SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg amoxicillin (as the sodium salt) and 100 mg clavulanic acid (as the potassium salt).

Excipient(s) with known effect:
The sodium content of each vial is 1.4 mmol. The potassium content of each vial is 0.5 mmol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
Crystalline, white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion 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.

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

4.2 Posology and method of administration

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

Posology

The dose of Amokisklav 500 mg/100 mg, powder for solution for injection/infusion that is 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 Amokisklav 500 mg/100 mg, powder for solution for injection/infusion (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 Amokisklav 500 mg/100 mg, powder for solution for injection/infusion is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

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

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

Adults and children ≥ 40 kg

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

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

Paediatric population

Children < 40 kg

Recommended doses:

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

Elderly

No dose adjustment is considered necessary.

Renal impairment

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

Adults and children ≥ 40 kg

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

Children < 40 kg

CrCl: 10 to 30 ml/min	25 mg/5 mg per kg given every 12 hours

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

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion is for intravenous use.

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion may be administered either by slow intravenous injection over a period of 3 to 4 min directly into a vein or via a drip tube or by infusion over 30 to 40 min. Amokisklav 500 mg/100 mg, powder for solution for injection/infusion is not suitable for intramuscular administration.

Children aged less than 3 months should be administered amoxicillin/clavulanic acid by infusion only.

Treatment with amoxicillin/clavulanic acid may be initiated by the use of an intravenous preparation and completed with an appropriate oral presentation as considered appropriate for the individual patient.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

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

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactam agents (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. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy should be discontinued and appropriate alternative therapy instituted.

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

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

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

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

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

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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires amoxicillin/clavulanic acid discontinuation and contra-indicates 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 diarrhoea 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 contra-indicated in this situation.

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

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are

prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (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 has been observed very rarely, predominantly with parenteral therapy. During administration of high doses of amoxicillin it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 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/clavulanic acid 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.

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion
This medicinal product contains 31.4 mg (1.4 mmol) of sodium per vial, equivalent to 1.57% of the WHO recommended maximum daily intake of 2g sodium for an adult.

This medicinal product contains 19.6 mg (0.5 mmol) of potassium per vial.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Convulsions[2]	Not known
Aseptic meningitis	Not known
Vascular disorders	
Thrombophlebitis[3]	Rare
Gastrointestinal disorders	
Diarrhoea	Common
Nausea	Uncommon
Vomiting	Uncommon
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon

Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

1 See section 4.4
2 See section 4.4
3 At the site of injection
4 Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
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 4.4
10 See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 drug.safetyssa@novartis.com.

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 haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

PK/PD relationship

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

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial

resistance, particularly in Gram-negative bacteria.

Breakpoints

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

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus[2]	≤ 2	-	> 2
Coagulase-negative staphylococci[2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

1 The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.
2 The reported values are Oxacillin concentrations.
3 Breakpoint values in the table are based on Ampicillin breakpoints.
4 The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
5 Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Enterococcus faecalis
Gardnerella vaginalis
*Staphylococcus aureus (*methicillin-susceptible)[£]

Streptococcus agalactiae *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other beta-haemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative micro-organisms *Actinobacillus actinomycetemcomitans* *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Neisseria gonorrhoeae*[§] *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* [$] Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydia trachomatis* *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*

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

Mean (±SD) pharmacokinetic parameters
Bolus intravenous injection

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

AMX – amoxicillin, CA – clavulanic acid

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (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 faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 500/100 mg or a single 1000/200 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).

Paediatric population

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination.

Older people
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data

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

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion must not be mixed with amino acid solutions, lipid emulsions, blood and glucose solutions.

Amokisklav 500 mg/100 mg, powder for solution for injection/infusion is less stable in infusions containing dextran or bicarbonate. Reconstituted solution should, therefore, not be added to such infusions but may be injected into the drip tubing over a period of three to four minutes.

Because of the inactivation of aminoglycosides by amoxicillin, *in-vitro* mixing should be avoided.

6.3. Shelf-life

2 years
Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for the reconstituted solution for injection for 15 minutes if stored at 25 °C and for the reconstituted solution for infusion 60 minutes if stored at 25 °C.

6.4. Special precautions for storage

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

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

Storage conditions after reconstitution:
Do not store above 25 °C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

20 ml vials of colourless glass type II with halogenated butyl rubber stopper and flip-off aluminium cap;
Pack sizes for 1, 5, 10, 20, 30, 50 and 100 vials

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

The reconstitution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter prior to administration. The solution should only be used if the solution is clear and free from particles. Any unused solution should be discarded.

For single use only.

Preparation of intravenous injections:

Vials of 500/100 mg are diluted with 10 ml or up to 20 ml of water for injections.

Vial of	Water for injection	Volume after reconstitution *	Concentration after reconstitution *
500/100 mg	10 ml	10,0 ml	50,0/10,0 mg/ml
500/100 mg	20 ml	20.2 ml	24,8/5,0 mg/ml

* data based on laboratory studies

Preparation of intravenous infusions:

The reconstitution of the ready to use solution for infusion has to take place in two steps in order to allow the reconstitution of the necessary volume for solution for infusion:
The vial of 500/100 mg is first reconstituted with one of the compatible intravenous fluids in its vial. This solution has then to be transferred into a suitable infusion bag which should contain the same compatible fluid as used for reconstitution. Controlled and validated aseptic conditions have to be observed.
Vials of 500/100 mg are diluted with 25 ml or up to 50 ml of water for injection or of the following fluids: Physiological saline, Sodium lactate 167 mmol/l, Ringer's solution, Hartmann's solution.
If the product is dissolved in water for injection as specified, this solution may be mixed with the following solvents: Water for injection, Physiological saline, Sodium lactate 167 mmol/l, Ringer's solution, Hartmann's solution.

Solutions for intravenous infusion should be administered in full within 60 min of preparation.

After dissolution in water for injection, a transient pink colour may occur; the solution will become clear again rapidly afterwards.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.

Verovskova 57, 1000 Ljubljana Slovenia

8. **MARKETING AUTHORISATION NUMBER**

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION

Date of first authorization: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]