SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMOKLAVIN ES 600 mg + 42.9 mg/5 ml Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Each 5 ml suspension contains:
Amoxicillin (produced from bovine milk) ..... 600 mg (as 688.67 mg amoxicillin trihydrate)
Clavulanic acid ..... 42.9 mg (as 51.105 mg potassium clavulanate)

Excipient(s):
For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
White to off-white, homogenous powder mixture with fruit-vanillin odor; constitutes a white to creamy white, homogeneous, fruit- vanillin flavored suspension, when reconstituted.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

AMOKLAVIN ES is indicated for the short-term treatment of bacterial infections that are suspected to be caused by amoxicillin resistant beta-lactamase producing strains in the following systems. In other situations, amoxicillin alone should be considered.

- Upper respiratory tract infections (including ear, nose and throat):
  For example recurrent or chronic otitis media due to *Streptococcus pneumoniae* (penicillin minimum inhibitory concentration (MIC) ≤4 µg/ml), *Haemophilus influenzae** and *Moraxella catarrhalis**. Such patients are often characterized by antibiotic exposure for acute otitis media within the preceding 3 months, and are either aged ≤2 years or attend daycare.
- Tonsillo-pharyngitis and sinusitis typically caused by *Streptococcus pneumoniae, Haemophilus influenzae**, *Moraxella catarrhalis** and *Streptococcus pyogenes*.
- Lower respiratory tract infections; e.g. lobar pneumonia and bronchopneumonia typically caused by *Streptococcus pneumoniae, Haemophilus influenzae** and *Moraxella catarrhalis**.
- Skin and soft tissue infections typically caused by *Staphylococcus aureus** and *Streptococcus pyogenes*.

*Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin (see section 5.1).

Susceptibility to AMOKLAVIN ES will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

4.2 Posology and method of administration

Posology/frequency and duration of administration
The recommended dose of AMOKLAVIN ES is 90/6.4 mg/kg/day in two divided doses at 12-hourly intervals for 10 days (see table below). There is no experience in pediatric patients weighing over 40 kg and in adults. There are no clinical data on AMOKLAVIN ES in children under 3 months of age.

Body weight (kg)	AMOKLAVIN ES amount providing 90/6.4 mg/kg/day dosage
8	Twice daily 3.0 ml
12	Twice daily 4.5 ml
16	Twice daily 6.0 ml
20	Twice daily 7.5 ml
24	Twice daily 9.0 ml
28	Twice daily 10.5 ml
32	Twice daily 12.0 ml
36	Twice daily 13.5 ml

AMOKLAVIN ES 600 mg + 42.9 mg/5 ml powder for oral suspension does not contain the same amount of clavulanic acid (as potassium salt) as any of the other amoxicillin-clavulanate suspensions.

AMOKLAVIN ES 600 mg + 42.9 mg/5 ml powder for oral suspension contains 42.9 mg clavulanic acid per 5 ml whereas AMOKLAVIN-BID 200 mg + 28 mg contains 28.5 mg clavulanic acid per 5 ml powder for oral suspension and AMOKLAVIN-BID 400 mg + 57 mg/5 ml Forte powder for oral suspension contains 57 mg clavulanic acid per 5 ml. Therefore, the AMOKLAVIN-BID 200 mg + 28 mg/5 ml powder for oral suspension and AMOKLAVIN-BID 400 mg + 57 mg/ 5ml Forte powder for oral suspension should not be substituted for AMOKLAVIN ES 600 mg + 42.9 mg/5 ml powder for oral suspension, as these products are not interchangeable.

Method of administration
AMOKLAVIN ES is for oral use. It should be taken with meals to minimize the potential gastrointestinal intolerance.
Treatment should not be extended beyond 14 days without check up.
Therapy can be started parenterally and continued with an oral preparation.
Oral suspension should be well-shaken before use.

Additional information on special populations

Renal/Hepatic impairment
No dose adjustment is required in children with creatinine clearance of 30 ml/min or over. In children with creatinine clearance less than 30 ml/min, the use of AMOKLAVIN ES is not recommended.

Caution is advised in the dose adjustment of patients with hepatic impairment. Hepatic functions should be monitored at regular intervals. There is insufficient data for dosage recommendations.

Pediatric population:
Posology/frequency and duration of administration indicated above are valid for pediatric population.

Geriatric population:
Not applicable.

