SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ABIOCLAV 875 mg/125 mg film-coated tablets
ABIOCLAV 400 mg/57 mg/5 ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ABIOCLAV *875 mg/125 mg film-coated tablets*
One tablet contains:
Active substances: amoxicillin trihydrate equal to amoxicillin mg 875; clavulanate potassium equal to clavulanic acid mg 125.

ABIOCLAV *400 mg/57 mg/5 ml powder for oral suspension*
When reconstituted, each ml of suspension contains amoxicillin trihydrate corresponding to 80 mg of amoxicillin and potassium clavulanate corresponding to 11.4 mg of clavulanic acid.
Excipients with known effects: aspartame

For a full list of excipients, see paragraph 6.1

3. PHARMACEUTICAL FORM
875 mg/125 mg film-coated tablets
Film-coated tablet

400 mg/57 mg/5 ml powder for oral suspension
Powder for oral suspension

4. CLINICAL INFORMATION
4.1 Therapeutic Indications
ABIOCLAV is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1).

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- 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

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 o fan individual component.
The dose of ABIOCLAV 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 amoxicillin/clavulanic acid (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).

For adults and children ≥ 40 kg this formulation of ABIOCLAV provides a total daily dose of 1750 mg amoxicillin/250 mg clavulanic acid when administered twice a day and 2625 mg amoxicillin/375 mg clavulanic acid when administered three times a day, as recommended below. For children < 40 kg, this formulation of ABIOCLAV provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered at the recommended dose. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of amoxicillin/clavulanic acid is selected in order to avoid administration of unnecessarily high doses of clavulanic acid (see sections 4.4 and 5.1).

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).

<u>Adults and children ≥ 40 kg</u>
Recommended doses:

- standard dose: (for all of the indications) 875 mg/125 mg twice a day.
- higher dose – (particularly for infections such as otitis media, sinusitis, infections of the lower respiratory tract and urinary tract infections): 875 mg/125 mg three times a day.

<u>Children < 40 kg</u>
Children may be treated with amoxicillin/clavulanic acid tablets, suspensions or paediatric sachets.
Recommended doses:
- 25 mg/3,6 mg/kg/day to 45 mg/6,4 mg/kg/day given in two divided doses;
- till 70 mg/10 mg/kg/day given in two divided doses can be considered for some infections (such as otitis media, sinusitis, infections of the lower respiratory tract).

No clinical data are available on doses of ABIOCLAV 7:1 formulations higher than 45 mg/6.4mg/kg per day in children under 2 years.

No clinical data are available for the formulations of ABIOCLAV 7:1 in children under the age of 2 months. Therefore it is not possible to provide dose recommendations in this population.

<u>Elderly</u>
No dose adjustment is considered necessary.

<u>Renal impairment</u>
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.
In patients with a creatinine clearance less than 30 ml / min, there is no recommendation for the use of formulations of ABIOCLAV with a ratio amoxicillin - clavulanic acid of 7:1, as dose adjustments are not available.

<u>Hepatic impairment</u>
Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

<u>Method of administration</u>
ABIOCLAV is for oral use.
Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally according the SPC of the IV-formulation and continued with an oral preparation.

400 mg/57 mg/5 ml powder for oral suspension
Shake the powder, add water as indicated, invert and shake.
Shake the bottle before each dose (see section 6.6)

4.3 Contraindications
Hypersensitivity to the active substances, to any of the penicillines or to any of the excipients listed in paragraph 6.1.
Hystory of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).
Hystory 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 ABIOCLAV, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reaction) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also evolve into Kounis syndrome, a severe allergic reaction that can cause myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

Drug-induced enterocolitic syndrome (DIES) has been reported mainly in children taking amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction with the main symptom of prolonged vomiting (1-4 hours after taking) in the absence of allergic skin or respiratory symptoms. Additional symptoms could include abdominal pain, diarrhea, hypotension, or leukocytosis with neutrophilia. Severe cases have occurred, including progression to shock.

In the case that an infection is proven to be due to an amoxicillin-susceptible organism(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin on accordance with official guidance.
This presentation of ABIOCLAV is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or 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).

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 probability of allergic skin reactions.
Prolunged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustule may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires ABIOCLAV discontinuation and contra-indicates any subsequent administration ofamoxicillin.

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 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 medicinal products 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 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 has been observed very rarely (including acute kidney damage), 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 section 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 nonenzymatic methods.

The presence of Clavulanic acid in ABIOCLAV 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.

ABIOCLAV 400 mg/57 mg/5 ml powder for oral suspension contains 1,7 mg of aspartame (E951) per ml, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Oral anticoagulants</u>

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 coadministration 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 treated with mycophenolate mofetil, after beginning the oral tratment with amoxicillin and clavulanic acid, the pre-dose concentration of active metabolite mycophenolic acid (MPA) was reduced by about 50%. Changing the pre-dose level may not represent the changes of the MPA total exposure accurately. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical signs of transplant dysfunction. However, close clinical monitoring should be performed during the combination and immediately after antibiotic treatment.

4.6 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.

