SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

1. Amoxicillin Oral Suspension BP 250 mg/5 ml

2. Respillin 250 mg/5 ml (OPD Pharmaceuticals Ltd)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every 5 ml of oral suspension contains amoxicillin trihydrate Ph.Eur equivalent to 250 mg amoxicillin (50 mg per ml).

Excipients with known effect

Contains 3.3 mg sodium per 5 ml.

Contains 1.38 g of sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension.

An off-white powder for oral suspension, which, on reconstitution with water, produces a white, lime flavoured suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Acute bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis, urethritis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Gynaecological infections including puerperal sepsis and septic abortion
- Gonorrhoea
- Peritonitis

- Intra-abdominal sepsis
- Septicaemia
- Bacterial endocarditis
- Typhoid and paratyphoid fever
- Skin and soft tissue infections
- Osteomyelitis
- Dental abscess (as an adjunct to surgical management) with spreading cellulitis
- Prosthetic joint infections
- *Helicobacter pylori* eradication in peptic (duodenal and gastric) ulcer disease
- Lyme disease

In children with urinary tract infection the need for investigation should be considered.
Amoxicillin Oral Suspension is also indicated for the prophylaxis of endocarditis.

Prophylaxis of endocarditis
Amoxicillin may be used for the prevention of bacteraemia, associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.
Consideration should be given to official guidance (e.g. national requirements) on the appropriate use of antibacterial agents. Susceptibility of the causative organisms to the treatment should be tested (if possible), although the therapy may be initiated before the results are available (see section 5.1).

4.2 Posology and method of administration

Posology
The dose of Amoxicillin Oral Suspension 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 ≥ 40kg
Standard dosage:
For less severe infections the usual adult dose is 250 mg three times daily. In more severe conditions the dosage may be doubled.
High-dosage therapy

(Maximum recommended oral dosage 6 g daily in divided doses):

A dosage of 3 g twice daily is recommended in appropriate cases for the treatment of severe or recurrent purulent infection of the respiratory tract.
Short-course therapy
In simple, acute urinary tract infection in adults: two 3 g doses with 10 - 12 hours between the doses.

A single dose of 3g is recommended for the treatment of gonorrhoea.

Dental abscess: two 3 g doses with 8 hours between the doses.

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	For severe infections 750 mg to 1 g every 8 hours
Dental abscess with spreading cellulitis	
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	For severe infections 750 mg to 1 g every 8 hours for 10 days
Community acquired pneumonia	500 mg to 1 g every 8 hours
Typhoid and paratyphoid fever	500 mg to 2 g every 8 hours
Prosthetic joint infections	500 mg to 1 g every 8 hours
Prophylaxis of endocarditis	2 g orally, single dose 30 to 60 minutes before procedure
Helicobacter pylori eradication	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)	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) 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
*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 Paediatric Suspension is recommended for children under six months of age.

Children weighing more than 40 kg should be given the usual adult dosage.

The daily dosage for children is 40 - 90 mg/kg/day in two to three divided doses* (not exceeding 3 g/day) depending on the indication, severity of the disease and the susceptibility of the pathogen (see special dosage recommendations below and sections 4.4, 5.1 and 5.2).

*PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.

Recommended doses:

Indication[+]	**Dose**[+]
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)	Early stage: 25 to 50 mg/kg/day in three divided doses for 10 to 21 days Late stage (systemic involvement): 100 mg/kg/day in three divided doses for 10 to 30 days
Tonsillitis	50mg/kg/day in two divided doses
+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 ** In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations. In severe or recurrent acute otitis media, especially where compliance may be a problem, 750 mg twice a day for two days may be used as an alternative course of treatment in children aged 3 to 10 years.	

Elderly

No dose adjustment is considered necessary.

Dosage in impaired renal function:
The dose should be reduced in patients with severe renal function impairment. In patients with a creatinine clearance of less than 30 ml/min an increase in the dosage interval and a reduction in the total daily dose is recommended (see section 4.4 and 5.2).

Renal impairment

GFR (ml/min)	**Adults and children ≥ 40 kg**	**Children < 40 kg[#]**
greater than 30	No adjustment necessary	No adjustment necessary
10 to 30	Maximum 500 mg twice daily	15 mg/kg given twice daily (maximum 500 mg twice daily)
less than 10	Maximum 500mg/day.	15 mg/kg given as a single daily dose (maximum 500 mg)
[#] In the majority of cases, parenteral therapy is preferred.		

