.
Doubling the dosage of Amoxicillin & Clavulanate Potassium approximately doubles the serum levels achieved.

5.3 Preclinical Safety data

No further information of relevance

6. Pharmaceutical Particulars

6.1 List of Excipients

Mannitol
Aspartame
Colloidal silicone dioxide
Sodium citrate
Citric acid anhydrous
Sodium benzoate
Sunset yellow
Orange dry flavor
Xanthan gum

6.2 Incompatibilities

Not known.

6.3 Shelf Life

24 months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light
Reconstituted suspensions should be stored in a refrigerator (2-8°C) used within 7 days.
Keep out of reach of children.

6.5 Nature and contents of container

1 X 100 HDPE bottle.

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder

Manufacturer:
Name : STALLION LABORATORIES PVT. LTD.
Address : Rajkot Bhavnagar Highway,
Near Global Institute Of Atyurveda,
Kasturbadham , Rajkot, Gujrat- 360020

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
