Summary Product Characteristics (SPC)

1. Name of the medicinal product

Labclav 312.5 DT.

2. Qualitative and quantitative composition

Each Dispersible Tablet Contains: Amoxicillin Trihydrate BP equivalent to Amoxicillin 250mg and Potassium Clavulanate BP equivalent to Clavulanic Acid 62.5mg.

3. Pharmaceutical form

Tablets for oral administration.

4. Clinical particulars

4.1 Therapeutic indications

Labclav is an antibiotic agent with a notably broad spectrum or activity against the commonly occurring bacterial pathogens in hospital & general practice. The beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organism including many resistant to other beta lactam antibiotics.
Labclav is indicated for short term treatment of bacterial infections at the following sites:

1. Upper respiratory tract infections (including ENT) e.g. Tonsillitis, sinusitis, otitis media.
2. Lower respiratory tract infections e.g acute and chronic bronchitis, lobar and bronchopneumonia.
3. Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis.
4. Skin and soft tissue infections, e.g boils, abscesses, cellulitis, wound infections.
5. Bone and joints infections e.g osteomyelitis.
6. Dental infections e.g dent alveolar abscess.
7. Other infections e.g septic abortion, puerperal sepsis, intra-abdominal sepsis.

4.2 Posology and method of administration.

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

Adults	
Mild to moderate infections	250/125mg given 3 times daily, or 500/125mg given 2 or 3 times daily, OR 875/125mg given twice daily.
Severe infections (Including chronic and recurrent urinary tract infections and those of the lower respiratory tract.	2 times 250/125mg given 3 times daily, or 1 to 2 times 500/125mg given 3 times daily, or 875/125mg given 2 times daily.
Dental infections (e.g dent alveolar abscess)	500/125mg given 3 times daily for 5 to7 days or 875/125mg given 2 times daily for 5 to7 days.

Labclav 625mg and 1g tablets are not recommended in children of 12 years and under, in such cases labclav dispersible tablets or suspension are recommended.

Children up to 12 years		
Lower dose(mg/kg/day	Three times(4:1) formulations 20/5 to 40/10	Twice daily(7:1) formulations 25/3.6 to 45/6.4
Higher dose(mg/kg/day)	40/10 to 60/15	45/6.4 to 70/10

The lower dose is recommended for infections such as skin and soft tissue and recurrent tonsillitis. The higher dose is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections.

Elderly:

No adjustment needed; dose as for adults.

Dosage in renal impairment:

The Labclav 1g tablets should only be used in patients with a glomerular filtration rate of >30mL/min. In patients with mild impairment (creatinine clearance <30mL/min) no change in dosage (i.e. either one 625mg tablets bid or one 1g tablet) is recommended, in patients with moderate impairment (creatinine clearance 10-30ml/min) one 625mg tablet bid is recommended. The 1g tablet should not be administered. In patients with severe impairment (creatine clearenace? 10ml/min not more than 625mg tablet every 24hours is recommended.

Dosage in hepatic impairment:

Dose with caution; monitor hepatic function at regular intervals.

Oral administration

Tablets should be swallowed whole without chewing, if required, tablets may be broken in half and swallowed without chewing. To minimize potential gastrointestinal intolerance and optimize the absorption of co-amoxiclav, administer at the start of a meal.
Treatment should not be extended beyond 14 days without review.

4.3 Contraindications.
Penicillin hypersensitivity; attention should be paid to possible cross- sensitivity with other beta-lactam antibiotics e.g. Cephalosporins.
A previous history of co-amoxiclav or penicillin-associated jaundice/ hepatic dysfunction.

4.4 Special warnings and precautions for use.
Change in liver function tests have been observed in some patients receiving co-amoxiclav. The clinical significance of these changes is uncertain but co-amoxiclav 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 moderate or severe renal impairment co-amoxiclav dosage should be adjusted as recommended in the dosage and administration section. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. Erythematorus rashes have been associated with glandular fever in patients receiving amoxicillin. Co-amoxiclav should be avoided if glandular fever is suspected. Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

4.5 Interaction with other medicinal products and other forms of interaction.
Prolongation of bleeding time and prothrombin time have been reported in some patients receiving co-amoxiclav. Co-amoxiclav should be used with care in patients on anti-coagulation therapy. In common with other broad spectrum antibiotics. Co-amoxiclav may reduce the efficacy or oral contraceptives and patients should be warned accordingly. Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with co-amoxiclav may result in increased and prolonged blood levels of amoxicillin but not clavulanic acid. 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 co-amoxiclav and allopurinol.

4.6 Pregnancy and lactation.
There is limited experience of the use of co-amoxiclav in human pregnancy. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician. Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitization associated with the excretion of trace quantities on breast milk, there are no detrimental effects for the infant.

