

## **1 NAME OF THE MEDICINAL PRODUCT**

Amoxicillin 250 mg / 5 ml Granules for Oral Suspension Sugar free

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Amoxicillin trihydrate (equivalent to 250 mg Amoxicillin per 5 ml of reconstituted product).

### Excipients with known effect

Contains 0.933g of sorbitol (E420)per 5 ml

Contains 4 mg of Sodium methyl parahydroxybenzoate (E219) per 5ml.

For the full list of excipients, see section 6.1.

## **3 PHARMACEUTICAL FORM**

### Granules for oral suspension

White/off-white coloured granules with an odour of lemon. When reconstituted as directed, a white suspension is produced.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Amoxicillin Oral Suspension 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
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis (AECB)/acute exacerbation of chronic obstructive pulmonary disease (AECOPD)
- Community acquired pneumonia
- Acute cystitis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- *Helicobacter pylori* eradication
- Lyme disease

Amoxicillin is also indicated for the prophylaxis of endocarditis.

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

## 4.2 Posology and method of administration

### Posology

The dose of Amoxicillin 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 duration of therapy should be determined by the type of infection and the response of the patient, and should generally be as short as possible. Some infections require longer periods of treatment (see section 4.4 regarding prolonged therapy).

### Adults and children $\geq 40$ kg

Indication*	Dose*
Acute bacterial sinusitis	250 mg to 500 mg every 8 hours or 750 mg to 1 g every 12 hours
Asymptomatic bacteriuria in pregnancy	
Acute pyelonephritis	
Dental abscess with spreading cellulitis	For severe infections 750 mg to 1 g every 8 hours
Acute cystitis	Acute cystitis may be treated with 3 g twice daily for one day
Acute otitis media	500 mg every 8 hours, 750 mg to 1 g every 12 hours
Acute streptococcal tonsillitis and pharyngitis	
Acute exacerbations of chronic bronchitis	
Community acquired pneumonia	For severe infections 750 mg to 1 g every 8 hours for 10 days
Typhoid and paratyphoid fever	500 mg to 1 g every 8 hours
Prosthetic joint infections	500 mg to 2 g every 8 hours
Prophylaxis of endocarditis	500 mg to 1 g every 8 hours
<i>Helicobacter pylori</i> eradication	2 g orally, single dose 30 to 60 minutes before procedure.
	750 mg to 1 g twice daily in combination with a proton pump inhibitor (e.g. omeprazole, lansoprazole) and another antibiotic (e.g. clarithromycin, metronidazole) for 7 days.

Lyme disease (see section 4.4)	<p>Early stage: 500 mg to 1 g every 8 hours up to a maximum of 4 g/day in divided doses for 14 days (10 to 21 days)</p> <p>Late stage (systemic involvement): 500 mg to 2 g every 8 hours up to a maximum of 6 g/day in divided doses for 10 to 30 days</p>
*Consideration should be given to the official treatment guidelines for each indication	

### **Children <40 kg**

Children may be treated with Amoxicillin capsules, dispersible tablets suspensions or sachets.

Amoxicillin Oral Suspension is recommended for children under six months of age.

Children weighing 40 kg or more should be prescribed the adult dosage.

*Recommended doses:*

<b>Indication<sup>+</sup></b>	<b>Dose<sup>+</sup></b>
Acute bacterial sinusitis	20 to 90 mg/kg/day in divided doses*
Acute otitis media	
Community acquired pneumonia	
Acute cystitis	
Acute pyelonephritis	
Dental abscess with spreading cellulitis	
Acute streptococcal tonsillitis and pharyngitis	40 to 90 mg/kg/day in divided doses*
Typhoid and paratyphoid fever	100 mg/kg/day in three divided doses
Prophylaxis of endocarditis	50 mg/kg orally, single dose 30 to 60 minutes before procedure
Lyme disease (see section 4.4)	<p>Early stage: 25 to 50 mg/kg/day in three divided doses for 10 to 21 days</p> <p>Late stage (systemic involvement): 100 mg/kg/day in three divided doses for 10 to 30 days</p>

+ Consideration should be given to the official treatment guidelines for each indication.

\*Twice daily dosing regimens should only be considered when the dose is in the upper range.

### **Elderly**

No dose adjustment is considered necessary.

