SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
AMOKLAVIN 875 mg/125 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Each tablet contains:
Amoxicillin (INN) (from bovine, sheep or goat milk) ..... 875 mg
Clavulanic Acid (INN) ..... 125 mg

Excipient(s) with known effect:
Sodium starch glycolate ..... 29 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
White-colored, odorless, slightly biconvex, oblong-shaped, film-coated tablets with a homogenous appearance, and scored in the middle on one side and debossed with DEVA on the other side.
The purpose of the scored is to make it easier to break the tablet while swallowing.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
AMOKLAVIN-BID is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1).

- Upper respiratory tract infections :Such as acute bacterial sinusitis (diagnosed with appropriate diagnosis), acute otitis media, recurrent tonsillitis
- Lower respiratory tract infections :Such as acute exacerbations of chronic bronchitis (diagnosed with appropriate diagnosis), community acquired pneumonia
- Urinary system infections :Such as cystitis, pyelonephritis
- Skin and soft tissue infections :Especially cellulite, animal bites
- Dental infections :Severe dental abscesses with widespread cellulitis
- Bone and joint infections :Especially osteomyelitis

Official guidelines on the appropriate use of antibacterial agents should be observed.

4.2 Posology and method of administration
Posology/frequency and duration of administration
Doses are defined according to the amoxicillin/clavulanic acid content, except for doses specified for each ingredient. The following conditions should be taken into account for the dose of AMOKLAVIN selected to treat an infection:

- Expected pathogens and their possible susceptibility to antibacterial agents (see section 4.4)
- Severity and site of infection
- Patient's age, weight and kidney function as indicated below

When necessary, the use of alternative forms of AMOKLAVIN (e.g. those providing higher

doses of amoxicillin and/or containing different amoxicillin/clavulanic acid ratios) should be considered (see sections 4.4 and 5.1).

In adults and children weighing ≥ 40 kg, this AMOKLAVIN formula provides a total of 1750 mg amoxicillin/250 mg clavulanic acid when received twice daily as recommended below, or 2625 mg amoxicillin/375 mg clavulanic acid when received three times daily as recommended below.

In children < 40 kg, this AMOKLAVIN formula provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid when given as recommended below. If a higher daily dose of amoxicillin is considered necessary, it is recommended to select another form of AMOKLAVIN to avoid administration of high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of treatment should be determined according to the patient's response. Some infections (e.g. osteomyelitis) require longer treatment periods. It should not be extended beyond 14 days without review (for extended treatment, see section 4.4).

Adults and children weighing ≥ 40 kg
Recommended doses:
- Standard dose (for all indications): 875 mg/125 mg twice daily;
- High dose (especially for otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day.

Children weighing < 40 kg
Children can be treated with AMOKLAVIN tablets or suspensions.
Recommended doses:
- 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given in two divided doses;
- Doses up to 70 mg/10 mg/kg/day given in two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

Children under 25 kg should not be treated with AMOKLAVIN tablets.

The table below shows the dose (mg/kg body weight) received in children weighing 25 kg to 40 kg when a single 875 mg/125 mg tablet is administered.

Body weight (kg)	40	35	30	25	Single dose recommended (mg/kg body weight) (see above)
Amoxicillin per single dose (1 film coated tablet) (mg/kg body weight)	21.9	25	29.2	35	12.5 – 22.5 (up to 35)
Clavulanic acid per single dose (1 film coated tablet) (mg/kg/body weight)	3.1	3.6	4.2	5	1.8 – 3.2 (up to 5)

Children weighing less than 25 kg should preferably be treated with AMOKLAVIN suspension.

There are no clinical data on doses of AMOKLAVIN 7:1 formulations higher than 45 mg/6.4 mg/kg per day in children under 2 years of age.

No clinical data are available for AMOKLAVIN 7:1 formulations for infants under 2 months of age. Therefore, dosage recommendations cannot be made in this population.

Method of administration
AMOKLAVIN is for oral use. AMOKLAVIN should be taken with meals to minimize potential gastrointestinal intolerance.

Tablets should be swallowed whole without chewing. If needed, due to difficulty swallowing, tablets can be divided into two parts and swallowed consecutively without chewing.

AMOKLAVIN is available in intravenous form. Please see "Summary of Product Characteristics" of intravenous form of AMOKLAVIN for further information.