Lactation
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 ABIOCLAV, 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)

Classification for Systems and Organs	Frequency
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
Prolungation 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
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
875 mg/125 mg film-coated tablets	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Drug-induced enterocolitic syndrome	Not known
Acute pancreatitis	Not known
Antibiotici-associated colitis[4]	Not known
Black hairy tongue	Not known
400 mg/57 mg/5 ml powder for oral suspension	
Diarrhoea	Common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Drug-induced enterocolitic syndrome	Not known
Acute pancreatitis	Not known
Antibiotici-associated colitis[4]	Not known
Black hairy tongue	Not known
Tooth discolouration [11]	Not known

Cardiac disorders	
Kounis syndrome (see section 4.4)	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
Linear IgA disease	Not known
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] (including acute kidney damage)	Not known

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking ABIOCLAV acid at the start of a meal.
[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 4.3
[10] See section 4.4
[11] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Reporting suspected adverse reactions
Suspected adverse reaction reports that occur after the authorization of the medicine is important, as it allows continuous monitoring of the benefit / risk ratio of the medicine. Healthcare professionals are required to report any suspected adverse reaction via the national alert system at http://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

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, included 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 (③g/ml)**		
	Susceptible	**Intermediate**	**Resistant**
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus[2]	≤ 2	-	> 2
Coagulase-negative staphyilococci [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 *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psitaci*

Coxiella burnetti *Mycoplasma pneumonite*
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1] *Streptococcus pneumoniae* that is fully susceptible to penicillin may be treated with this presentation of amoxicillin/clavulanic acid. Organisms that show any degree of reduced susceptibility to penicillin should not be treated with this presentation (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

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 (T_{max}) in each case is approximately one hour.
The pharmacokinetic results for separated studies, in which amoxicillin/clavulanic acid (875/125 mg tablets administered twice a day) was administered in the fasting state to groups of healthy volunteers, are presented below.

Mean (±SD) pharmacokinetics parameters					
Active substance administered	**Dose (mg)**	**C_{max} (µg/ml)**	**T_{max}* (h)**	**AUC $_{(0-24h)}$ (µg.h/ml)**	**T 1/2 (h)**
Amoxicillin					
AMX/CA 875 mg/125 mg	875	11,64 ± 2,78	1,50 (1,0-2,5)	53,52 ± 12,31	1,19 ± 0,21
Clavulanic acid					
AMX/CA 875 mg/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 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).
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 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 single amoxicillin/clavulanic acid 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 hours 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).

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.

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 ABIOCLAV or its components.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
ABIOCLAV 875 mg/125 mg film-coated tablets
Colloidal anhydrous silica, magnesium stearate, talc, povidone (K25), croscarmellose sodium, microcrystalline cellulose
Film: triethyl citrate, ethylcellulose aqueous dispersion, hypromellose, talc, titanium dioxide

ABIOCLAV 400 mg + 57 mg/5 ml powder for oral suspension
Lemon flavor powder, flavor peach apricot powder, citric acid anhydrous, sodium citrate anhydrous, aspartame, talc, orange flavor powder, guar, colloidal silica

6.2 Incompatibilities
Not known incompatibilities.

6.3 Shelf life
Unopened package:
Film-coated tablets: 2 years
Powder for oral suspension: 3 years.

6.4 Special precautions for storage
Unopened package
Film-coated tablets and powder for oral suspension
Do not store above 25 °C, store in the original package to repair the product from light and moisture.

Powder for oral suspension: after reconstitution store the bottle at 2-8° C (in a refrigerator) for a maximum of 7 days. After this period, the product not administered should be discarded.

6.5 Nature and contents of container
ABIOCLAV 875 mg/125 mg Film-coated tablets – 12 tablets
Blister coupled Aluminum / Polyethylene

ABIOCLAV 400 mg/57 mg/5 ml powder for oral suspension – bottle 70 ml
Amber glass bottles with child-proof closure and spoon with a notch to 1.25 ml, 2.5 ml and 5 ml.

6.6 Special precautions for disposal and other handling
No special requirements.
The unused medicine and refused derived from it must be disposed of in compliance with local laws.

400 mg + 57 mg/5 ml powder for oral suspension
Before use, check cap seal is intact. Shake the bottle to loosen powder. Add volume of water (as indicated below) invert and shake well. Alternatively, fill the bottle with water to just below the mark on bottle label, invert and shake well. Then top up with water exactly to the mark, invert and again shake well.

Strenght	Volume of water to be added at reconstitution (ml)	Final volume of reconstituted oral suspension (ml)
400 mg/57 mg/5 ml	63,7	70

Shake the bottle well before each dose.

875 mg/125 mg film-coated tablets
In order to facilitate swallowing, the tablets can be divided but they must be taken immediately.

7. MARKETING AUTHORIZATION HOLDER
Aesculapius Farmaceutici S.r.l. – Via Cefalonia, 70 – 25124 Brescia

8. MARKETING AUTHORIZATION NUMBER(S)
ABIOCLAV 875 mg/125 mg Film-coated tablets – 12 tablets
M.A. n. 037350016
ABIOCLAV 400 mg + 57 mg/5 ml powder for oral suspension – bottle of 70 ml with measuring spoon
M.A. n. 037350028

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
July 2009/October 2014

10. DATE OF REVISION OF THE TEXT

April 2023