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.
Side effects with amoxicillin, are uncommon and mainly of a mild and transitory nature.
Gastrointestinal reactions.
Effects include diarrhoea, indigestion, nausea and vomiting, candidiasis, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely, nausea, although uncommon, is more often associated with higher oral dosages. If gastrointestinal side effects occur with oral therapy, they may be reduced by taking Labclav at the start of meals.
Hepatic effects
A moderate rise in AST and/or ALT has been noted in patients with semi-synthetic penicillins but the significance of these findings is unknown. Hepatitis and cholestatic jaundice have been reported rarely with co-amoxiclav. They may however be severe and continue for several months. They are reported as occurring predominantly in adult or elderly patients and slightly more frequently in males.
Signs and symptoms may occur during treatment but are more frequently reported after cessation of therapy with a delay of up to six weeks. The hepatic events are usually reversible. However, in extremely rare circumstances, deaths have been reported. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

Hypersensitivity reactions
Urticarial and erythematous rashes sometimes occur rarely erythema multiforme. Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis have been reported. Treatment should be discontinued if one of these types of rash appears. In common with other beta-lactam antibiotics angioedema, oedema, anaphylaxis, serum sickness-like syndrome and hypersensitivity vasculitis have been reported. Interstitial nephritis can occur rarely.
Hematological effects.
As with other beta-lactams, reversible leucopenia (including neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia have been reported rarely.
CNS Effects.
CNS effects have been seen very rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

4.9 Overdose.
Cases of overdosage with Labclav are unlikely to occur if encountered gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically with attention to the water electrolyte balance. Co-amoxiclav may be removed from the circulation by haemodialysis.

5. 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 antibiotic with a broad spectrum of antibacterial activity many gram-positive and gram-negative microorganisms. Amoxicillin is bactericidal; it adheres to bacterial penicillin-binding proteins, thus inhibiting bacterial cell wall synthesis. Amoxicillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes. Clavulanic is a beta-lactam, which has the ability to inactivate a wide range of beta-lactamase enzymes found in micro-organisms resistant to penicillins. The clavulanic acid in co-amoxiclav protects amoxicillin from degradation by beta-lactamases and extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin. Thus Co-amoxiclav is a broad spectrum antibiotic and a beta-lactamase inhibitor.
Pharmacodynamic Effects: In the list below, organisms are categorized according to their in vitro susceptibility to amoxicillin-Clavulanate:
Gram-Positive: **Aerobes**: *Enterococcus faecalis, streptococcus pneumonia, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus, Coagulase negative Staphylococci (including staphylococcus epidermidis).Corynebacterium species, Bacillus anthracis.Listeria monocytogenes.* **Anaerobes:** *Clostridium species, Peptococcus species, Peptostreptococcus.*
Gram-Negative: Aerobes: *Haemophilus influenza, Escherichia coli, Proteus mirabilis,Proteus vulgaris,Klebsiella species, Moraxella catarrhalis,salmonella species,shigella species, Bordetella pertussis, Brucella species, Neisseria gonorrhoeaea,Neisseria meningitidis, Vibrio cholera,Pasteurella multocida,* **Anaerobes:** *Bacteriodes spp.including B. fragilis.*

5.2 Pharmacokinetic properties.
Absorption: The two components, Amoxicillin and Clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both are rapidly and well absorbed by the oral route of administration. Absorption of Co-amoxiclav is optimized when taken at the start of a meal. Pharmacokinetic results in two separate studies, in which co-amoxiclav 250/125 (375) or 2 x 250/125 and 500/125 (625) mg tablets (in comparison with the two components given separately) were administered in the fasting state to groups of healthy volunteers and produced the following results:Amoxicillin:Cmax 3.7-6.5mg/1,Tmax 1.1-1.5h,AUG 10.5-23.2mg.h/1,T1/21.0-13h;Clavulanate: Cmax 2.2-4.1mg/1,Tmax 0.9-1.3h,Auc 6.2-11.8mg.h/1,T1/2-1.2h.Amoxicillin serum concentration achieved with co-amoxiclav are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.
Distribution:
Following i.v. administration, therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentration of both drugs have been found in gall bladder, abdominal tissue, skin, fat and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence that either component accumulates in any organ. Amoxicillin and trace quantities of Clavulanate can be detected in breast milk. With the exception of the risk of sensation associated with

excretion, there are no known detrimental effects for the breast-fed infant. Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. No evidence of impaired fertility or harm to the foetus was detected.
Metabolism: Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man to 2, 5-dihydo-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.
Elimination: The major route of elimination for amoxicillin is via the kidney, whereas for Clavulanate it is by both renal and non-renal mechanisms.Approx.60 to 70% of the amoxicillin and approx., 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 250/125mg or single 500/125mg tablet. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

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 discolored tongue.
Carcinogenicity studies have not been conducted with Amoxicillin & Clavulanate Potassium tablets USP or its components**.**

6. Pharmaceutical particulars.
6.1 List of excipients.
- Microcrystalline Cellulose pH 112 (Dried)
- Croscarmellose Sodium (Dried)
- Crospovidone (Kollidon CL)
- Aspartame
- Vanilla Flavour (spray-dried)
- Aerosil 200 Pharma
- Magnesium Stearate

6.2 Incompatibilities:
None known.

6.3 Shelf life:
24 months.

6.4 Special precautions for storage:
Store in a dry place below 30°C.
Protect from light.
Keep all medicines out of reach of children.

6.5 Nature and contents of the container:
Packed in blisters of 1x10’s, 2x10’s and 10x10’s and contained in a unit box with literature insert.

6.6 Special precautions for disposal:
No special requirements

7. Marketing Authorization Holder and Manufacturing Site Addresses Marketing Authorization Holder:
Company name: LABORATORY & ALLIED LTD
Address: PLOT NO: 209/10349 OFF MOMBASA ROAD,
P.O BOX 42875, CODE 00100 NAIROBI
Country: KENYA
Telephone: + 254 – 20-8040306
Telefax: 254 – 020 - 8040309
E-Mail: info@laballied.com

Manufacturing Site Address:

Company name: LABORATORY & ALLIED LTD
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