### **Renal impairment**

<b>GFR (ml/min)</b>	<b>Adults and children <math>\geq</math> 40 kg</b>	<b>Children &lt; 40 kg<sup>#</sup></b>
<b>greater than 30</b>	no adjustment necessary	no adjustment necessary
<b>10 to 30</b>	maximum 500 mg twice daily	15 mg/kg given twice daily (maximum 500 mg twice daily)
<b>less than 10</b>	maximum 500 mg/day.	15 mg/kg given as a single daily dose (maximum 500 mg)

<sup>#</sup> In the majority of cases, parenteral therapy is preferred.

*In patients receiving haemodialysis*

Amoxicillin may be removed from the circulation by haemodialysis.

	<b>Haemodialysis</b>
<b>Adults and children <math>\geq</math> 40 kg</b>	15 mg/kg/day given as a single daily dose. Prior to haemodialysis one additional dose of 15 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15 mg/kg should be administered after haemodialysis.
<b>Children under 40 kg</b>	15 mg/kg/day given as a single daily dose (maximum 500 mg). Prior to haemodialysis one additional dose of 15 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15 mg/kg should be administered after haemodialysis.

*In patients receiving peritoneal dialysis*

Amoxicillin maximum 500 mg/day.

### **Hepatic impairment**

Dose with caution and monitor hepatic function at regular intervals (see sections 4.4 and 4.8).

### **Method of administration**

Amoxicillin is for oral use.

Absorption of Amoxicillin is unimpaired by food.

Therapy can be started parenterally according to the dosing recommendations of the intravenous formulation and continued with an oral preparation.

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

## **4.3 Contraindications**

Hypersensitivity to the active substance, 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 betalactam agent (e.g. acephalosporin, carbapenem or monobactam).

## **4.4 Special warnings and precautions for use**

### **Hypersensitivity reactions**

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other betalactam 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 receiving beta-lactam antibiotics (see section 4.3). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug intake) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock.

If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

#### Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin (see section 5.1). This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

#### Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders (see section 4.8).

#### Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

#### Skin reactions

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

Amoxicillin 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.

#### Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease (see section 4.8). It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

#### Overgrowth of non-susceptible microorganisms

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

Antibiotic associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during, or subsequent to, the administration of any antibiotics. Should antibiotic associated colitis occur, amoxicillin should immediately be discontinued, a physician consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

#### Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported (see section 4.8).

#### Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. 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).

#### Crystalluria

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 section 4.8 and 4.9).

#### Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

#### Important information about excipients

**Sorbitol (E420):** Sorbitol may cause gastrointestinal discomfort and mild laxative effect. Each 5ml dose of this medicine contains 933 mg of sorbitol.

**Sodium:** This medicine contains less than 1mmol sodium (23mg) per 5ml, that is to say essentially “sodium-free”

This medicinal product contains Sodium methyl parahydroxybenzoate (E219). May cause allergic reactions (possibly delayed).

## **4.5 Interaction with other medicinal products and other forms of interaction**

### 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.

### Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

### Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

### 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.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

### Breastfeeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breastfed infant, so that breastfeeding might have to be discontinued. Amoxicillin should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

### Fertility

There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

## **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 skin rash.

The ADRs derived from clinical studies and post marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below.

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

Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ). Not known (cannot be estimated from the available data).

<b><u>Infections and infestations</u></b>	
Very rare	Mucocutaneous candidiasis
<b><u>Blood and lymphatic system disorders</u></b>	
Very rare	Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.  Prolongation of bleeding time and prothrombin time (see section 4.4).
<b><u>Immune system disorders</u></b>	
Very rare	Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis (see section 4.4).
Not known	Jarisch-Herxheimer reaction (see section 4.4)
<b><u>Nervous system disorders</u></b>	
Very rare	Hyperkinesia, dizziness and convulsions (see section 4.4).
Not known	Aseptic meningitis
<b><u>Cardiac disorders</u></b>	
Not known	Kounis syndrome (see section 4.4).
<b><u>Gastrointestinal disorders</u></b>	
Clinical trial data	
*Common	Diarrhoea and nausea
*Uncommon	Vomiting
Post-marketing data	
Very rare	Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis-see section 4.4). Black hairy tongue. Superficial tooth discolouration #
Not known	Drug-induced enterocolitis syndrome
<b><u>Hepato-biliary disorders</u></b>	
Very rare	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT.
<b><u>Skin and subcutaneous tissue disorders</u></b>	
Clinical trial data	
*Common	Skin rash
*Uncommon	Urticaria and pruritus.
Post-marketing data	
Very rare	Skin reactions such as erythema multiforme,