4.3 Contraindications
Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.
AMOKLAVİN ES is contraindicated in patients 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 impairment due to amoxicillin/clavulanate (see section 4.8).

4.4 Special warnings and precautions for use
Before initiating therapy with AMOKLAVIN ES, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalolosporins and other allergens (see section 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 may also progress to Kounis syndrome, a severe allergic reaction that may 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 (see section 4.3). Drug-induced enterocolitis syndrome (DIES) has been reported mostly in children receiving amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction in which the main symptom is prolonged vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Other symptoms may consist of abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. Serious cases progressing to shock have been observed. If an allergic reaction occurs, treatment with amoxicillin/clavulanate should be stopped and an alternative treatment should be initiated.

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.

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

Amoxicillin/clavulanate 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 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 amoxicillin/clavulanate discontinuation and contraindicates any subsequent

administration 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 known to have the potential for hepatic effects (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, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs 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 is required when prescribed with anticoagulants. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

Crystalluria (including acute kidney injury) has been observed very rarely in patients with reduced urine output, particularly with parenteral therapy. During high-dose amoxicillin therapy, adequate fluid intake and urine output management are recommended to reduce the possibility of amoxicillin crystalluria. In patients with a bladder catheter, the patency of the catheter should be checked regularly (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 amoxicillin/clavulanate 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.

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 (INR) 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 (INR) 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 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. 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. No data is available regarding the concomitant use of allopurinol and amoxicillin/clavulanate.

Oral contraceptives:
In common with other antibiotics, amoxicillin/clavulanate may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

Additional information on special populations
No interaction studies have been performed. Data is not available.

Pediatric population
No interaction studies have been performed. The information given above is also applicable for the pediatric population.

4.6 Fertility, pregnancy and lactation

General Principles
Pregnancy category is B

Women of child-bearing potential/Contraception
As with other antibiotics, AMOKLAVIN ES may affect the gut flora, leading to lower estrogen

reabsorption and reduced efficacy of combined oral contraceptives. Therefore, an effective, reliable and alternative method of contraception should be applied during treatment.

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 may be associated with an increased risk of necrotizing enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Caution is advised when prescribing to pregnant women.

In reproductive studies conducted on animals (10 times the human dose administered to mice and rats) administered orally or parenterally, amoxicillin/clavulanate did not show teratogenic effects.

As with all medicines, use should be avoided during pregnancy (especially during the first trimester) unless considered essential by the doctor.

Breast-feeding
Both drug substances of AMOKLAVIN ES 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 doctor in charge.

Fertility
The amoxicillin/clavulanic acid combination at oral doses up to 1,200 mg/kg/day (5.7 times the maximum adult human dose on a body surface area basis) was found to have no effects on fertility and reproductive performance in rats dosed with a 2:1 amoxicillin:clavulanate formulation.

4.7 Effects on ability to drive and use machines
No studies on the effects of amoxicillin/clavulanate on the ability to drive and use machines have been performed. However, patients should be advised that undesirable effects (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines, may occur (see section 4.8).

4.8 Undesirable effects
The most commonly reported adverse drug reactions (ADRs) are diarrhea, nausea and vomiting.

Adverse drug reactions from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, classified by MedDRA system organ class, are listed below.

The following terminology is used to classify adverse reactions according to their frequency of occurrence:
Very common : affects at least 1 in 10 patients
Common : affects 1 to 10 patients in 100
Uncommon : affects 1 to 10 patients in 1000

Rare : affects 1 to 10 patients in 10.000
Very rare : affects less than 1 patient in 10.000
Unknown : cannot be estimated from the available data.