Helicobacter *eradication in peptic (duodenal and gastric) ulcer disease*:
Amoxicillin is recommended twice daily in association with a proton pump inhibitor and antimicrobial agents as detailed below:
(Omeprazole 40mg daily, Amoxicillin 1g BID, Clarithromycin 500mg BID) x 7 days

Or
(Omeprazole 40mg daily, Amoxicillin 750mg-1g BID, Metronidazole 400mg TID) x 7days

Treatment should be continued for 2-3 days following the disappearance of symptoms. It is recommended that at least 10 days treatment be given for any infection caused by beta-haemolytic streptococci in order to achieve eradication of the organism.

In patients receiving haemodialysis

Amoxicillin Oral Suspension may be removed from the circulation by haemodialysis.

	Haemodialysis
Adults and children ≥ 40 kg	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.

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).

Prophylaxis of endocarditis

Condition		**Adult's dosage (including elderly)**	**Children's dosage (<40kg)**	**Notes**
Dental procedures: Prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues and who have not received a penicillin in the previous month. (N.B. Patients with prosthetic	Patient not having general anaesthetic	3 g amoxicillin orally, 1 hour before procedure. A second dose may be given 6 hours later, if considered necessary.	50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure	Note 1. If prophylaxis with amoxicillin is given twice within one month, emergence of resistant streptococci is unlikely to be a problem. Alternative antibiotics are recommended if more
	Patient having general anaesthetic:	Initially 3 g amoxicillin orally 4 hours prior		

Condition		Adult's dosage (including elderly)	Children's dosage (<40kg)	Notes
heart valves should be referred to hospital - see below).	if oral antibiotics considered to be appropriate.	to anaesthesia, followed by 3 g orally (or 1 g IV or IM if oral dose not tolerated) as soon as possible after the operation.		frequent prophylaxis is required, or if the patient has received a course of treatment with a penicillin during the previous month. Note 2. To minimise pain on injection, amoxicillin may be given as two injections of 500 mg dissolved in sterile 1% lidocaine solution (See Method of administration)
	Patient having general anaesthetic: if oral antibiotics not appropriate.	1 g amoxicillin IV or IM immediately before induction; with 500 mg orally, 6 hours later.		
Dental procedures: patients for whom referral to hospital is recommended: a) Patients to be given a general anaesthetic who have been given a penicillin in the previous month. b) Patients to be given a general anaesthetic who have a prosthetic heart valve. c) Patients who have had one or more attacks of endocarditis.		Initially: 1 g amoxicillin IV or IM with 120 mg gentamicin IV or IM immediately prior to anaesthesia (if given) or 15 minutes prior to	50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure	See Note 2. Note 3. Amoxicillin and gentamicin should not be mixed in the same syringe. Note 4. Please consult the appropriate data sheet for full prescribing

Condition		Adult's dosage (including elderly)	Children's dosage (<40kg)	Notes
		dental procedure. Followed by (6 hours later): 500 mg amoxicillin orally.		information on gentamicin.
Genitourinary surgery or instrumentation: prophylaxis for patients who have no urinary tract infection and who are to have genito-urinary surgery or instrumentation under general anaesthesia. In the case of *obstetric and gynaecological procedures* and g*astrointestinal procedures*– routine prophylaxis is recommended only for patients with prosthetic heart valves.		Initially: 1 g amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction. Followed by (6 hours later): 500 mg amoxicillin orally or IV or IM according to clinical condition.		See Notes 2, 3 and 4 above.
Surgery or instrumentation of the upper respiratory tract	Patients other than those with prosthetic heart valves.	1 g amoxicillin IV or IM immediately before induction; 500 mg amoxicillin IV or IM 6 hours later.	50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure	See Note 2 above. Note 5. The second dose of amoxicillin may be administered orally as amoxicillin syrup SF/DF.
	Patients with prosthetic heart valves.	Initially: 1 g amoxicillin IV or IM with 120 mg gentamicin	50 mg amoxicillin/kg body weight given as a single dose one hour	See Notes 2, 3, 4 and 5 above.

