Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

DAFRACLAV® 625
Amoxicillin -Clavulanic acid

1.1. Strength 500 mg + 125 mg
1.2. Pharmaceutical form Film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate).

Excipients with known effect: none

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

White to off-white , oblong.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Dafraclav 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 mode of administration

4.2.1. Posology

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

The dose of Dafraclav 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 infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Dafraclav (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 Dafraclav 625 film coated tablet provides a total daily dose of 1500 mg amoxicillin 375 mg clavulanic acid, when administered as recommended below. If it is considered that a higher dose of amoxicillin is required it is recommended that another formulation of Dafraclav is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determine 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 5see section 4.4 and 5.1 regarding prolonged therapy).

<u>Adults and children ≥ 12 ans</u> (≥ 40 kg)
One tablet Dafraclav 625 (500/125mg), three times daily.

4.2.2. Special populations

Elderly

No dose adjustment is considered necessary

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals .

Renal impairment

- No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.
- Adults and children with body weight of 40 kg or more

- In patient with creatinine clearance 10-30 ml/min: 500mg/125mg twice daily.
- In patients with creatinine clearance < 10 ml/min : 500 mg/125mg once daily.
- Haemodialysis: 500mg/125mg every 24 hours, plus 500 mg/125mh during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).

4.2.3. Paediatric population

Children with a body weight less than 40 kg

Standard posology: 20mg/5mg/kg/day to 60mg/15mg/kg/day , divided over 3 intakes.

Renal impairment

- In children with creatinine clearance 10-30 ml/min: 15 mg/3.75 mg/kg twice daily
- In children with creatinine clearance < 10 ml/min : 15 mg/3.75 mg /kg once daily.
- Haemodialysis: 15 mg/3.75 mg/kg , once daily. Before hemodialysis 15mg/3.75 mg/kg. In order to restore the circulating medication level, administer 15mg/3.75 mg/kg after hemodialysis.

Children may be treated with Dafraclav tablets or Dafraclav suspension.

Since the Dafraclav 625 film coated tablets cannot be divided, other presentations of Dafraclav are available for the treatment of children weighing less than 25 kg .

The table below shows the dose received (mg/kg body weight) by children weighing between 25 and 40 kg when administering a single dose of 625 mg (500/125).

Poids (en kg)	40	35	30	25	Recommended single dose (mg/kg)
Amoxicillin [mg/kg] per single dose (1 film coated tablet 500/125)	12,5	14,3	16,7	20,0	6,67 - 20

Poids (en kg)	40	35	30	25	Recommended single dose (mg/kg)
Clavulanic acid [mg/kg] per single dose (1 film coated tablet 500/125)	3,1	3,6	4,2	5,0	1,67 - 5

Children below 6 years of age or weighing less than 25 kg should, preferably, be treated with Dafraclav suspension.
No clinical data are available in **children under 2 years** of age for doses higher than 40 mg-10 mg/kg (ratio 4/1).

4.2.4. Method of administration

- Dafraclav 625 is for oral use only
- To minimise potential gastrointestinal intolerance Dafraclav should be administered at the beginning or during the meal.

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 β-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).
- History of jaundice or hepatic impairment due to amoxicillin/clavulanic acid.

4.4. Special warning and precautions for use

4.4.1. General information

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other β-lactam agents (see sections 4.3 and 4.8)

Serious and occasionally fatal hypersensitivity (anaphylactoid) 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 must be discontinued and appropriate alternative therapy instituted.

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

The use of Dafraclav is not suitable when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to β-lactam agents that is not mediated by β-lactamases susceptible to inhibition by clavulanic acid. Dafraclav should not be used to treat penicillin-resistant *S. pneumoniae*.

In patients with impaired renal function or in those receiving high doses convulsions may occur (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 generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires discontinuation of the treatment with Dafraclav and contraindicates any subsequent administration of amoxicillin.

In patients with evidence of hepatic impairment amoxicillin/clavulanic acid should be used with caution (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. 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 contraindicated in this situation.

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

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 the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Dafraclav 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.

4.4.2. Paediatric population

See section 4.4.1

4.5. Interactions with other medicinal products and other forms of interactions

4.5.1. General information

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases renal tubular secretion of amoxicillin and elevates its plasma concentrations. 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.

4.5.2. Additional information on special populations

See 4.5.1

4.5.3. Paediatric population

See 4.5.1

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

There are no data on the effects of amoxicillin or clavulanic acid on human fertility. Animal reproduction studies have shown no effect on fertility.

4.6.2. 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.

4.6.3. 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 sensitization should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician.

4.7. Effects on the ability to drive and use machines

Effects on the ability to drive and use machines have not been studied. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

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

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

Tabulated summary of adverse reaction

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).