	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis acute generalised exanthematous pustulosis (AGEP) (see section 4.4) and drug reaction with eosinophilia and systemic symptoms (DRESS), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also Immune system disorders).
Not known	Linear IgA disease
<u>Renal and urinary tract disorders</u>	
Very rare	Interstitial nephritis.
Not known	Crystalluria (including acute renal injury)
* The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.	
# Superficial tooth discolouration has been reported 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 Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

### Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) 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 (see sections 4.4 and 4.8).

### Treatment of intoxication

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

Amoxicillin can be removed from the circulation by haemodialysis.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: penicillins with extended spectrum; ATC code: J01CA04.

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.

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 main mechanisms of resistance to amoxicillin are:

- Inactivation by bacterial beta-lactamases.
- 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 are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 11.0.

Organism	Susceptibility breakpoint (µg/L)	
	Susceptible	Resistant
Enterobacterales <sup>10</sup>	≤ 8	> 8
<i>Staphylococcus</i> spp.	Note <sup>3,4,5</sup>	Note <sup>3,4,5</sup>
<i>Enterococcus</i> spp. <sup>6</sup>	≤ 4 <sup>7</sup>	> 8 <sup>7</sup>
Streptococcus groups A, B, C and G (indications other than meningitis)	Note <sup>8</sup>	Note <sup>8</sup>
<i>Streptococcus pneumoniae</i> <sup>9</sup>	≤ 0.5	> 1
Viridans group streptococci	≤ 0.5	> 2
<i>Haemophilus influenzae</i> <sup>1</sup>	≤ 0.001	> 2
<i>Moraxella catarrhalis</i>	Note <sup>2</sup>	Note <sup>2</sup>
<i>Neisseria meningitidis</i>	≤ 0.125	> 1
Gram positive anaerobes <sup>11</sup> except <i>Clostridium difficile</i> <sup>8</sup>	≤ 4	> 8

Gram negative anaerobes <sup>11</sup>	≤ 0.5	> 2
<i>Helicobacter pylori</i>	≤0.125	>0.125
<i>Pasteurella multocida</i>	≤1	>1
Non- species related breakpoints	≤ 2	> 8

<sup>1</sup>Beta-lactamase positive isolates can be reported resistant to ampicillin, amoxicillin and piperacillin without inhibitors. Tests based on a chromogenic cephalosporin can be used to detect the beta-lactamase.

<sup>2</sup> Most *M. catarrhalis* produce beta-lactamase, although beta-lactamase production is slow and may give weak results with in vitro tests. Beta-lactamase producers should be reported resistant to penicillins and aminopenicillins without inhibitors.

<sup>3</sup> Most *S. aureus* are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactam β-lactamase inhibitor combinations, the isoxazolympenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Isolates that test resistant to cefoxitin are resistant to all penicillins.

<sup>4</sup> Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in coagulase-negative staphylococci but methicillin resistance can be detected with cefoxitin as described.

<sup>5</sup> Ampicillin susceptible *S. saprophyticus* are mecA-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

<sup>6</sup> Aminopenicillin breakpoints in enterococci are based on intravenous administration. For oral administration the breakpoints are relevant for urinary tract infections only.

<sup>7</sup> Susceptibility to ampicillin, amoxicillin and piperacillin (with and without betalactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

<sup>8</sup> The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolympenicillins for streptococcus group B.

<sup>9</sup> The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/l) all beta-lactam agents for which clinical breakpoints are available, can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as “susceptible, increased exposure” (I). When the screen is positive (inhibition zone <20 mm, or benzylpenicillin MIC >0.06 mg/l), refer to EUCAST flow chart.

<sup>10</sup> Aminopenicillin breakpoints in Enterobacterales are based on intravenous administration. For oral administration the breakpoints are relevant for urinary tract infections only. Breakpoints for other infections are under review.

<sup>11</sup> Susceptibility to ampicillin, amoxicillin, piperacillin and ticarcillin can be inferred from susceptibility to benzylpenicillin.

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.

