SUMMARY OF PRODUCT CHARACTERISTICS

1. Product name:

KLABIL ® BID 200/28 mg Dry Powder for Oral Suspension

2. Qualitative and Quantitative Composition:

Active substance:

Each 5 ml suspension contains:

223.96 mg Amoxicillin Trihydrate equivalent to 200 mg Amoxicillin and 35.535 mg Potassium Clavulanate equivalent to 28.5 mg Clavulanic Acid.

Excipients:

Each 5 ml suspension contains:

Granule powder sugar (sucrose)…….....q.s..*
*quantity sufficient.

Please see section 6.1. for other excipients.

3. Pharmaceutical Form:

Dry Powder for Oral Suspension.

Creamy-white colored raspberry odorous, homogeny powder. It is formed of creamy-white colored suspension with raspberry odorous when it is reconstituted.

4. Clinical Information:

4.1 Therapeutic Indications:

KLABIL should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

KLABIL 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 along with creeping cellulitis.

Susceptibility to KLABIL 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 KLABIL susceptible beta-lactamase-producing organisms may be treated with KLABIL suspension 228 mg/5ml. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

4.2. Posology and method of administration:

Posology:

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)

Children over 2 years;

25/3.6 mg/kg/day	2 - 6 years (13 - 21 kg)	5.0 ml KLABIL suspension 228 mg/5 ml twice daily
	7 - 12 years (22 - 40 kg)	10.0 ml KLABIL suspension 228 mg/ 5 ml twice daily

45/6.4 mg/kg/day	2 - 6 years (13 - 21 kg)	10.0 ml KLABIL suspension 228 mg/5 ml twice daily

Children aged 2 months to 2 years

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

Weight (kg)	**Dose (ml) to be administrated every 12 hours in Mild/Moderate infection**	**Dose (ml) to be administrated every 12 hours in severe infection**
2	0.6	1.2
3	1.0	1.6
4	1.2	2.2
5	1.6	2.8
6	1.8	3.4
7	2.2	4.0
8	2.6	4.6
9	2.8	5.0
10	3.2	5.6
11	3.4	6.2
12	3.8	6.8
13	4.0	7.4
14	4.4	7.8
15	4.6	8.4

There is insufficient experience with KLABIL suspension 228 mg/5 ml and 457 mg/5 ml to make dosage recommendations for children under 2 months old.

Method of administration:

Taken orally twice a day. To minimize potential gastrointestinal intolerance, administer at the start of a meal. The absorption of KLABIL 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.

Preparation of suspension:
Add boiled and cooled water approximately up to half of the bottle and shake well. Wait for 5 minutes for homogeneous dispersion. Then, add the water up to the marked level on the label and again shake.

An amount of drug recommended by doctor is given to patient by 5 mL measuring spoon.

Powder not reconstituted should keep at room temperature below 25°C, and dry place. Reconstituted suspension should keep in refrigerator (2-8°C) and be used within 7-10 days.

Should not be frozen.

Special populations:

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 KLABIL suspension 228 mg/5 ml are not recommended.

Infants with immature kidney function

For infants with immature renal function KLABIL suspension 228 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.

4.3 Contraindication:

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

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

4.4 Warnings and Precautions:

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

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 (see Contraindications).

KLABIL 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 KLABIL 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 KLABIL. The clinical significance of these changes is uncertain but KLABIL 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 KLABIL suspension 228 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).

This medicinal product contains powder sugar (sucrose). Patients with rare glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

4.5 Drug and other Interactions:
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with KLABIL 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 KLABIL and allopurinol.

In common with other antibiotics, KLABIL 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 KLABIL.

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

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.

Lactation

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. The possibility of sensitisation should be taken into account. 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 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 (see section 4.8).

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 KLABIL, 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
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
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[2]	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Tooth discolouration[11]	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.
[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[5] 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.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

[8] See section 4.9
[9] See section 4.4
[10] See sections 4.3 and 4.4
[11] 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.

4.9 Overdosage:

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 (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 Pharmacodynamics:

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in KLABIL 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 KLABIL it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

In the list below, organisms are categorized according to their in vitro susceptibility to KLABIL.

In vitro susceptibility of micro-organisms to KLABIL
Where clinical efficacy of KLABIL 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 KLABIL.