Infections and infestations	
Common	Mucocutaneous candidiasis
Unknown	Overgrowth of non-susceptible organisms
Blood and lymphatic system disorders	
Rare	Reversible leucopenia (including neutropenia) and thrombocytopenia
Unknown	Reversible agranulocytosis and hemolytic anemia. Prolongation of bleeding and prothrombin time[1]
Immunity system disorders	
Unknown	Angioneurotic edema[9], anaphylaxis[9], serum disease-like syndrome[9], hypersensitivity vasculitis[9]
Nervous system disorders	
Uncommon	Dizziness, headache
Unknown	Reversible hyperactivity, convulsions[1], aseptic meningitis.
Cardiac disorders	
Unknown	Kounis syndrome
Gastrointestinal disorders	
Common	Diarrhea, nausea[2], vomiting
Uncommon	Indigestion
Unknown	Antibiotic-associated colitis[3], drug-induced enterocolitis syndrome (DIES), acute pancreatitis, black hairy tongue (tongue papillae become prominent and turn black), tooth discoloration[4]
Hepatobiliary disorders	
Uncommon	Increase in AST and/or ALT[5]
Unknown	Hepatitis[6] and cholestatic jaundice[6].
Hepatic events have been reported more frequently in males and elderly patients and may be related to long-term therapy. These events have been reported rarely in children. Signs and symptoms generally occur during or shortly after treatment in all populations, but in some cases may not become apparent until several weeks after discontinuation of therapy. They are usually reversible. Hepatic events can be serious, and in extremely rare cases, deaths have been reported. They have almost always occurred in patients with serious underlying disease or in those receiving concomitant medications known to have hepatic effects.	
Skin and subcutaneous tissue disorders[7]	
Uncommon	Skin rash, itching, urticaria
Rare	Erythema multiforme
Unknown	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalized exanthematous pustulosis (AGEP)[1] Drug reaction with eosinophilia and systemic symptoms (DRESS), linear IgA disorder
Renal and urinary disorders	
Unknown	Interstitial nephritis, crystalluria (including acute renal injury)[8]

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid at the start of a meal.
[3] Including pseudomembranous colitis and hemorrhagic colitis (see section 4.4)

[4] Superficial tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration as it can usually be removed by brushing
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See section 4.3 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 impaired renal function or in those receiving high doses. Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4)

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.
Amoxicillin/clavulanic acid can be removed from the circulation by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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.

Breakpoints
MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.

Organism	Sensitivity Cutoff Points (mg/L)	
	Susceptible	Resistant
Enterobacteriaceae in uncomplicated urinary tract infections	32[1]	32[1]
Staphylococcus spp.	See footnotes [2,3,4]	See footnotes 2,3,4
Enterococcus spp.[5]	4[1,6]	8[1,6]
Streptococcus A, B, C, G[7]	See footnotes[8]	See footnotes[8]
Streptococcus pneumoniae[7]	0,5[1]	1[1]
Viridans group streptococci[7]	See footnotes [9,10]	See footnotes [9,10]
Haemophilus influenzae	0.001[1]	2[1]
Moraxella catarrhalis	1[1]	1[1]
Pasteurella multocida	1[1]	1[1]
Burkholderia pseudomallei	0.001[1]	8[1]
Non-species-related breakpoints	2[1]	8[1]

[1] For the purpose of susceptibility testing, the clavulanic acid concentration has been fixed at 2 mg/l.

[2] Most staphylococci produce penicillinase and some are resistant to methicillin. Both mechanisms make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci found susceptible to benzylpenicillin and cefoxitin in the test may be reported as susceptible to all penicillins. Staphylococci resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to combinations of beta-lactamase inhibitors, isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For oral agents, care should be taken to ensure adequate exposure at the site of infection. Staphylococci resistant to cefoxitin are resistant to all penicillins.

[3] Most staphylococci produce penicillinase, and some are resistant to methicillin. Both mechanisms make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin, and ticarcillin. No method currently reliably detects penicillinase production in all staphylococci, but methicillin resistance can be detected with cefoxitin, as mentioned above.

[4] Ampicillin-susceptible *S. saprophyticus* is *mec*A-negative and is susceptible to ampicillin, amoxicillin, and piperacillin (with or without a beta-lactamase inhibitor).

[5] Aminopenicillin breakpoints for enterococci are based on intravenous administration. Oral administration is valid only for urinary tract infections.

[6] Susceptibility to ampicillin, amoxicillin, and piperacillin (with or without a beta-lactamase inhibitor) can be interpreted based on ampicillin. Resistance to ampicillin is uncommon in *E. faecalis* (verify with MIC), but it is common in *E. faecium*.

[7] Addition of a beta-lactamase inhibitor provides no additional clinical benefit.

[8] In the interpretation of penicillin susceptibility for Streptococcus groups A, B, C, and G (in non-meningitis indications), susceptibility to benzylpenicillin is used as a reference, but phenoxymethylpenicillin and isoxazolylpenicillins are exceptions for group B streptococci.

[9] Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorized as screen negative may be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those reported as “Note”). Isolates classified as screen positive should be tested for susceptibility to each agent.