System organ Class/ Undesirable effect	Frequency
Infections and infestations	
Mucocutaneous candidosis	common
Overgrowth of non-susceptible organisms	not known
Blood and lymphatic system disorders	
Reversible leukopenia (including neutropenia)	rare
Thrombocytopenia	rare
Reversible agranulocytosis	not known
Haemolytic anaemia	not known
Prolongation of bleeding time and prothrombin time	not known
Immune system disorders	
Angioneurotic oedema	not known

System organ Class/ Undesirable effect	Frequency
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	not known
Aseptic meningitis	not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	very common
Nausea	common
Vomiting	common
Indigestion	uncommon
Antibiotic-associated colitis	not known
Drug-induced enterocolitis syndrome	not known
Acute pancreatitis	not known
Black hairy tongue	not known
Hepatobiliary disorders	
Rises in AST and/or ALT	uncommon
Hepatitis	not known
Cholestatic jaundice	not known
Skin and subcutaneous tissue disorders	
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 generalized exanthemous pustulosis (AGEP)	not known
Drug rash with eosinophilia and systemic symptoms (DRESS)	not known
Linear IgA dermatosis	not known
Renal and urinary disorders	

System organ Class/ Undesirable effect	Frequency
Interstitial nephritis	not known
Crystalluria	not known

Reporting of suspected adverse reactions

Reporting of suspected adverse reaction to the Authorities by Health Care Professionals is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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.
- 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.

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 and ATC code**:**

Pharmacotherapeutic group: Combinations of penicillins, including β-lactamase inhibitors

ATC code: J01CR02

Mechanism of action

Amoxicillin is a semisynthetic penicillin (β-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs)

in the biosynthetic pathway of bacterial peptidoglycan, 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 β-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 β-lactam structurally related to penicillins. It inactivates some β-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacodynamic - Pharmacokinetic 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 β-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	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8

organism	susceptibility breakpoints (µg/ml)		
	susceptible	*intermediate*	*resistant*
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	≤ 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)[1]
  - Coagulase-negative staphylococci (methicillin-susceptible)[1]
  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae* [2]
  - *Streptococcus pyogenes* and other β-haemolytic streptococci
  - *Streptococcus viridans* group
- Aerobic Gram-negative micro-organisms
  - *Capnocytophaga* spp.
  - *Eikenella corrodens*
  - *Haemophilus influenzae*[3]
  - *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*[4]
- 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 psittaci*
  - *Coxiella burnetti*
  - *Mycoplasma pneumoniae*

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1. All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid
2. *Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid.
3. Strains with decreased susceptibility have been reported in some countries in the European Union with a frequency higher than 10%.

4. Natural intermediate susceptibility in the absence of acquired mechanism of resistance

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 optimized 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.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below:

Mean Pharmacokinetic parameters (± SD)					
Active substance(s) administered	Dose	C_{max}	T_{max}[1]	AUC (0-24H)	$T_{1/2}$
	(mg)	(µg/ml)	(h)	(µg.h/ml)	(h)
Amoxicillin					
Amoxicillin/Clavulanic acid	500	7,19 ± 2,26	1,5 (1,0-	53,5 ± 8,87	1,15 ±
Clavulanic acid					
Amoxicillin/Clavulanic acid	125	2,40 ± 0,83	1,5 (1,0-	15,72 ± 3,86	0,98 ±
[1] 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.
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 kidneys, 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 hours after administration of single tablets with amoxicillin/clavulanic acid 250 mg/125 mg or 500 mg/125 mg. 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).

Pediatric 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 new-borns) 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.

Geriatric population

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

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.

Patients with 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).

Patients with hepatic impairment

Patients with hepatic impairment 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

Tablet core

- Crospovidone (Type A)
- Croscarmellose sodium
- Colloidal anhydrous silica
- Magnesium stearate
- Microcrystalline cellulose

Film coating – Opadry white OY-S-7191

- Titanium dioxide (E171)
- Hypromellose
- Propylene glycol
- Ethylcellulose

6.2. Incompatibilities

not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store below 30°C.

Store in the original package to protect from moisture.

6.5. Nature and contents of container

Cardboard box with 15 film coated tablets in aluminium/aluminium blister (3 blisters of 5 tablets)

6.6. Special precautions for disposal and other handlings

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Steinentorstrasse 23, 4051 Basel, Switzerland.

7.2. Manufacturer

Bilim Ilaç Sanayii ve Ticaret A.Ş
(Bilim Pharmaceuticals)
Çerkezköy Plant – Çerkezköy Organize Sanayi Bölgesi (ÇOSB),
Karaağaç Mah. 7, Sk.N°7A Kapaklı/Tekirdağ, 59510, Turkey

8. MARKETING AUHORISATION NUMBER

H2006/263

9. DATE OF FIRST REGISTRATION**/** RENEWAL OF THE AUTHORIZATION

01/2026

10. PRODUCT SUPPLY CATEGORY

Prescription Only Medicine (POM)

11. DATE OF REVISION OF TEXT

01/2026