SUMMARY OF MEDICINAL PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Augmentin ES 600 mg / 42.9 mg / 5 ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, each ml of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8,58 mg clavulanic acid.

Excipient with known effect

Excipients: Each ml of oral suspension contains 2.72 mg of aspartame (E951). Augmentin flavoring contains maltodextrin (glucose) (see section 4.4).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for oral suspension

Off-white powder.

4. CLINICAL INFORMATION

4.1 Therapeutic indications

Augmentin is indicated for the treatment of the following infections in children at least 3 months of age and less than 40 kg of body weight, actually caused or probably caused by *Streptococcus pneumoniae* penicillin-resistant (see sections 4.2, 4.4 and 5.1):

- Acute otitis media
- Community acquired pneumonia

Official guidance on the appropriate use of antibacterial agents should be taken into account.

4.2 Dose and method of administration

Dose
Doses are expressed in terms of the content of amoxicillin/clavulanic acid unless they are presented in terms of individual components.

The dose of Augmentin selected to treat a specific infection should take into account:
- Expectable pathogens and likely susceptibility to antibacterial agents (see Section 4.4)
- The severity and site of infection
- The patient's age, weight and kidney function as described below.

Treatment should not last longer than 14 days without evaluation (see section 4.4 on prolonged therapy).

Adults and children> 40 kg
There is no experience with Augmentin oral suspension in adults and children > 40 kg, and therefore a dose recommendation cannot be made.

Children <40 kg (aged> 3 months)
The recommended dose of Augmentin oral suspension is 90 mg/6.4 mg/kg/day, divided into two doses.

No clinical data are available in children under 3 months of age with Augmentin.

Renal impairment
No dose adjustment is necessary in patients with creatinine clearance (CrCL) greater than 30 ml/min.

In patients with creatinine clearance less than 30 ml/min, the use of Augmentin is not recommended as no dose adjustment recommendations are available.

Hepatic impairment
Dosing with caution and monitoring liver function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin should be taken orally.

Augmentin should be taken with a meal to minimize potential gastrointestinal intolerance

Shake to release the powder, add water as directed, invert and shake. Shake the bottle before each dose (see section 6.6).

For instructions on reconstituting the drug before taken, see section 6.6.

4.3. Contraindications

Hypersensitivity to active substances, to any penicillin or to any of the excipients mentioned in Section 6.1.

History of severe immediate hypersensitivity reaction (e.g., anaphylaxis) to another beta-lactam agent (e.g., cephalosporins, carbapenems, monobactam).

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

4.4. Special warnings and precautions for use

Prior to initiation of amoxicillin/clavulanic acid therapy, the possibility of a history of hypersensitivity reactions to penicillin, cephalosporins or beta-lactam agents should be carefully investigated (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including severe adverse skin reactions and anaphylactoid reactions) have been reported in patients taking penicillin. Hypersensitivity reactions can also progress to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of hypersensitivity to penicillin and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children being treated with amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction whose main symptom is prolonged vomiting (1-4 hours after drug administration) in the absence of skin or respiratory allergy symptoms. Other symptoms may include abdominal pain, diarrhea, hypotension, or leukocytosis with neutrophilia. There have been serious cases including progression to shock. If an allergic reaction occurs, therapy with amoxicillin/clavulanic acid should be suspended and appropriate alternative therapy instituted.

If infection is shown to be due to organisms susceptible to amoxicillin, consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance standards.

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

Amoxicillin/clavulanic acid should be avoided in case of suspected infectious mononucleosis, since the occurrence of morbilliform rash has been associated in these cases with the use of amoxicillin.

Concomitant administration of allopurinol during treatment with amoxicillin may increase the likelihood of skin allergic reactions.

Prolonged administration may occasionally cause marked growth of non-sensitive micro-organisms.

The occurrence of generalized and febrile erythema associated with pustules at the start of treatment may be a symptom of acute generalized Pustulosis, rash (PEGA) (see Section 4.8). This reaction requires the suspension of Augmentin and is a contraindication to 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).