Additional information on special populations
Renal impairment
No dose adjustment is needed in patients with creatinine clearance (CrCl) higher than 30 mL/min. Since there is no advice for dose change in patients with creatinine clearance less than 30 mL/min, the use of AMOKLAVIN forms with an amoxicillin/clavulanic acid ratio of 7:1 is not advised.

Hepatic impairment
Dose change should be made carefully and hepatic function should be monitored at regular intervals (see sections 4.3 and 4.4).

Pediatric population
Children under 25 kg should not be treated with AMOKLAVIN tablets. Children aged 6 years and under or weighing less than 25 kg should preferably be treated with AMOKLAVIN suspension. See "Summary of Product Characteristics" of AMOKLAVIN suspension for further information.

Geriatric population
No dose adjustment is deemed necessary.

4.3 Contraindications
- It is contraindicated in patients with hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.
- AMOKLAVIN is contraindicated in those with a history of hypersensitivity (e.g. anaphylaxis) to other beta-lactam agents (e.g. cephalosporin, carbapenem or monobactam).
- It is contraindicated in patients with a history of jaundice/hepatic insufficiency due to amoxicillin/clavulanic acid (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 beta-lactam agents (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.

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 intake), 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. If an allergic reaction occurs, AMOKLAVIN therapy must be discontinued and appropriate alternative treatment instituted.

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

This presentation of AMOKLAVIN is not 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. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

AMOKLAVIN 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 also 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 exanthematous pustulosis (AGEP) (see section 4.8). This reaction requires discontinuation of AMOKLAVIN and contraindicates subsequent use of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 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. 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 with known potential to affect the liver (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin 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 or subsequent to the administration of any antibiotics. Should antibiotic-associated

colitis occur, AMOKLAVIN should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products 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 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 (see sections 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 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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet so it is essentially “sodium-free”.

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 (INR) in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or INR should be carefully monitored with the addition or withdrawal of AMOKLAVIN. 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 with probenecid is not recommended. Probenecid reduces renal tubular secretion of amoxicillin. Concomitant use of probenecid with AMOCLAVIN may result in increased blood levels of amoxicillin and prolonged blood exposure, whereas this does not

occur for 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. 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
Use of allopurinol during amoxicillin therapy may increase the possibility of allergic skin reactions. There is no data on the combined use of allopurinol and AMOKLAVİN.

Oral contraceptives
As with other antibiotics, AMOKLAVİN may affect the intestinal flora. This leads to decreased estrogen reabsorption and reduces the effectiveness of combined oral contraceptives.

Additional information on special populations
No data available.

Pediatric population
No data available.

4.6 Fertility, pregnancy and lactation
General Recommendation
Pregnancy category is “B”.

Women of childbearing potential/Contraception
As with other antibiotics, AMOKLAVIN may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives. Therefore, additional birth control methods may need to be used.

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 (pPROM), it was reported that prophylactic treatment with amoxicillin/clavulanic acid combination might be associated with an increased risk of necrotizing enterocolitis in neonates. As with all medicines, use should be avoided during pregnancy (especially during the first trimester) unless considered essential by the physician.

Breast-feeding
Both active substances of AMOKLAVIN 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.

Fertility
No data available.

4.7 Effects on ability to drive and use machines
No studies on the effects of AMOKLAVIN 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, 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 drug 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 in order to classify undesirable effects according to their frequency of occurrence:

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 (frequency 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 leukopenia (including neutropenia) and thrombocytopenia
Not known : Reversible agranulocytosis and hemolytic anemia. Prolongation of bleeding time and prothrombin time[1]

Immune system disorders[8]:
Not known : Angioneurotic edema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous **system disorders:**
Uncommon : Dizziness, headache
Not known : Aseptic meningitis, reversible hyperactivity and convulsions[1]

Cardiac disorders:
Not known : Kounis syndrome

Gastrointestinal disorders:
Very common : Diarrhea (in adults)
Common : Nausea[2], vomiting, diarrhea (in children)
Uncommon : Difficulty in digestion
Not known : Antibiotic-associated colitis[3], drug-induced enterocolitis syndrome, acute pancreatitis, black hairy tongue (the papillae on the tongue become prominent and turn black)

Hepato-biliary disorders:

Uncommon : Rises in AST and/or ALT[4]
Not known : Hepatitis[5] and cholestatic jaundice[5]

Skin and subcutaneous tissue disorders[6]:
Uncommon : Skin rash, pruritus, urticaria
Rare : Erythema multiforme
Not known : Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalized exanthemous pustulosis (AGEP)[1]. Drug reaction with eosinophilia and systemic symptoms (DRESS), symmetric drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome), Linear IgA disease

Renal and urinary disorders:
Not known : Interstitial nephritis, crystalluria (including acute renal damage)[7]

[1] See section 4.4
[2] Nausea is often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and hemorrhagic colitis (see section 4.4).
[4] 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.
[5] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[6] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[7] See section 4.9
[8] See sections 4.3 and 4.4

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, has been observed (see section 4.4).

Convulsions may occur in patients with renal dysfunction 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 hemodialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials; Combinations of penicillins, including 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.

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.

Sensitivity breakpoints
MIC (Minimum Inhibitory Concentrations) interpretation criteria for susceptibility testing were established by the European Antimicrobial Susceptibility Testing (EUCAST) for Amoxicillin/clavulanic acid.

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.

Generally susceptible species
Aerobic Gram-positive microorganisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus (sensitive to methicillin)* £ *Coagulase negative staphylococci (sensitive to methicillin)* *Streptococcus agalactiae* *Streptococcus pneumoniae*1

Streptococcus pyogenes and other beta-hemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative microorganisms *Capnocytophaga spp.* *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic microorganisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella spp.*
Species where acquired resistance may be a problem
Aerobic Gram-positive microorganisms *Enterococcus faecium* $
Aerobic Gram-negative microorganisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Organisms that are inherently resistant
Aerobic Gram-negative microorganisms *Acinetobacter spp.* *Citrobacter freundii* *Enterobacter spp.* *Legionella pneumophila* *Morganella morganii* *Providencia spp.* *Pseudomonas spp.* *Serratia spp.* *Stenotrophomonas maltophilia* Other microorganisms *Chlamydophila pneumoniae* *Chlamydophila psittaci*
$ Moderate natural susceptibility in the absence of an acquired resistance mechanism £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. 1 *Streptococcus pneumoniae* that is resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). 2 In some EU countries, strains with reduced susceptibility have been reported at a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption:

The two components of AMOKLAVIN, 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.

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 (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study in which amoxicillin/clavulanic acid 875/125 mg tablets twice daily were 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} (mcg/ml)	T_{max}* (h)	$AUC_{(0-24h)}$ (mcg.h/ml)	$T_{1/2}$ (h)
Amoxicillin					
AMX / CA 875 / 125 mg	875	11.64 ±2.78	1,5 (1.0-2.5)	53.52 ±12.31	1.19 ±0.21
Clavulanic acid					
AMX / CA 875 / 125 mg	125	2.18 ±0.99	1.25 (1.0-2.0)	10.16 ±3.04	0.96 ±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 tissue, 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 humans and excreted in urine and feces and in the air as carbon dioxide.

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 combination 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 single amoxicillin + clavulanic acid tablet 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 renal excretion but does not affect the excretion of clavulanic acid (see section 4.5).

Linearity/Non-linearity:
Amoxicillin has linear pharmacokinetics over the therapeutic dose range.

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 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.

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 discolored tongue.

Carcinogenicity studies have not been conducted with AMOKLAVIN or its components.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Tablet Core:

Sodium starch glycolate
Microcrystalline cellulose
Silica anhydrous colloidal
Silica colloidal hydrate
Magnesium stearate

Film Coating:

Aquar. Prfrd. Hspbpp218011:

Hypromellose
Titanium dioxide (E171)
Macrogol 3350
Polydextrose
Copovidone
Medium chain triglycerides

6.2 Incompatibilities
No known incompatibilities exist.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store at room temperature below 25°C and in a dry place.

6.5 Nature and contents of container
Alu-Alu blister.
Each cardboard box contains 10, 14 or 20 film-coated tablets.
Not all pack sizes may be marketed.

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.

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

8. MARKETING AUTHORIZATION NUMBER
184/68

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 06.10.1997
Date of latest renewal : 22.06.2011

10. DATE OF REVISION OF THE TEXT