SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Augmentin Duo 400 mg/57 mg/5 ml powder for oral suspension (mixed fruit flavour)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every ml of oral suspension contains amoxicillin trihydrate equivalent to 80 mg amoxicillin and potassium clavulanate equivalent to 11.4 mg of clavulanic acid.

5 ml of oral suspension contains amoxicillin trihydrate equivalent to 400 mg amoxicillin and potassium clavulanate equivalent to 57 mg of clavulanic acid.

Excipients with known effect

Every ml of oral suspension contains 2.5 mg aspartame (E951). The flavouring in Augmentin contains maltodextrin (glucose) and benzyl alcohol (0.003 mg in each ml of oral suspension) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Augmentin 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

Posology

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

The dose of Augmentin 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 Augmentin (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 children < 40 kg, this formulation of Augmentin provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Augmentin 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 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).

Adults and children ≥ 40 kg should be treated with the adult formulations of Augmentin

Children < 40 kg

- Lower dose: 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;
- Higher dose: 45 mg/6.4 mg/kg/day to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

Body weight (kg)	25 mg/3.6 mg/kg/ day. Dose in ml to be **given every 12 hours**.	45 mg/6.4 mg/kg/ day. Dose in ml to be **given every 12 hours**.	70 mg/10 mg/ kg/day. Dose in ml to be **given every 12 hours**.
4.0	0.6	1.2	NR
5.0	0.8	1.4	NR
6.0	1.0	1.8	NR
7.0	1.2	2.0	NR
8.0	1.4	2.4	NR
9.0	1.4	2.6	NR
10.0	1.6	2.8	NR
11.0	1.8	3.2	NR
12.0	2.0	3.4	5.4
13.0	2.0	3.8	5.8
14.0	2.2	4.0	6.2
15.0	2.4	4.2	6.6
16.0	2.6	4.6	7.0
17.0	2.8	4.8	7.4
18.0	2.8	5.2	8.0
19.0	3.0	5.4	8.4
20.0	3.2	5.6	8.8
21.0	3.4	6.0	9.2

Body weight (kg)	25 mg/3.6 m g/kg/ day. Dose in ml to be **given every 12 hours**.	45 mg/6.4 mg/kg/ day. Dose in ml to be **given every 12 hours**.	70 mg/10 mg/ kg/day. Dose in ml to be **given every 12 hours**.
22.0	3.4	6.2	9.6
23.0	3.6	6.6	10.2
24.0	3.8	6.8	10.6
25.0	4.0	7.0	11.0
26.0	4.2	7.4	11.4
27.0	4.2	7.6	11.8
28.0	4.4	8.0	12.4
29.0	4.6	8.2	12.8
30.0	4.8	8.4	13.2
31.0	4.8	8.8	13.6
32.0	5.0	9.0	14.0
33.0	5.2	9.4	14.4
34.0	5.4	9.6	15.0
35.0	5.6	9.8	15.4
36.0	5.6	10.2	15.8
37.0	5.8	10.4	16.2
38.0	6.0	10.8	16.6
39.0	6.2	11.0	17.2

NR - Not recommended. No clinical data are available for Augmentin 7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years.

There are no clinical data for Augmentin 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Alternative oral formulations of Augmentin should be considered to deliver practical dose recommendations.

Children may be treated with Augmentin tablets, suspensions or paediatric sachets. Children aged 6 years and below should preferably be treated with Augmentin suspension or paediatric sachets.

The dose (ml) to be given to the patient two times daily can also be calculated using the following formula below:

$$\textit{Dose (ml) given two times daily} = \frac{\textit{Recommended amoxicillin}^{*}\textit{ dose (mg/kg/day)} \times \textit{weight (kg)}}{\textit{Reconstituted amoxicillin}^{*}\textit{ in suspension (mg/ml)} \times \textit{2 (divided doses)}}$$

* Only consideration of the amoxicillin component is required for this calculation.

For example, a 14 kg child treated at 25 mg/3.6 mg/kg/day:

$$\textit{Dose (ml) given two times daily} = \frac{\textit{25 (mg/kg/day)} \times \textit{14 (kg)}}{\textit{80 (mg/ml)} \times \textit{2 (divided doses)}}$$

$$\textit{Dose (ml) given two times daily} = \frac{\textit{350 (mg)}}{\textit{160 (mg/ml)}}$$

$$\textit{Dose (ml) given two times daily} = \textit{2.2 ml}$$

Elderly

No dose adjustment is considered necessary. Elderly patients should be treated with adult formulations of Augmentin.