Liver events have been reported predominantly in male and elderly patients and may be associated with prolonged therapy. These events have been reported very rarely 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 been completed. These are usually reversible. Liver events may be serious and deaths have been reported in extremely rare circumstances. These have almost always occurred in patients with serious underlying disease or taking concomitant medication known to have potential hepatic effects (see section 4.8).

colitis associated with the use of virtually all antibacterial agents including amoxicillin has been reported, and its severity may vary from mild to possible life risk (see Section 4.8). Therefore, it is important to consider its diagnosis in patients who develop diarrhea during or after administration of any antibiotic. If colitis associated with antibiotics occurs, amoxicillin/clavulanic acid should be discontinued immediately, a doctor should be consulted and appropriate therapy should be initiated. Anti-erythematic medicines are contraindicated in this situation.

Periodic verification of the good functional status of the various organ systems, including renal, hepatic and hematopoietic systems, is advised during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients taking amoxicillin/clavulanic acid. Appropriate monitoring should therefore be carried out when anticoagulants are concomitantly prescribed. Dose adjustments for oral anticoagulants may be necessary to maintain the desired level of anti-clotting (see sections 4.5 and 4.8).

In patients with low urine output, crystalluria (including acute kidney injury) has occurred very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain an adequate water intake and urine output in order to reduce the likelihood of crystalluria due to amoxicillin. In algalic patients, the condition of the catheter should be checked regularly (see sections 4.8 and 4.9).

During treatment with amoxicillin, the enzyme method of glucose oxidase should be used when testing for glucose in the urine is required as false positive results with non-enzymatic methods may occur.

The presence of clavulanic acid in Augmentin may cause non-specific binding of IgG and albumin by red blood cell membranes, leading to a falsely positive result in the Coombs test.

Positive results have been reported when using EIA tests for *Platelia Aspergillus* from Bio-Rad Laboratories in patients receiving amoxicillin/clavulanic acid which was subsequently found not to be infected by this micro-organism. Cross-reactions have been reported with polysaccharides and not polyfluorenes-*Aspergillus* when using EIA test Platelia *Aspergillus* Bio-Rad Laboratories. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted with caution and confirmed by other diagnostic methods.

Augmentin ES powder for oral suspension contains 2.72 mg of aspartame (E951) per ml, which is a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. No clinical or non-clinical data are available to evaluate the use of aspartame in children under 12 weeks of age.

Augmentin ES powder for oral suspension contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

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

Oral Anticoagulants
Oral anticoagulants and antibiotics from the penicillin family have been widely used in clinical practice without reports of interaction. However, in the literature there are cases of increased international normalized relationship in patients taking Acenocoumarol or warfarin who have been prescribed amoxicillin therapy. If concomitant administration is necessary, prothrombin time or international normalized relationship should be closely monitored with the addition or withdrawal of amoxicillin. Additionally, dose adjustments for oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate
Penicillin may reduce methotrexate excretion, leading to potential increased toxicity.

Probenecid
Concomitant administration of probenecid is not recommended. Probenecid decreases renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not those of clavulanic acid.

Mycophenolate Mofetil
In patients taking mycophenolate mofetil after initiation of amoxicillin plus oral clavulanic acid, a reduction of approximately 50% in the pre-dose concentration of the active metabolite mycophenolic acid (MPA) was reported. The change in pre-dose level may not accurately represent changes in total MPA exposure. However, in the literature there are cases of increased international normalized relationship in patients taking Acenocoumarol or warfarin who have been prescribed amoxicillin therapy. However, close clinical monitoring should be performed during the combination and immediately after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate any direct or indirect harmful effects with regard to pregnancy, embryonal/fetal development, parturition or postnatal development (see Section 5.3). Limited data related to 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 premature fetal membrane rupture before the end of pregnancy, cases have been reported where prophylactic treatment with amoxicillin/clavulanic acid may be associated with increased risk of necrotizing enterocolitis in the newly born. The use of Augmentin during pregnancy should be avoided unless your doctor considers your prescription essential.

