MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

Generic Name/INN Name: Clavulanate Potassium & Amoxicillin for Injection 600 mg
Trade Name: AMOVIN 600

Strength:

Each vial contains:

Clavulanate Potassium BP eq. to

Clavulanic Acid 100 mg

Amoxicillin Sodium BP eq. to

Amoxicillin 500 mg

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2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Spec	Std. Qty. (mg/vial)	% w/w	Function
1.	Sterile mixture of Clavunate Potassium with Amoxicillin Sodium (1:5)	In House	600	100%	Active

* Add the calculated quantity based on the Assay (potency) and Water content of sterile mixture.

3. Pharmaceutical form:

Dosage Form:

Powder for Injection

Visual & Physical characteristics of the product:

A white coloured free flowing powder filled in an intactly sealed clear glass vial.

4. Clinical particulars:

4.1 Therapeutic indications:

Clavulanate Potassium & Amoxicillin for Injection 600 mg is indicated for the treatment of the following infections in adults and children

• Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis and sinusitis when accompanied by severe systemic signs and symptoms)
• Acute exacerbations of chronic bronchitis (adequately diagnosed)
• Community acquired pneumonia
• Cystitis
• Pyelonephritis
• Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
• Bone and joint infections, in particular osteomyelitis
• Intra-abdominal infections
• Female genital infections

Prophylaxis against infections associated with major surgical procedures in adults, such as those involving the:

• Gastrointestinal tract
• Pelvic cavity
• Head and neck
• Biliary tract surgery

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Consideration should be given to the official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration:

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.
The dose of Clavulanate Potassium & Amoxicillin for Injection 600 mg that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Clavulanate Potassium & Amoxicillin for Injection 600 mg (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

This amoxicillin/clavulanic acid powder for solution for injection or infusion provides a total daily dose of 3000 mg amoxicillin and 600 mg clavulanic acid when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that an alternative intravenous formulation of Clavulanate Potassium & Amoxicillin for Injection 600 mg is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Consideration should be given to local guidelines on appropriate dosing frequencies for amoxicillin/clavulanic acid.

Adults and children ≥ 40 kg

For treatment of infections as indicated in section 4.1: 1000 mg/ 200 mg every 8 hours

For surgical prophylaxis	For procedures less than 1 hour in duration, the recommended dose is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anaesthesia (Doses of 2000 mg/200 mg can be achieved by using an alternative intravenous formulation of Clavulanate Potassium & Amoxicillin for Injection 600 mg). For procedures greater than 1 hour in duration, the recommended dose is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anaesthesia, with up to 3 doses of 1000 mg/200 mg in 24 hours. Clear clinical signs of infection at operation will require a normal course of intravenous or oral therapy post-operatively.

Children < 40 kg
Recommended doses:

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• Children aged 3 months and over: 25 mg/5 mg per kg every 8 hours
• Children aged less than 3 months or weighing less than 4 kg: 25 mg/5 mg per kg every 12 hours.

Elderly
No dose adjustment is considered necessary.

Renal impairment
Dose adjustments are based on the maximum recommended level of amoxicillin.
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given twice daily
CrCl < 10 ml /min	Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given every 24 hours
Haemodialysis	Initial dose of 1000 mg/200 mg and then followed by 500 mg/100 mg every 24 hours, plus a dose of 500 mg/100 mg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10 to 30 ml/min	25 mg/5 mg per kg given every 12 hours
CrCl < 10 ml /min	25 mg/5 mg per kg given every 24 hours
Haemodialysis	25 mg/5 mg per kg given every 24 hours, plus a dose of 12.5 mg/2.5 mg per kg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals.

Method of administration
Clavulanate Potassium & Amoxicillin for Injection 600 mg is for intravenous use.
Clavulanate Potassium & Amoxicillin for Injection 600 mg may be administered either by slow intravenous injection over a period of 3 to 4 min directly into a vein or via a drip tube or by infusion over 30 to 40 min. Clavulanate Potassium & Amoxicillin for Injection 600 mg is not suitable for intramuscular administration.
Children aged less than 3 months should be administered amoxicillin/clavulanic acid by infusion only.
Treatment with amoxicillin/clavulanic acid may be initiated by the use of an intravenous preparation and completed with an appropriate oral presentation as considered appropriate for the individual patient.

For instructions on reconstitution of the medicinal product before administration.

4.3 Contraindications:

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients used in the manufacturing of the said product.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another β-lactam agent (e.g. acephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4 Special warnings and precautions for use:

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactam agents.

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 and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy should be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Clavulanate Potassium & Amoxicillin for Injection 600 mg may not be suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. As no specific data for T>MIC are available and the data for comparable oral presentations are borderline, this presentation (without additional amoxicillin) may not be suitable for the treatment of penicillin-resistant S. pneumoniae.

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin/clavulanic acid 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.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires Clavulanate Potassium & Amoxicillin for Injection 600 mg discontinuation and contra-indicates any subsequent administration of amoxicillin.

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Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment.

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. In all populations, 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.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, Clavulanate Potassium & Amoxicillin for Injection 600 mg should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

In patients with renal impairment, the dose should be adjusted according to the degree of impairment.

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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. In patients with bladder catheters, a regular check of patency should be maintained.

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Clavulanate Potassium & Amoxicillin for Injection 600 mg may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving

amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

1000 mg/200 mg powder for solution for injection or infusion

This medicinal product contains 3.1 mmol of sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

1000 mg/200 mg powder for solution for injection or infusion

This medicinal product contains 1.0 mmol of potassium per vial. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) 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. A change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment

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4.6 Fertility, 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.

Breastfeeding
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.

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.

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/clavulanic acid, 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

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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
Convulsions[2]	Not known
Aseptic meningitis	Not known
Vascular disorders	
Thrombophlebitis[3]	Rare
Gastrointestinal disorders	
Diarrhoea	Common
Nausea	Uncommon
Vomiting	Uncommon
Indigestion	Uncommon
Antibiotic-associated colitis[4]	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

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. Pharmacological properties:

5.1 Pharmacodynamic properties:

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

ATC code: J01CR02.

Mechanism of action

Amoxicillin is 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.

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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.

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,

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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.

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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 Pharmacokinetic properties:

Absorption

The pharmacokinetic results for studies in which amoxicillin/clavulanic acid was administered to groups of healthy volunteers as either 500 mg/100 mg or 1000 mg/200 mg given as a bolus intravenous injection are presented below.

Mean (±SD) pharmacokinetic parameters
Bolus intravenous injection

Dose administered	Amoxicillin				
	Dose	Mean peak serum conc (µg/ml)	T 1/2 (h)	AUC (h.mg/l)	Urinary recovery (%, 0 to 6 h)
AMX/CA 500 mg/100 mg	500 mg	32.2	1.07	25.5	66.5
AMX/CA 1000 mg/200 mg	1000 mg	105.4	0.9	76.3	77.4
	Clavulanic acid				
AMX/CA 500 mg/100 mg	100 mg	10.5	1.12	9.2	46.0
AMX/CA 1000 mg/200 mg	200 mg	28.5	0.9	27.9	63.8

AMX – amoxicillin, CA – clavulanic acid

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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.

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 a single 500 mg/100 mg or a single 1000 mg/200 mg bolus intravenous injection. 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.

Paediatric population

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.

Older people

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.

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Not applicable

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage:

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the injection and infusion solutions should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Do not store above 25°C, keep the container in the outer carton.

Storage conditions after reconstitution:

Do not store above 25 °C.

6.5 Nature and contents of container:

Clavulanate Potassium & Amoxicillin for Injection 600 mg supplied in 10 ml Clear Tubular glass vial USP Type-I.

Such1 vial is packed in one Monocarton with patient information leaflet.

6.6 Special precautions for disposal:

No special requirements.Any unused product or waste material should be disposed of in accordance with local requirements.