<b><i>In vitro</i> susceptibility of micro-organisms to Amoxicillin</b>
<b><u>Commonly Susceptible Species</u></b>
<u>Gram-positive aerobes:</u> <i>Enterococcus faecalis</i> Beta-hemolytic streptococci (Groups A, B, C and G) <i>Listeria monocytogenes</i>
<b><u>Species for which acquired resistance may be a problem</u></b>
<u>Gram-negative aerobes:</u> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Helicobacter pylori</i> <i>Proteus mirabilis</i> <i>Salmonella typhi</i> <i>Salmonella paratyphi</i> <i>Pasteurella multocida</i>
<u>Gram-positive aerobes:</u> Coagulase negative staphylococcus <i>Staphylococcus aureus</i> <sup>‡</sup> <i>Streptococcus pneumoniae</i> Viridans group streptococcus
<u>Gram-positive anaerobes:</u> <i>Clostridium</i> spp.
<u>Gram-negative anaerobes:</u> <i>Fusobacterium</i> spp.
<u>Other:</u> <i>Borrelia burgdorferi</i>
<b><u>Inherently resistant organisms</u></b> <sup>†</sup>
<u>Gram-positive aerobes:</u> <i>Enterococcus faecium</i> <sup>†</sup>
<u>Gram-negative aerobes:</u> <i>Acinetobacter</i> spp. <i>Enterobacter</i> spp. <i>Klebsiella</i> spp. <i>Pseudomonas</i> spp.
<u>Gram-negative anaerobes:</u> <i>Bacteroides</i> spp. (many strains of <i>Bacteroides fragilis</i> are resistant).
<u>Others:</u>

<i>Chlamydia</i> spp. <i>Mycoplasma</i> spp. <i>Legionella</i> spp.
<sup>†</sup> Natural intermediate susceptibility in the absence of acquired mechanism of resistance. <sup>‡</sup> Almost all <i>S.aureus</i> are resistant to amoxicillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin.

## 5.2 Pharmacokinetic properties

### Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration ( $T_{max}$ ) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

$C_{max}$	$T_{max}$ *	AUC <sub>(0-24h)</sub>	$T_{1/2}$
( $\mu\text{g/ml}$ )	(h)	(( $\mu\text{g.h/ml}$ )	(h)
$3.3 \pm 1.12$	1.5 (1.0-2.0)	$26.7 \pm 4.56$	$1.36 \pm 0.56$
*Median (range)			

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as  $C_{max}$  and AUC). The absorption is not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of amoxicillin.

### Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has 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. Amoxicillin, like most penicillins, can be detected in breast milk (see section 4.6).

Amoxicillin has 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.

#### Elimination

The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24-hour period.

Concomitant use of probenecid delays amoxicillin excretion (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 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. 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/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

#### Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function (see sections 4.2 and 4.4).

#### Hepatic impairment

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

### **5.3 Preclinical safety data**

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

Carcinogenicity studies have not been conducted with amoxicillin.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lemon flavour (maltodextrin, Gum acacia, and flavouring substances)  
Apricot flavour (maltodextrin, Gum acacia, and flavouring substances)  
Sodium methyl parahydroxybenzoate (E219)  
Carmellose sodium (Carboxymethylcellulose sodium)  
Sodium citrate  
Colloidal anhydrous silica  
Sorbitol (E420)

### **6.2 Incompatibilities**

None.

### **6.3 Shelf life**

Granules for oral suspension: 2 years

Shelf life after reconstitution: 7 days

### **6.4 Special precautions for storage**

Granules for oral suspension: Do not store above 25<sup>0</sup> C.

Storage after reconstitution: Store upright in a refrigerator (2<sup>0</sup> C – 8<sup>0</sup> C). Use within 7 days of preparation. Keep the bottle tightly closed.

### **6.5 Nature and contents of container**

HDPE bottles and PP/HDPE child resistant caps with EPE induction seal liner.

Amoxicillin 250 mg / 5 ml Oral Suspension.

Pack size: 100 ml.

**6.6 Special precautions for disposal**

To reconstitute the granules to make the suspension, add 85 ml of water and shake well until the granules dissolved. When reconstituted as directed a white suspension is produced.

**7 MARKETING AUTHORISATION HOLDER**

Crescent Pharma Limited

Key House, Sarum Hill,

Basingstoke,

RG21 8SR,

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20416/0716

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**10 DATE OF REVISION OF THE TEXT**

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