Breastfeeding
Both substances are excreted in breast milk (nothing is known about the effects of clavulanic acid on infants). Therefore, if diarrhea and fungal infections of the mucous membranes occur in the infant, breast-feeding may need to be discontinued. Awareness raising should be taken into account. Amoxicillin/clavulanic acid should only be administered during the breast-feeding period after a risk/benefit assessment by the physician.

4.7Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. However, undesirable effects (for example allergic reactions,

dizziness, seizures) may occur, 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 diarrhea, nausea and vomiting.

ADRs collected from clinical trials and post-marketing surveillance with Augmentin, organized according to the MedDRA organ classification system, are listed below.

The following convention was used for the classification of frequencies:
Very common (> 1/10)
Common (> 1/100, <1/10)
Uncommon (> 000 1/1 <1/100)
Rare (> 000 1/10 <1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidiasis	Common
Proliferation of non-susceptible organisms	Unknown
Blood and lymphatic system disorders	
Reversible leukopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Unknown
Hemolytic anemia	Unknown
Prolongation of bleeding time and prothrombin time[1]	Unknown
Immune system diseases[9]	
Angioneurotic edema	Unknown
Anaphylaxis	Unknown
Syndrome similar to serum disease	Unknown
Hypersensitivity vasculitis	Unknown
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Unknown
seizures [1]	Unknown
Aseptic meningitis	Unknown
Heart disease	
Kounis syndrome	Unknown
Gastrointestinal diseases	
Diarrhea	Common

Nausea [2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis [3]	Unknown
Syndrome of drug-induced enterocolitis	Unknown
Acute pancreatitis	Unknown
Black hairy tongue.	Unknown
Alteration of tooth staining[4]	Unknown
Hepatobiliary disorders	
Increase in AST and / or ALT values[5]	Uncommon
Hepatitis [6]	Unknown
cholestatic jaundice [6]	Unknown
Skin and subcutaneous tissue disorders[7]	
Cutaneous Eruption	Uncommon
Itching	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Unknown
Toxic epidermal necrolysis	Unknown
Exfoliative and bullous dermatitis	Unknown
Acute generalized rash Pustulosis (PEGA) [1]	Unknown
Drug Reaction with Eosinophilia and Systemic Symptoms DRESS Syndrome	Unknown
Linear IgA disease	Unknown
Renal and urinary diseases	
Interstitial nephritis	Unknown
Crystalluria (including acute kidney injury) [8]	Unknown

[1] See section 4.4

[2] Nausea is most often associated with high oral doses. If gastrointestinal reactions occur, they can be reduced by administering amoxicillin/clavulanic acid with a meal.

[3] Including pseudomembranous colitis and hemorrhagic colitis (see section 4.4).

[4] Changing the surface staining of teeth has been reported very rarely in children. Good oral hygiene can help prevent dental coloring since this can normally be removed with brushing.

[5] A moderate increase in AST and/or ALT has been reported in patients being treated with beta-lactam antibiotics, but the significance of this finding is unknown.

[6] These events have been reported with other penicillin and cephalosporins (see Section 4.4).

[7] If any skin hypersensitivity reaction occurs, treatment should be suspended (see section 4.4).

[8] See section 4.9

[9] See section 4.3 and 4.4

Notification of suspected adverse reactions

The notification of suspected adverse reactions after authorization of the drug is important, as it allows continuous monitoring of the benefit-risk balance of the drug. Health professionals are asked to report any suspected adverse reactions directly to INFARMED, I.P.:
Website:
http://www.infarmed.pt/web/infarmed/submissaoram (preferably) or through the following contacts:
Directorate of Risk Management for Medicines
Health Park in Lisbon, Av. Brazil 53
1749-004 Lisbon
Tel: +351 21 798 73 73
Line of the medicinal product: 800222444 (free)
E-mail: farmacovigilancia@infarmed.pt

4.9 Overdosage

Symptoms and signs of overdosage
Gastrointestinal symptoms and disturbances of fluid and electrolyte balance may occur. A crystalluria associated with amoxicillin has been observed in some cases causing renal failure (see section 4.4).

Seizures may occur in patients with renal impairment or receiving high doses.

It has been reported that amoxicillin may precipitate into urinary catheters, predominantly following high dose intravenous administration. The clearance of the catheters should be checked regularly (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms should be treated symptomatically, taking into account the hydro electrolyte balance.

Amoxicillin / clavulanic acid can be removed from the circulation by hemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.5 - Anti-infective medicines. Antibacterial Associations of penicillin with beta lactamase inhibitors, ATC code: J01CR02

Mechanism of Action
amoxicillin is a semisynthetic antibiotic of the penicillin (beta-lactam) family that inhibits one or more enzymes (often referred to in the literature as penicillin binding proteins, PBPs) in the pathway of metabolic synthesis of bacterial peptidoglycan. This biopolymer is a structural component of the bacterial cell wall whose function is related to the maintenance of cell shape and integrity. Inhibition of peptidoglycan synthesis leads to a weakening of the cell wall structure, usually followed by cell lysis and death of the bacterium.

Amoxicillin is likely to be degraded by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms producing these enzymes.

Clavulanic acid is a beta-lactam antibiotic, structurally related to penicillin. Inactivates some beta-lactamases, thus preventing amoxicillin inactivation. The clavulanic acid alone does not exert any clinically useful antibacterial effect.

Pharmacokinetic / Pharmacodynamic Ratio
The time interval in which the drug concentration is maintained above the Minimum Inhibitory Concentration (T> MIC) is considered the main determinant of the effectiveness of amoxicillin.
Mechanisms of resistance
There are two main mechanisms of resistance to amoxicillin / clavulanic acid:
- Inactivation by bacterial beta-lactamases that are not inhibited by clavulanic acid, including classes B, C and D.
- Changes in PBPs, which reduce the affinity of the antibacterial agent to its target.

Impermeability of bacteria or efflux mechanisms that may cause or contribute to bacterial resistance, particularly in gram-negative bacteria.

Critical concentrations (breakpoints)
The critical minimum inhibitory concentrations (MIC) for amoxicillin/clavulanic acid are those designated by the European Commission in the Antimicrobial Susceptibility Test (EUCAST) version 12.

Organism	Critical MIC (µg/ml)	
	Susceptible ≤	Resistant >
Enterobacterales in uncomplicated urinary tract infections	32[1]	32[1]
Staphylococcus spp.	Notes [2,3,4]	Notes [2,3,4]
Enterococcus spp.5	4 [1,6]	8 [1,6]
Streptococcus groups A, B, C and G[7]	Nota[8]	Nota[8]
Streptococcus pneumoniae[7]	0,5[1]	1[1]

Streptococci of the viridans group[7]	Notes [9,10]	Notes [9,10]
Haemophilus influenzae	0,001[1]	2[1]
Moraxella catarrhalis	1[1]	1[1]
Pasteurella multocida	1[1]	1[1]
Burkholderia pseudomallei	0,001[1]	8[1]
Critical concentrations not related to species	2[1]	8[1]

[1] In order to test susceptibility, the concentration of clavulanic acid is set at 2 mg/l.

[2] Most S. aureus are penicillinase producers and some are resistant to methicillin. Both mechanisms make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates that test susceptible to benzylpenicillin and cefoxitin can be declared susceptible to all penicillin. Isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to beta-lactamase inhibitor combinations, isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For orally administered agents, care should be taken to achieve sufficient exposure at the site of infection. Isolates that test resistant to cefoxitin are resistant to all penicillin.

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

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

[5] Critical concentrations of aminopenicillin in enterococci are based on intravenous administration. Oral administration is only relevant for urinary tract infections.

[6] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be determined from ampicillin. Resistance to ampicillin is infrequent in E. faecalis (confirm with MIC) but frequent in E. faecium.

[7] The addition of a beta-lactamase inhibitor does not add clinical benefit.

[8] The penicillin susceptibility of group A, B, C and G streptococci is determined on the basis of benzylpenicillin susceptibility (indications other than meningitis), with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for group B streptococcus.

[9] Benzylpenicillin (MIC or disk diffusion) can be used to detect beta-lactam resistance in viridans streptococci. Isolates that have been classified as diffusion negative can be declared susceptible to beta-lactam agents for which clinical concentrations are listed (including those with "Note"). Isolates that have been classified as diffusion positive should be tested for susceptibility to individual agents or declared resistant.

[10] For benzylpenicillin-negative isolates (zone of inhibition >18 mm or MIC <0.25 mg/l), susceptibility can be determined from benzylpenicillin or ampicillin. For benzylpenicillin-positive isolates (zone of inhibition <18 mm or MIC >0.25 mg/l), susceptibility is determined using ampicillin.

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

Species often susceptible
Gram-positive aerobic micro-organisms Staphylococcus aureus (methicillin-susceptible) $ Streptococcus pneumoniae1 Streptococcus pyogenes and other beta-hemolytic Streptococci Gram-negative aerobic micro-organisms Hemophilus influenzae2 Moraxella catarrhalis
Species for which acquired resistance may be problematic
Gram-negative aerobic microorganisms Klebsiella pneumoniae
Inherently resistant organisms Aerobic Gram-negative Legionella pneumophila Other microorganisms Chlamydophila pneumoniae Chlamydophila psittacine Coxiella Brunetti Mycoplasma pneumoniae
$ All methicillin resistant staphylococci are resistant to amoxicillin / clavulanic acid. [1] This amoxicillin / clavulanic acid formulation is suitable for the treatment of penicillin-resistant Streptococcus pneumoniae only in the approved indications (see section 4.1). [2] Strains with decreased susceptibility have been reported in some European countries with a frequency greater than 10%.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid are completely dissociated into aqueous solution at physiological ph. Both components are quickly and easily absorbed orally. Following oral administration, the bioavailability of amoxicillin and clavulanic acid is approximately 70%. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.
Mean pharmacokinetic data obtained after administration of Augmentin at a dose of 45 mg/3.2 mg/kg every 12 hours in pediatric patients are presented in the table below:

Formulation	C_{max} (µg/ml)	T_{max}* (h)	AUC (0-t) (µg, h/ml)	T 1/2 (h)
Augmentin dosed at 45 mg/kg AMX e 3,2 mg/kg CA of 12h to 12h	Amoxicillin			
	15.7 +/- 7,7	2.0 (1,0-4,0)	59.8 +/-20,0	1.4 +/-0,35
	Clavulanic Acid			
	1.7 +/- 0,9	1.1 (1,0-4,0)	4.0 +/- 1,9	1.1 +/- 0,29
AMX - CA amoxicillin - clavulanic acid * Mean (range)				

Serum amoxicillin and clavulanic acid concentrations achieved with amoxicillin/clavulanic acid are similar to those obtained by oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
Approximately 25% clavulanic acid and 18% amoxicillin of the total serum amount of each of the compounds circulates protein bound. The apparent volume of distribution is about 0,3-0,4 l/kg for amoxicillin and about 0,2 l/kg for clavulanic acid.

Following intravenous administration, amoxicillin and clavulanic acid concentrations may be detected in the gallbladder, abdominal tissue, skin, adipose and muscular tissues, peritoneal and synovial fluids, bile and pus. Amoxicillin is not adequately distributed in the cerebrospinal fluid.

In animal studies there was no evidence of significant organic accumulation of any of the compounds or their derivatives. Amoxicillin, like most penicillin, can be detected in breast milk. Traceable quantities of clavulanic acid may also be detected in breast milk (see Section 4.6).

Both amoxicillin and clavulanic acid pass through the placental barrier (see Section 4.6).

Biotransformation
Amoxicillin is partially excreted in the urine as inactive penicilloic acid in equivalent amounts of up to 10 - 25% of the dose initially administered. In humans, clavulanic acid is extensively metabolized and eliminated in urine and faces, and expired air as carbon dioxide.

Elimination
The primary route of excretion of amoxicillin is renal, while elimination of clavulanic acid is by renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60-70% of amoxicillin and about 40-65% of clavulanic acid are excreted unchanged in the urine during the first 6 hours following administration of a single tablet of Augmentin 250 mg/125 mg or 500 mg/125 mg. Several studies have shown a urinary excretion of 50-85% for amoxicillin and 27-60% for clavulanic acid within 24 hours. In the case of clavulanic acid, most of the drug is excreted within the first 2 hours after administration.

Concomitant use of probenecid retards the excretion of amoxicillin but not the renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar in children aged 3 months to 2 years when compared to older children and adults. For very young children (including preterm neonates) at the first week of life, the dosing interval should not exceed twice daily due to immaturity of the renal elimination pathway. Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection, and monitoring of renal function may be useful.

Gender:
Following oral administration of amoxicillin/clavulanic acid to healthy male and female volunteers, gender did not show any significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
Total serum clearance of amoxicillin/clavulanic acid decreases proportionally with decreased renal function. The reduction in the clearance of these drugs is more pronounced for amoxicillin than for clavulanic acid, since a greater proportion of amoxicillin is excreted by the renal route. Doses in renal impairment should therefore prevent the undesirable accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
In patients with hepatic impairment, dosage should be chosen with caution and liver function monitored at regular intervals.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on safety pharmacology, genotoxicity and reproductive toxicity studies.

Repeated-dose toxicity studies of amoxicillin/clavulanic acid in dogs showed gastric irritation and vomiting and a change in tongue color.

No carcinogenicity studies have been carried out with amoxicillin/clavulanic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Xanthan gum
Hydrated colloidal silica
Anhydrous colloidal silica
Carboxymethylcellulose sodium
Artificial strawberry cream flavor (including maltodextrin)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder for oral suspension: 2 years
Reconstituted suspensions must be stored at 2 ° C - 8 ° C (but not frozen) for up to 10 days.

6.4. Special precautions for storage

Store in the original package, in order to protect from moisture. Do not store above 25 ° C. Storage conditions for the medicinal product after reconstitution, see section
6.3.

6.5 Nature and Contents of Container

Colorless glass bottle containing powder for reconstitution for 50 ml, 75 ml, 100 ml or 150 ml with a child resistant plastic cap and a removable protective seal. The packaging can be supplied with a plastic measuring spoon.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Make sure the bottle protective seal is intact before using. When preparing, shake the bottle to release the powder and remove the protective seal. Add water volume (according to the table below). Place the cap on the bottle, invert and shake well.

Alternatively, fill the bottle with water just below the mark on the bottle label. Place the cap on the bottle, invert and shake well, then complete with water exactly until the mark. Place the cap on the bottle, invert the bottle and shake well again.

Concentration	Volume of water to be added when reconstyling (ml)	Final volume of suspension oral reconstituted (ml)
600 mg / 42.9 mg / 5ml	50	50
	70	75
	90	100
	135	150

Shake the bottle well before each dose.

Any unused product or waste material should be disposed of in accordance

with local requirements.

7. MARKETING AUTHORIZATION HOLDER

GlaxoSmithKline - Produtos Farmacêuticos, Lda.
Street Dr. António Loureiro Borges, 3,
Arquiparque Miraflores
1495-131 Algés

8. MARKETING AUTHORIZATION NUMBER(S)

Registry number: 5323688 - powder for 50 ml oral suspension, 600 mg/5 ml+42,9 mg/5 ml, colorless glass bottle

Registry number: 5323787 - powder for 75 ml oral suspension, 600 mg/5 ml+42,9 mg/5 ml, colorless glass bottle

Registry number: 5323886 - powder for 100 ml oral suspension, 600 mg/5 ml+42,9 mg/5 ml, colorless glass bottle

Registry number: 5323985 - powder for 150 ml oral suspension, 600 mg/5 ml+42,9 mg/5 ml, colorless glass bottle

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: February 4, 2005
Date of last renewal: Mar 6, 2015

10.DATE OF REVISION OF THE TEXT

June 13th, 2023