# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE HUMAN MEDICINAL PRODUCT

AMOKLAVIN 1.2 g Powder for Solution for IV Injection/Infusion

Sterile

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

**Active Substance(s):**

Amoxicillin sodium……1060.208 mg (equivalent to 1000 mg Amoxicillin)

Potassium clavulanate…….238.253 mg (equivalent to 200 mg Clavulanic acid)

If reconstituted as recommended, it contains 53.01 mg amoxicillin sodium equivalent to 50 mg amoxicillin and 11.913 mg potassium clavulanate equivalent to 10 mg clavulanic acid per ml.

**Excipient(s) with known effect:**

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Vial containing powder for injection/infusion.

White to cream colored, crystal powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

AMOKLAVIN is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

— 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

## 4.2 Posology and method of administration

**Posology/frequency and duration of administration**

The dose of AMOKLAVIN selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- 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 AMOKLAVIN (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

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 amoxicillin/clavulanic acid be selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

Adults and children weighing 40 kg and above
For treatment of infections as indicated, 1.2 g of AMOKLAVIN is given every 8 hours.

For surgical prophylaxis
For procedures less than 1 hour in duration, the recommended dose of AMOKLAVIN is 1.2 g to 2200 mg given at induction of anesthesia. For procedures greater than 1 hour in duration, the recommended dose is 1200 mg to 2200 mg given at induction of anesthesia, with up to 3 doses of 1200 mg in 24 hours. Clear clinical signs of infection at operation will require a normal course of intravenous or oral therapy post-operatively.

**Method of administration**

AMOKLAVIN is for intravenous use. It is not suitable for intramuscular administration.

AMOKLAVIN is dissolved in the solvent (20 ml water for injection) provided in the package. It may be then administered either by 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. Compatible intravenous infusion solutions for AMOKLAVIN and stability periods with these solutions are given in section 6.6.

Children aged less than 3 months should be administered AMOKLAVIN by infusion only.

Treatment with AMOKLAVIN may be initiated by the use of an intravenous preparation and completed with an appropriate oral presentation as considered appropriate.

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment both children and adults should not be extended beyond 14 days without review.

**Additional information on special populations**

Renal impairment
No dose adjustment is required in patients with creatinine clearance greater than 30 ml/min.

Adults and children weighing 40 kg and above:

| | |
|---|---|
| Creatinine clearance: 10-30 ml/min | Treatment is started with 1.2 g AMOKLAVIN and continued with 600 mg AMOKLAVIN every 12 hours. |
| Creatinine clearance: <10 ml/min | Treatment is started with 1.2 g AMOKLAVIN and continued with 600 mg AMOKLAVIN every 24 hours. |
| Hemodialysis patients | The treatment is started with 1.2 g of AMOKLAVIN and continued with 600 mg every 24 hours. Since dialysis reduces serum concentrations of both amoxicillin and clavulanic acid, 600 mg of AMOKLAVIN should be administered additionally after dialysis. |

Children weighing less than 40 kg:

| | |
|---|---|
| Creatinine clearance: 10-30 ml/min | 30 mg/kg every 12 hours |
| Creatinine clearance: <10 ml/min | 30 mg/kg every 24 hours |
| Hemodialysis patients | 30 mg/kg every 24 hours. Since dialysis reduces serum concentrations of both amoxicillin and clavulanic acid, 15 mg/kg of AMOKLAVIN should be administered additionally after dialysis. |

Hepatic impairment
Dosage should be adjusted carefully and liver function should be monitored at regular intervals.

Pediatric populations
Prescribed doses for adults are administered in children weighing 40 kg and above.
Children weighing less than 40 kg:
- Recommended dose is 30 mg/kg* every 8 hours in children aged 3 months and over.
- Recommended dose is 30 mg/kg* every 12 hours in children aged less than 3 months or weighing less than 4 kg.

*: 30 mg AMOKLAVIN contains 25 mg amoxicillin and 5 mg clavulanic acid.

Geriatric populations
No dose adjustment is considered necessary.

### 4.3 Contraindications
AMOKLAVIN is contraindicated in patients with:
- Hypersensitivity to the active substance, penicillins or, any excipients listed in section 6.1.
- History of severe immediate hypersensitivity reaction (e.g. anaphylaxis) to other beta-lactam antibiotics (e.g. cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to treatment of amoxicillin/clavulanic acid or penicillin (see section 4.8).

### 4.4 Special warnings and precautions for use
Before initiating therapy with AMOKLAVIN, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other beta-lactam antibiotics (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhea, hypotension or leukocytosis with neutrophilia. There have been severe cases including progression to shock.

Where amoxicillin-susceptible organism(s) are known to cause infection, replacement of amoxicillin/clavulanic acid with amoxicillin should be considered in accordance with national guidelines.

The use of AMOKLAVIN is not suitable when suspected pathogens are at risk of becoming resistant to beta-lactam antibiotics that are not mediated by beta-lactamases sensitive to inhibition of 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 (see section 4.8).

AMOKLAVIN therapy 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 of AMOKLAVIN may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires AMOKLAVIN discontinuation and contra-indicates any subsequent administration of amoxicillin.

AMOKLAVIN should be used with caution in patients with hepatic impairment (see section 4.2, 4.3 and 4.8).

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 (see section 4.8).

Antibiotic-associated colitis has been reported with all antibacterial agents and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhea during to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicines are contraindicated in this situation.

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

Prolongation of prothrombin time has been reported rarely in some patients receiving anticoagulants/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustment in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria (including acute renal injury) 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. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

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 AMOKLAVIN may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There are reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA (enzyme–immunoassay) 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.

This medicinal product contains 62.9 mg (2.7 mmol) of sodium per vial equivalent to 3.145% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

AMOKLAVIN contains 39.3 mg (1 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 normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

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.

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. 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.

Allopurinol

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

**Additional information for special populations**

No data available.

**Pediatric population**

No data available.

## 4.6 Fertility, pregnancy and lactation

**General recommendation**

Pregnancy category “B”.

**Women with childbearing potential/Birth-control (Contraception)**

No data available.

**Pregnancy**

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal 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 fetal membrane, it was reported that prophylactic treatment with amoxicillin/clavulanic acid might 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, diarrhea 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 sensitization should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

**Reproductive ability / Fertility**
No data available.

### 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, patients should be informed that undesirable effects may occur (e.g. allergic reactions, dizziness, and 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 are diarrhea, nausea and vomiting.

The adverse reactions 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 to classify the occurrence of undesirable effects.

| | |
|---|---|
| Very common | : ≥1/10 |
| Common | : ≥1/100 to <1/10 |
| Uncommon | : ≥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**

| | |
|---|---|
| Common | : Mucocutaneous candidiasis |
| Not known | : Overgrowth of non-susceptible organisms |

**Blood and lymphatic system disorders**

| | |
|---|---|
| Rare | : Reversible leucopenia (including neutropenia) and thrombocytopenia |
| Not known | : Reversible agranulocytosis and hemolytic anemia, prolongation of bleeding and prothrombin time (see section 4.4) |

**Immunity system disorders (see sections 4.3 and 4.4)**
Not known : Angioneurotic edema, anaphylaxis, serum sickness-like syndrome,

hypersensitivity vasculitis

**Nervous system disorders**
Uncommon : Dizziness, headache
Not known : Convulsions (see section 4.4), aseptic meningitis

**Cardiac disorders**
Not known : Kounis syndrome

**Vascular disorders**
Rare : Thrombophlebitis (at the site of injection)

**Gastrointestinal disorders**
Common : Diarrhea
Uncommon : Nausea, vomiting, indigestion
Not known : Antibiotic-associated colitis (including pseudomembranous colitis and hemorrhagic colitis [see section 4.4]), drug-induced enterocolitis syndrome (DIES), pancreatitis acute

**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.
Not known : Hepatitis and cholestatic jaundice have been reported, these events have also been noted with other penicillins and cephalosporins (see section 4.4)

**Skin and subcutaneous tissue disorders**
Uncommon : Skin rash, pruritus, urticaria
Rare : Erythema multiforme
Not known : Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis and acute generalized exanthematous pustulosis (AGEP) (see section 4.4), drug reaction with eosinophilia and systemic symptoms (DRESS), Linear IgA disease
If any hypersensitivity dermatitis reaction occurs, treatment should be stopped (see section 4.4).

**Renal and urinary disorders**
Not known : Interstitial nephritis, crystalluria (including acute renal injury) (see section 4.9)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

## 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, was observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those using 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 hemodialysis.

## 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 penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (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, 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 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.

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 (microgram/ml) | | |
|---|---|---|---|
| | Susceptibility | 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** |
|---|
| Gram-positive aerobes<br>*Enterococcus faecalis*<br>*Gardnerella vaginalis*<br>*Staphylococcus aureus* (methicillin-susceptible)[£]<br>Coagulase-negative staphylococci (methicillin-susceptible)<br>*Streptococcus agalactiae*<br>*Streptococcus pneumoniae*[1]<br>*Streptococcus pyogenes* and other beta-hemolytic streptococci<br>*Streptococcus* viridans group<br><br>Gram-negative aerobes<br>*Actinobacillus actinomycetemcomitans*<br>*Capnocytophaga* spp.<br>*Eikenella corrodens*<br>*Haemophilus influenzae*[2]<br>*Moraxella catarrhalis*<br>*Neisseria gonorrhoeae*§<br>*Pasteurella multocida*<br><br>Anaerobic microorganisms<br>*Bacteroides fragilis*<br>*Fusobacterium nucleatum*<br>*Prevotella* spp. |
| **Species for which acquired resistance may be a problem** |
| Gram-positive aerobes<br>*Enterococcus faecium* $ |

| |
|---|
| Gram-negative aerobes<br>*Escherichia coli*<br>*Klebsiella oxytoca*<br>*Klebsiella pneumoniae*<br>*Proteus mirabilis*<br>*Proteus vulgaris* |
| **Inherently resistant organisms** |
| Gram-negative aerobes<br>*Acinetobacter* sp.<br>*Citrobacter freundii*<br>*Enterobacter* sp.<br>*Legionella pneumophila*<br>*Morganella morganii*<br>*Providencia* spp.<br>*Pseudomonas* sp.<br>*Serratia* sp.<br>*Stenotrophomonas maltophilia*<br><br>Other microorganisms<br>*Chlamydia trachomatis*<br>*Chlamydophila pneumoniae*<br>*Chlamydophila psittaci*<br>*Coxiella burnetti*<br>*Mycoplasma pneumonia* |

$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.
£ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid.
§ All strains with resistance to amoxicillin that is not mediated by beta-lactamases are resistant to amoxicillin/clavulanic acid.
[1] This presentation of amoxicillin/clavulanic acid may not be suitable for treatment of *Streptococcus pneumoniae* that are resistant to penicillin (see sections 4.2 and 4.4).
[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 a study, in which amoxicillin/clavulanic acid 500 mg/100 mg or 1000 mg/200 mg was administered by bolus intravenous injection route in the healthy volunteers are presented below.

Mean Pharmacokinetic Parameters
*Bolus intravenous injection*

| Dose administered | Amoxicillin | | | | |
|---|---|---|---|---|---|
| | Dose | Mean peak serum concentration (mcg/ml) | $T_{1/2}$ (hour) | AUC (h.mg/l) | Urinary recovery (%, 0 to 6 h) |
| Amox 500 mg/ CA 100 mg | 500 mg | 32.2 | 1.07 | 25.5 | 66.5 |
| Amox 1000 mg/ CA 200 mg | 1000 mg | 105.4 | 0.9 | 76.3 | 77.4 |

| | Clavulanic acid | | | | |
|---|---|---|---|---|---|
| Amox 500 mg/ CA 100 mg | 100 mg | 10.5 | 1.12 | 9.2 | 46 |
| Amox 1000 mg/ CA 200 mg | 200 mg | 28.5 | 0.9 | 27.9 | 63.8 |
| Amox: Amoxicillin, CA: Clavulanic acid | | | | | |

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 application, 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).

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 feces 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 60-70% of the amoxicillin and approximately 40- 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 (see section 4.5)

**Characteristics in patients**
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.

Age
The elimination half-life of amoxicillin is same 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.

**Pharmacokinetic/Pharmacodynamic relationship**
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

### 5.3 Preclinical safety data
Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

In repeated dose toxicity studies in dogs with amoxicillin/clavulanic acid, gastric irritation, vomiting, and tongue discoloration were observed.

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

## 6. PHARMACEUTICAL PARTICULARS
### 6.1 List of Excipients
Vial : None.
Solvent ampoule : Water for injection.

### 6.2 Incompatibilities
AMOKLAVIN must not be mixed with other medicinal products, except those mentioned in section 6.6.
AMOKLAVIN should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
Because of the risk of loss of activity of aminoglycosides in the presence of any of the aminopenicillins, antibiotics should be reconstituted and administered separately when AMOKLAVIN is prescribed together with aminoglycosides.
AMOKLAVIN solutions should not be mixed with infusions containing glucose, dextran or bicarbonate.

### 6.3 Shelf life
36 months.

### 6.4 Special precautions for storage
Dry powder should be stored at room temperature below 25°C.

Reconstituted solution should be used immediately.

### 6.5 Nature and contents of container

Colorless Type III glass bottle sealed with aluminum safety capsule and teflon-coated butyl rubber stopper, and colorless, ringed, Type I glass ampoule containing water for injection.
Each box contains 1 vial and 1 solvent ampoule.

### 6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements
For single use only. Discard any unused solution.
The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.
Any unused product or waste material should be disposed of in accordance with local requirements

Preparation of solutions for intravenous injection
AMOKLAVIN is dissolved in solvent (20 ml water for injection) accompanying the product. The intravenous injection should be administered within 20 min of reconstitution.

Preparation of solutions for intravenous infusion
AMOKLAVIN is not suitable for multi-dose use.
AMOKLAVIN is dissolved in solvent (20 ml water for injection) accompanying the product and should be added to 100 ml of infusion solution without delay.

Time periods for intravenous infusion with different solvents are given below:

| Compatible infusion solutions with AMOKLAVIN | Stability period |
|---|---|
| Water for injection | 2 hours |
| Sodium chloride 0.9% | 2 hours |
| Sodium lactate (M/6) | 1 hour |
| Ringer's solution | 1 hour |
| Lactated Ringer's Solution | 1 hour |
| Potassium chloride and sodium chloride intravenous infusion | 1 hour |

AMOKLAVIN is less stable in infusions containing glucose, dextran or bicarbonate. Therefore AMOKLAVIN should not be added to such infusions but may be injected into the drip tubing over a period of 3-4 minutes.
Any remaining antibiotic solution should be discarded.

## 7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

## 8. MARKETING AUTHORIZATION NUMBER(S)

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## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 19.10.2000
Date of last renewal :

## 10. DATE OF REVISION OF THE TEXT

04.10.2024