Commonly susceptible species

Gram-positive aerobes:

Bacillius anthracis
Gram-positive aerobes:
Enterococcus faecalis
Gardnerella vaginalis
Listeria monocytogenes
*Streptococcus pneumoniae**
Streptococcus pyogenes†*
Streptococcus agalactiae†*
Viridans group streptococcus†
Streptococcus spp. (other β-hemolytic)†*
Staphylococcus aureus (methicillin susceptible)†*
Staphylococcus saprophyticus (methicillin susceptible)
Coagulase negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

Bordetella pertussis
Gram-negative aerobes:
*Haemophilus influenzae**

Helicobacter pylori
*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholera

Gram-positive anaerobes:
Clostridium spp.
Gram-positive anaerobes:
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.

Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides spp.
Fusobacterium nucleatum
Fusobacterium spp.

Species for which acquired resistance may be a problem
Gram-negative aerobes:
*Escherichia coli**
Gram-negative aerobes:
Klebsiella oxytoca
*Klebsiella pneumoniae**
Klebsiella spp.
Proteus mirabilis
Proteus vulgaris
Proteus spp.
Salmonella spp.
Shigella spp

Gram-positive aerobes:

Corynebacterium spp.
Enterococcus faeciium

Inherently resistant organisms
Gram-negative aerobes:
Acinetobacter spp.
Gram-negative aerobes:
Citrobacter freundii
Enterobacter spp.
Hafnia alvei
Legionella pneumophila
Morganella morganii
Providencia spp.
Pseudomonas spp.
Serratia spp.
Stenotrophomas maltophilia
Yersinia enterolitica

Others:
Chlamydia pneumoniae
Others:
Chlamydia psittaci
Chlamydia spp.
Coxiella burnetti
Mycoplasma spp.

Infections caused by amoxicillin-susceptible organisms are amenable to KLABIL treatment due to its amoxicillin content. Mixed infections caused by amoxicillin - susceptible organisms in conjunction with KLABIL-susceptible β-lactamase producing organisms may therefore be treated with KLABIL.

5.2 Pharmacokinetics properties:
Absorption:

The two components of KLABIL 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 KLABIL 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 KLABIL 875/125 mg tablet or three times a day dosing with the KLABIL 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 T1/2, or Cmax after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate T1/2, Cmax or AUC values after appropriate dose normalisation.

The time of dosing of KLABIL relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the KLABIL 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 Cmax, the highest mean values and smallest inter-subject variabilities were achieved by administering KLABIL 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	C_{maks}	T_{maks}*	AUC	$T_{1/2}$
	(mg)	(µg/mL)	(hours)	(mg.h/L)	(hours)
Co-amoxilav 1 g					
Amoxicillin	875	12.4	1.5	29.9	1.36
Clavulanate	125	3.3	1.3	6.88	0.92

***Median values**

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).

Biotransformation
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 KLABIL 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 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:

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 discoloured tongue.

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

6. Pharmaceutical Particulars:

6.1 List of excipients:

Citric Acid (Anhydrous)
Sodium Citrate Dihydrate
Sodium Benzoate
Microcrystalline cellulose / Sodium Carboxy methyl cellulose
Xanthan Gum
Colloidal Anhydrous Silica
Silicon Dioxide
Essence Raspberry
Powdered Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life:

36 months

6.4 Special precautions for storage:

Store below 30 ^{0}C, in a dry place.
After reconstitution, 70 ml suspension can be kept for 7 days, 100 ml suspension can be kept for 10 days in a refrigerator (2-8ºC). Do not freeze.
Keep out of reach of children and in its original package.
Due to the hygroscopic, bottles should be well closed.

6.5 Nature and contents of container:

Our product is presented in amber colored Type III glass bottle well closed with HDPE cap, on which 70 mL level mark, with a 2.5-5 mL marked measuring spoon and leaflet in a carton box.

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.

Preparation of Suspension:

KLABIL is powder, so firstly reconstitution is necessary.

Please follow up the instructions below:

Please tap the bottle until the whole powder flows freely.

1. Add water until the half of marked line on the bottle and shake well to obtain suspension. (Boiled and cold water should be used)

2. To obtain completely dispersion, rest for 5 minutes.
3. Add remaining water until the marked line and shake bottle again.
4. Suspension can be administered with 5 ml measuring spoon.

Shake well the bottle after each dose.

After using, close the bottle tightly and immediately.

7. Marketing Authorization Holder:

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9.- Marketing Authorization Number :

10.- Data of First Authorization / Renewal of Authorization:

11.- Date of last revision of text:

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