[10] For isolates that are negative in the benzylpenicillin screening (MIC ≤0.25 mg/L), susceptibility interpretation can be made based on benzylpenicillin or ampicillin. For isolates that are positive in the benzylpenicillin screening (MIC >0.25 mg/L), susceptibility interpretation should be based on ampicillin.

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 *Staphylococcus aureus* (methicillin-susceptible) $ *Streptococcus pneumonia*[1] *Streptococcus pyogenes* and other beta hemolytic streptococci Aerobic Gram-negative microorganisms *Haemophilus influenzae*[2] *Moraxella catarrhalis*
Species for which acquired resistance may be a problem
Aerobic Gram-negative microorganisms *Klebsiella pneumoniae*
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Legionella pneumophila* Other microorganisms *Chlamydia pneumoniae* *Chlamydia psittaci* *Coxiella burnetii* *Mycoplasma pneumoniae*
$All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. [1] Only Streptococcus pneumoniae resistant to penicillin in approved indications are suitable for treatment with this presentation of amoxicillin/clavulanic acid (see section 4.1). [2] Isolates with reduced susceptibility have been reported at a frequency higher than 10% in some EU countries.

5.2 Pharmacokinetic properties

General properties

Absorption:
Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.
Below are the pharmacokinetic parameters for amoxicillin/clavulanic acid administered to pediatric patients at 45 mg/3.2 mg / kg every 12 hours.

Formulation	**C_{max} (µg/ml)**	**T_{max}* (hour)**	**AUC (µg.h/L)**	**$T_{1/2}$ (hour)**
Amoxicillin/clavulanic acid	Amoxicillin			

administered as 45 mg/kg AMC and 3.2 mg/kg CA every 12 hours	15.7 ±7.7	2.0 (1.0-4.0)	59.8 ±20.0	1.4 ±0.35
	Clavulanic acid			
	1.7 ±0.9	1.1 (1.0-4.0)	4.0 ±1.9	1.1 ±0.29
AMC: Amoxicillin, CA: Clavulanic acid *Median				

Amoxicillin and clavulanic acid serum concentrations achieved with Amoxicillin/clavulanic acid combination are similar to those produced by the oral administration of equivalent doses of each 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 is excreted in urine and feces and as carbon dioxide with the 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 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).

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:
Caution is advised in the dose adjustment of patient with hepatic impairment and hepatic functions should be 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.

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

5.3 Preclinical safety data
Nonclinical data and pharmacology, genotoxicity and reproductive toxicity safety studies reveal no special hazard for humans.
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 amoxicillin/clavulanic acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Sodium saccharin
Microcrystalline sodium and Croscarmellose
Silicon dioxide
Succinic acid
Silica colloidal anhydrous
Xanthan gum
Vanillin flavour
Tutti frutti flavour

6.2 Incompatibilities
There is no known incompatibility.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Dry powder for reconstitution should be stored at room temperature below 25°C, in a dry place. Reconstituted suspension should be stored in a refrigerator (2-8°C) and should be used within 10

days. Suspension should not be frozen.

6.5 Nature and contents of container

The product is presented in amber-colored Type III glass bottles marked in 100 mL or 150 mL; it includes a white polypropylene cap with a 28-point child-resistant seal, safety strip, and aluminum gasket, and a transparent 5 mL measuring spoon.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

Preparation of AMOKLAVIN ES suspension:
AMOKLAVIN ES is in form of powder therefore it should be reconstituted first.
Follow the instructions below to reconstitute AMOKLAVIN ES:
Gently tap the bottle until the powder freely flows.

1. Add water gradually until it fills up to 2/3 of the mark on the bottle and shake vigorously (Boiled and cooled water should be preferred for preparing a suspension).

2. Allow to stand for 5 minutes to ensure full dispersion.
3. Add water up to the mark on the bottle (remaining 1/3) and **shake well again** Boiled and cooled water should be preferred for preparing a suspension).
4. The dose recommended by your doctor is given to the patient using a 5 ml measuring spoon that is supplied with the bottle.

Shake the bottle well before each dose.
Immediately and tightly close the bottle after use.

Slight yellowing of the suspension during use of AMOKLAVIN ES may be seen. This condition has no influence on the efficacy of the drug.

If the drug is to be administered to a child under 2 years of age, the amount of suspension to be given can be diluted just before administration. Do not dilute the full suspension, and do not keep the rest of the diluted suspension.

7. MARKETING AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

244/99

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 21.09.2012
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT