1. NAME OF THE MEDICINAL PRODUCT

Amoxicillin 250mg Powder for Solution for Injection
Amoxicillin 500mg Powder for Solution for Injection
Amoxicillin 1g Powder for Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amoxicillin Sodium equivalent to Amoxicillin Ph Eur 250mg
Amoxicillin Sodium equivalent to Amoxicillin Ph Eur 500mg
Amoxicillin Sodium equivalent to Amoxicillin Ph Eur 1g

3 PHARMACEUTICAL FORM

Powder for solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis
- Acute pyelonephritis
- Severe dental abscess with spreading cellulitis
- Prosthetic joint infections
- Lyme disease
- Bacterial meningitis
- Bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Amoxicillin is also indicated for the treatment and 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 ≥ 40 kg

Indication*	**Dose***
Severe infections of the ear, nose and throat (such as mastoiditis peritonsillar infections, epiglottis and sinusitis when accompanied by severe systemic signs and symptoms	750 mg to 2 g every 8 hours, or 2 g every 12 hours, maximum of 12 g/day
Acute exacerbations of chronic bronchitis	
Community acquired pneumonia	
Acute cystitis	
Acute pyelonephritis	
Severe dental abscess with spreading cellulitis	
Prosthetic joint infections	750 mg to 2 g every 8 hours, or 2 g every 12 hours, maximum of 12 g/day
Prophylaxis of endocarditis	2 g single dose 30 to 60 minutes before procedure.
Treatment of endocarditis	1 g to 2 g every 4 to 6 hours, maximum of 12 g/day
Bacterial meningitis	1 g to 2g every 4 to 6 hours, maximum of 12 g/day
Lyme disease (see section 4.4)	Late stage (systemic involvement): 2 g every 8 hours
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	1 g to 2 g every 4, 6 or 8 hours, maximum of 12 g/day
*Consideration should be given to the official treatment guidelines for each indication.	

Intramuscular
Maximum daily dosage: 4 g/day.
Maximum single dose: 1 g.

Children < 40 kg

Infants and toddlers >3 months and children < 40 kg Indication*	**Dose***
Severe infections of the ear, nose and throat (such as mastoiditis peritonsillar infections, epiglottis and sinusitis when accompanied by severe systemic signs and symptoms	20 to 200 mg/kg/day given in 2 to 4 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg

Community acquired pneumonia	

Neonates ≥ 4kg and infants up to 3 months **Indication***	**Dose***
Acute cystitis Acute pyelonephritis Severe dental abscess with spreading cellulitis	
Prophylaxis of endocarditis	50 mg/kg single dose 30 to 60 minutes before procedure
Treatment of endocarditis	200 mg/kg/day in 3 to 4 equally divided does of up to 25 mg/kg or infusions of up to 50 mg/kg
Bacterial meningitis	100 to 200 mg/kg/day in 3 to 4 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in three divided doses for 10 days (range 10 to 21 days) Late stage (systemic involvement): 50 mg/kg/day in three divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	50 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
*Consideration should be given to the official treatment guidelines for each indication.	

Most infections	Usual daily dose of 20 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Treatment of endocarditis	150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Bacterial meningitis	150 mg/kg/day given in three divided doses
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in three divided doses for 10 days (range 10 to 21 days) Late stage (systemic involvement): 50 mg/kg/day in three divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	Usual daily dose of 50 to 150 mg/kg/day given in 3 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
*Consideration should be given to the official treatment guidelines for each indication.	

Premature Neonates < 4kg **Indication***	**Dose***
Most infections	Usual daily dose of 20 to 100 mg/kg/day given in 2 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
Treatment of endocarditis	100 mg/kg/day given in two divided doses
Bacterial meningitis	100 mg/kg/day given in two divided doses
Lyme disease (see section 4.4)	Early stage: 25 to 50 mg/kg/day in two divided doses for 10 days (range 10 to 21 days) Late stage (systemic involvement): 50 mg/kg/day in two divided doses
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed in section 4.1	Usual daily dose of 50 to 100 mg/kg/day given in 2 equally divided doses of up to 25 mg/kg or infusions of up to 50 mg/kg
*Consideration should be given to the official treatment guidelines for each indication.	

Intramuscular:
Maximum daily dosage: 120 mg/kg/day as 2 to 6 equally divided doses.

Elderly
No adjustment needed; as for adults.

