1.3 PRODUCT INFORMATION

1.3.1 Summary of Product characteristics (SmPC)

1- Name of the Medicinal Product:

1.1 Name of the Medicinal Product

- Brand Name / Generic Name:

KIRACLAV 562.5 (Amoxicillin and Clavulanate Potassium Tablets USP)

- International Non-Proprietary Name (INN): Amoxicillin and Clavulanate Potassium Tablets USP)

1.2 Strength: Amoxicillin USP (As Trihydrate) eq. to Amoxicillin Anhydrous 500 mg and Diluted Potassium Clavulanate eq. to Clavulanic acid 62.5 mg

1.3 Pharmaceutical Form: Film coated tablet

2- Qualitative and Quantitative Composition :

Each film coated tablet contains:

Amoxicillin USP (As Trihydrate)	
Eq. to Amoxicillin Anhydrous	500 mg
Diluted Potassium Clavulanate BP	
Eq.to Clavulanic Acid	62.5 mg
Excipients	Q.S
Colour: Titanium Dioxide BP	

3- Pharmaceutical Form:

White coloured oval shape film coated tablet with on both sides plain.

4- Clinical Particulars

4.1 Therapeutic indications

Indications are limited to infections caused by susceptible strains such as:

- Acute otitis media
- Acute bacterial sinusitis
- Angina
- Lower respiratory tract infections, acute exacerbation of chronic bronchitis, lobar and bronchopneumonia
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis. Pyelonephritis

- Gynecolygical infections
- Periodontitis

Severe stomatological infections: abscess, phlegmons

Lower respiratory tract infections in infants and children unifier 5 years.

4.2 Posology and method of administration

The posology is exprimed in amoxicillin.

- Normorenal adult (weight a 40kg)

2 to 3g daily in 2 or 3 doses/day according to the medical prescription and the concerned infection

- Adult with renal failure (weights 40kg)

Creatinine clearance	Posology
More than 30 ml/min	No adaptation necessary
Between 10 and 30 ml/min	1g/ 125 mg every 12 to 24 h
Less than 10 ml/min	For patients treated or not by hemodialysis, condition of use aren't defined

- Ederly patients : No adaptation of posology except if creatinine clearance is < 30 m1/min (the same posology to the adult with renal failure).

- Normorenal children : The usual posology is 80mg/kg/day in 3 divided doses without exceeding 3g/ day posology.

- Children with renal failure (aged >30 months):

Kiraclav 100mg/12.5mg/m1 children

Creatinine clearance	Posology
More than 30 ml/min	No adaptation necessary
Between 10 and 30 ml/min	15 mg/kg /dose maximum twice a day
Less than 10 ml/min	15 mg/kg /dose maximum twice a day

Hentodialysis 15mg/kg/day and supplement of 15mg/kg during and after dialysis.

Normorenal infant aged < 30 months:

Kiraclav 100mg/12.5mg /m1 infant: 80 mg/kg/day in 3 doses

Method of administration

For oral use.

Take the drug preferably at the beginning of the meal.

4.3 Contraindications

- Absolutes:

Hypersensibility to any antibiotics, group of pennicillins, cephalosporins
Mononucleosis infection.
History of hcpatic dysfunction associatcd with amoxicillin + clavulanic acid.
Phenylketonuria (caused by aspartam).

- Relatives:

· Methotrexate.

4.4 Special warnings and precautions for use

The occurrence of allergic reaction requires the stop of treatment and the implementation of appropriate treatment.
Use this drug with precautions in the case of renal failure or hepatic failure.
To take account of the ration of the potassium in daily posology.
To take account of the ration of the sodium in patients following a diet low sodium strict.
The administration of high doses of beta-lactams in renal impairment or in patients who have had such convulsions previously. a treated or
damage meningeal epilepsy. may exceptionally lead to seizures

4.5 Interaction with others 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

Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of amoxicillin plus clavulanic acid. This effect tended to diminish with continued amoxicillin plus clavulanic acid use and to cease within a few days of their discontinuation. The change in predose 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: The use of association of amoxicillin and clavulanic acid should be avoided during pregnancy, unless if necessary.

Lactation: Lactation is possible in case of taking this antiobiotic. However, the lactation should be stopped (or the taking of medicine) in case of diarrhoea, candidiasis and cutanueous eruption in infant.

In general way, it is necessary during pregnancy or breastfeeding always seek advice of your doctor or pharmacist before using a medicine.

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

- Digestif manifestations : nausea, vomiting, mucocutaneous candidiasis, diarrhoea, dyspepsia. abdominal pain. pseudomembranous colitis have been reported occasionally.
- Cutanous eruption.
- Allergic manifestations urticaria. eosinophilia. quinke edema, respiratory genes and exceptional anaphylactic shock.
- Other manifestations are rarely reported :
  - Hepatitis
  - Moderate rise in AST and/or ALT and alkaline phosphatases have been reported a occasionally
  - Interstitiel nephritis

- Leucopenia. thrompocytopenia and reversible anemia

5. Pharmacological properties

5.1 Pharmacodynamics

Pharmacotherapeutic group: Combinations of penicillin, 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.

PK/PD relationship

The time above the minimum inhibitory concentration [T(time)>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. [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetics

Absorption

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 (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers, are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max}* (h)	AUC $_{(0-24h)}$ (µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500 mg/125mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125mg	125	2.10 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 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.

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

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 6h after administration of single Amoxicillin/Clavulanic acid 250mg/125mg or 500mg/125mg 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.

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.

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 amoxicillin/clavulanic acid or its components.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline Cellulose Granules (200#)
- Magnesium Stearate
- Sodium Starch Glycolate
- Croscarmellose Sodium
- Colloidal Anhydrous Silica
- Purified Talc
- Titanium Dioxide Moisture Protect (IC-MS-3582)
- Isopropyl Alcohol (Anhydrous)
- Methylene Chloride (Anhydrous)

6.2 Incompatibilities

None.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30º C

6.5 Nature and contents of container

2 X 8 Alu-Alu packing

7. Marketing Authorisation holder

BEKRA PHARMA UK LTD.
13/091, Lavington Road,
Beddington,
LONDON.
UNITED KINGDOM

8. Marketing Authorization Number

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9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text