Renal impairment

No dose adjustment is required 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 presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment

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

Method of administration

Augmentin 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 to the SmPC of the IV formulation and continued with an oral preparation.

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

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

4.3 Contraindications

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

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

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

4.4 Special warnings and precautions for use

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

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious 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 penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

Haemophagocytic lymphohistiocytosis (HLH) has been reported in patients receiving amoxicillin/clavulanic acid (see section 4.8). HLH is a life-threatening syndrome characterized by fever, skin rash, neurological symptoms, hepato- and/or splenomegaly, lymphadenopathy, cytopenias, high serum ferritin and hypertriglyceridaemia.

Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, amoxicillin/clavulanic acid must be interrupted for diagnostic workup and treatment for HLH initiated. If HLH is confirmed, administration of amoxicillin/clavulanic acid should be discontinued.

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

This presentation of Augmentin is not suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. 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 likelihood of allergic skin reactions.

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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with 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.

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 (including acute renal injury) 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 Augmentin 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-*Aspergillu*s 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.

Augmentin 400 mg/57 mg/5 ml powder for oral suspension contains 2.5 mg of aspartame (E951) per ml, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

The flavouring in Augmentin contains traces of benzyl alcohol. Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including gasping syndrome in paediatric patients.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment, pregnant or breast feeding because of the risk of accumulation and toxicity (metabolic acidosis). Additionally, there is an increased risk due to accumulation in young children. This medicinal product contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

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

Methotrexate

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

Probenecid

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

Mycophenolate mofetil

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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 Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1 000 to <1/100)
Rare (≥1/10 000 to <1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders	
Haemophagocytic lymphohistiocytosis[1]	Not known
Angioneurotic oedema[8]	Not known
Anaphylaxis[8]	Not known
Serum sickness-like syndrome[8]	Not known

Hypersensitivity vasculitis[8]	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Pancreatitis acute	Not known
Black hairy tongue	Not known
Tooth discolouration[9]	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[4]	Uncommon
Hepatitis[5]	Not known
Cholestatic jaundice[5]	Not known
Skin and subcutaneous tissue disorders[6]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear IgA disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury)[7]	Not known

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

[4] 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.
[5] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[6] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[7] See section 4.9
[8] See sections 4.3 and 4.4
[9] 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed below:

ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4)

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

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

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

Pharmacokinetic/pharmacodynamic relationship

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

Mechanisms of resistance

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

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

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

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for amoxicillin/clavulanic acid and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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)£
Coagulase-negative staphylococci (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 psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ 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 are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (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 a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets given twice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) 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 Augmentin 250 mg/125 mg or 500 mg/125 mg

tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin 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

Non-clinical 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

Aspartame (E951)
Colloidal anhydrous silica
Hypromellose
Silicon dioxide
Succinic acid
Xanthan gum
Golden syrup dry flavour (including maltodextrin)
Orange dry flavour 1 (including maltodextrin and benzyl alcohol)
Orange dry flavour 2 (including maltodextrin)

Raspberry dry flavour (including maltodextrin)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Dry powder: 2 years
Reconstituted suspension: 7 days
Reconstituted suspensions should be stored at 2°C – 8°C (but not frozen) for up to 7 days.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Clear glass bottles containing powder for reconstitution to 35 ml, 70 ml or 140 ml with a plastic child-resistant cap and removable foil-backed seal. This may be supplied with a plastic measuring spoon or syringe.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Check foil-backed bottle seal is intact before using. At time of preparation, shake bottle to loosen powder and remove foil-backed seal. Add volume of water (as indicated below). Replace bottle cap, invert and shake well.

Pack size (ml)	Volume of water to be added at reconstitution (ml)
35	31
70	62
140	124

Additional text for markets that have a fill line on the bottle or label:
Alternatively, fill the bottle with water to just below the line on the bottle or label. Replace bottle cap, invert and shake well, then top up with water exactly to the line. Replace bottle cap, invert and again shake well.

Shake the bottle well before each dose.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

MA192/01505

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th July 2017
Date of renewal: 25th September 2018

10. DATE OF REVISION OF THE TEXT

09th September 2026