Renal impairment

	Adults and children ≥ 40 kg		Children < 40 kg	
GFR (ml/min)	**Intravenous**	**Intramuscular**	**Intravenous**	**Intramuscular**
greater than 30	No adjustment	No adjustment	No adjustment	No adjustment
10 to 30	1g stat, then 500 mg to 1 g twice day	500 mg every 12 hours	25 mg/kg twice daily	15 mg/kg every 12 hours
less than 10	1 g stat, then 500 mg/day	500 mg/day given as a single dose	25 mg/kg/day given as a single dose	15 mg/kg/day given as a single dose

In patients receiving haemodialysis and peritoneal dialysis
Amoxicillin may be removed from the circulation by haemodialysis.

	Haemodialysis		Peritoneal dialysis	
	Intravenous	**Intramuscular**	**Intravenous**	**Intramuscular**
Adults and children ≥ 40 kg	1 g at the end of dialysis, then 500 mg every 24 hours	500 mg during dialysis, 500 mg at the end, then 500 mg every 24 hours	1 g stat, then 500 mg/day	500 mg/day given as a single dose
Children < 40 kg	25 mg/kg stat and 12.5 mg/kg at the end of the dialysis, then 25 mg/kg/day	15 mg/kg during and at the end of dialysis, then 15 mg/kg every 24 hours	25 mg/kg/day given as a single dose	15 mg/kg/day given as a single dose

Method of Administration

The standard recommended route of administration is by intravenous injection or intravenous infusion. Intramuscular administration should only be considered when the intravenous route is not possible or less appropriate for the patient.

Intravenous Injection:

Dissolve 250mg in 5mL Water for Injections Ph Eur (final volume 5.2mL).

Dissolve 500mg in 10mL Water for Injections Ph Eur (final volume 10.4mL).

Dissolve 1g in 20mL Water for Injections Ph Eur (final volume 20.8mL).

Amoxicillin for Injection, when diluted may be injected slowly into a vein or infusion line over a period of three to four minutes.

Intravenous Infusion:

Prepare as above and add to an iv solution in a minibag or in-line burette. Administer over 30 to 60 minutes. Alternatively the appropriate volume of iv fluid may be transferred from the infusion bag into the vial, using a suitable reconstitution device, and drawn back into the bag after dissolution.

Intramuscular Injection:	Add 1.5mL Water for Injections Ph Eur to 250mg and shake vigorously (final volume 1.7mL).
	Add 2.5mL Water for Injections Ph Eur to 500mg and shake vigorously (final volume 2.9mL).

The maximum single dose is 1 g in adults and children ≥ 40 kg.

Do not inject more than 60 mg/kg at one time in children < 40 kg.

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 beta-lactam agent (e.g. a cephalosporin, 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 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. 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> <administration> <use>) 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**.**

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.

Care is also necessary if large doses of sodium (as amoxicillin sodium) are given to patients with impaired renal function or heart failure. Renal and haematological status should be monitored during prolonged and high-dose therapy.

Amoxicillin should preferably not be given to patients with undiagnosed pharyngitis (who may have mononucleosis) or patients with lymphatic leukaemia or possibly HIV infection who may also be at increased risk of developing skin rashes with amoxicillin.

There is a potential for increased serum levels of amoxicillin in the newborn or in young infants due to reduced renal excretion.

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 contra-indicates 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 contra-indicated 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.

Amoxicillin 250mg, 500mg and 1g powder for solution for injection contains 0.65mmol (14.9mg), 1.3mmol (29.7mg) and 2.6mmol (59.4mg) of sodium per dose, respectively. To be taken into consideration by patients on a controlled sodium diet.

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.

Breast-feeding

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 breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin should only be used during breast-feeding 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 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	
Very rare	Mucocutaneous candidiasis
Blood and lymphatic system disorders	
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).
Immune system disorders	
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).
Metabolism and nutrition disorders	
Not known	Electrolyte disturbances such as hypokalaemia (due to administration of large amounts of sodium).
Nervous system disorders	
Very rare	Hyperkinesia, dizziness, aseptic meningitis and convulsions (see section 4.4).
Not known	Signs of central nervous system toxicity; generally associated with large intravenous doses of amoxicillin or impaired renal function. Encephalopathy has been reported following intrathecal administration and can be fatal. A coma may develop with high doses of amoxicillin. **Aseptic meningitis**
Gastrointestinal disorders	
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).
Not known	Sore mouth or tongue, commonly occur after oral administration but may also occur following parenteral administration Drug-induced enterocolitis syndrome
Hepatobiliary disorders	
Very rare	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT.
Skin and subcutaneous tissue disorders	
Clinical Trial Data	
*Common	Skin rash
*Uncommon	Urticaria and pruritus
Not known	Linear IgA disease

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).
Renal and urinary tract disorders	
Very rare:	Interstitial nephritis Crystalluria (see sections 4.4 and 4.9 Overdose)
Not known	Crystalluria (including acute renal injury)
Respiratory, thoracic and mediastinal disorders	
Not known	Bronchospasm, Acute severe dyspnoea and allergic pneumonitis; generally associated with large intravenous doses of amoxicillin or impaired renal function.
Psychiatric disorders	
Not known:	Hallucinations
Cardiac disorders	
Not known	Kounis syndrome
* The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.	

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

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. Convulsions may occur in patients with impaired renal function or in those receiving high doses (see sections 4.4 and 4.8).

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 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 5.0.

Organism	**MIC breakpoint (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacteriaceae	8[1]	8
Staphylococcus spp.	Note[2]	Note[2]
Enterococcus spp.[3]	4	8
Streptococcus groups A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	Note[5]	Note[5]
Viridans group steprococci	0.5	2
Haemophilus influenzae	2[6]	2[6]
Moraxella catarrhalis	Note[7]	Note[7]
Neisseria meningitidis	0.125	1
Gram positive anaerobes except *Clostridium difficile*[8]	4	8
Gram negative anaerobes[8]	0.5	2
Helicobacter pylori	0.125[9]	0.125[9]
Pasteurella multocida	1	1
Non- species related breakpoints[10]	2	8

[1]Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L

[2]Most staphylococci are penicillinase producers, which are resistant to amoxicillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.
[3]Susceptibility to amoxicillin can be inferred from ampicillin
[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility.
[5]Breakpoints relate only to non-meningitis isolates. For isolates categorised as intermediate to ampicillin avoid oral treatment with amoxicillin. Susceptibility inferred from the MIC of ampicillin.
[6]Breakpoints are based on intravenous administration. Beta-lactamase positive isolates should be reported resistant.
[7]Beta lactamase producers should be reported resistant
[8]Susceptibility to amoxicillin can be inferred from benzylpenicillin.
[9]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.
[10]The non-species related breakpoints are based on doses of at least 0.5 g x 3or 4 doses daily (1.5 to 2 g/day).

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.

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

Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.
† Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ Almost all *S.aureus* are resistant to amoxicillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin.

5.2 Pharmacokinetic properties

The pharmacokinetic results for studies in which amoxicillin was administered to groups of healthy volunteers given as a bolus intravenous injection are presented below.

Mean pharmacokinetic parameters *Bolus intravenous injection*				
Dose administered				
	Peak serum conc (µg/ml)	T 1/2 (h)	AUC (µg.h/ml)	Urinary recovery (%, 0 to 6 h)
500 mg	32.2	1.07	25.5	66.5
1000 mg	105.4	0.9	76.3	77.4

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).

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 dose of amoxicillin. Various studies have found the urinary excretion to be 50 to 85% for amoxicillin over a 24 hour period.

Concomitant use of probenecid delays amoxicillin excretion (see section 4.5).

Gender
Following oral administration of amoxicillin to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

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.

Renal impairment
The total serum clearance of amoxicillin decreases proportionately with decreasing renal function (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, 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

None.

6.2 Incompatibilities

Amoxicillin should not be mixed with blood products, other proteinaceous fluids such us protein hydrolysates or with intravenous lipid emulsions. If prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because of loss of activity of the aminoglycoside under these conditions.
Amoxicillin and aminoglycoside injections should be administered at separate sites.

Amoxicillin should not be mixed with ciprofloxacin.

Amoxicillin solutions should not be mixed with infusions containing dextran or bicarbonate.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC.

Reconstituted solutions should be administered immediately after preparation.

6.5 Nature and contents of container

Vials containing 250mg or 500mg or 1000mg of amoxicillin for injection in packs of 1, 5, 10, 20 or 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The vials are not suitable for multidose use.

All solutions should be shaken vigorously before injection and administered immediately after reconstitution.

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

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
U.K.

8. MARKETING AUTHORISATION NUMBER*(S)*

Amoxicillin 250mg Powder for Solution for Injection - PL 29831/0010
Amoxicillin 500mg Powder for Solution for Injection - PL 29831/0012
Amoxicillin 1g Powder for Solution for Injection - PL 29831/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 February 2008

10 DATE OF REVISION OF THE TEXT

09/05/2024