Condition		Adult's dosage (including elderly)	Children's dosage (<40kg)	Notes
		IV or IM, immediatel y before induction; followed by (6 hours later) 500 mg amoxicillin IV or IM.	preceding the surgical procedure	

Method of administration:

Amoxicillin Oral Suspension is for oral use.

Absorption of Amoxicillin Oral Suspension 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, other penicillins or to any of the excipients listed in section 6.1. History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another A beta-lactam agent (e.g. ampicillin, cephalosporins carbapenem or monobactam).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with any penicillins careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see section 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on beta-lactam antibiotics. 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. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin (see section 4.8). If

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

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

Erythematous (morbilliform) rashes have been associated with glandular fever in patients receiving amoxicillin.

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 accordingly to the degree of impairment (see section 4.2).

In patients with renal impairment, the rate of excretion of amoxicillin will be reduced depending on the degree of impairment and it may be necessary to reduce the total daily unit amoxicillin dosage accordingly.

Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

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 (AGEP, 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 also 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 sections 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

Paediatric population

Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

Important Information about excipients

This medicinal product contains sucrose. Sucrose is broken down in the digestive system, by substances called enzymes, into glucose and fructose and thus is unsuitable for patients who suffer from fructose intolerance, glucose-galactose malabsorption syndrome (faulty absorption from the digestive tract) or a deficiency in the enzyme which breaks down sucrose.

This medicinal product contains sodium benzoate (E211) which is a mild irritant to the eyes, skin and mucous membrane. May increase the risk of jaundice (yellowing of the skin or the whites of the eyes) in newborn babies.

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.

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

Tetracyclines

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

Oral typhoid vaccine
The oral typhoid vaccine is inactivated by antibacterials

Sulfinpyrazone
Excretion of penicillins is reduced by sulfinpyrazone.

Oral Anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there arecases 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).

Muscle relaxants
Piperacillin (and possibly other penicillins) enhance the effects of non-depolarising muscle relaxants and suxamethonium.

Antibacterials
Absorption of phenoxymethylpenicillin (and possibly other penicillins) reduced by neomycin.

Drug/laboratory test interactions
It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

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 congential malformations. The suitability of amoxicillin for use in human pregnancy has been well documented in clinical studies since 1972., Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding
Amoxicillin is excreted into the 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 teratogenic 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 or 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).

The majority of adverse events listed below are not unique to amoxicillin and may occur when using other penicillins.

Unless otherwise stated, the frequency of adverse events has been derived from more than 30 years of post-marketing reports.

Infections and infestations	
Very rare	Mucocutaneous candidiasis
Blood and lymphatic system disorders:	
Very rare	Reversible leucopenia (including severe neutropenia and agranulocytosis), reversible thrombocytopenia and haemolytic anaemia have been reported. 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). If a hypersensitivity reaction occurs, the treatment must be discontinued (see also skin and subcutaneous tissue disorders).
Not Known	Jarisch-Herxheimer reaction (see section 4.4).
Nervous system disorders	
Very rare	Hyperkinesia, dizziness and convulsions (see section 4.4). Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Post-marketing data	

Not known	Aseptic meningitis
Cardiac disorders	
Not Known	Kounis syndrome (see section4.4)
Gastrointestinal disorders	
Clinical trial data	
*Common	Diarrhoea and nausea
*Uncommon	Vomiting
Post-marketing data	
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis have been reported (see section 4.4). Black hairy tongue Superficial tooth discolouration[#]
Not known	Drug-induced enterocolitis syndrome
Hepatobiliary disorders	
Very rare	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT, but the significance of this is unclear.
Skin and subcutaneous tissue disorders	
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 and acute generalised exanthematous pustulosis (AGEP) (see section 4.4) drug reaction with eosinophilia and systemic symptoms (DRESS), symmetrical drug-related intertriginous and flexural exanthema (SDRIDE) (baboon syndrome) (see also Immune system disorders)
Not Known	Linear IgA disease
Renal and urinary tract disorders	
Very rare	Interstitial nephritis Crystalluria (see section 4.4 and 4.9 Overdose) can occur.
Not known	Crystalluria (including acute renal injury) (see section 4.4 and 4.9 Overdose) can occur.
*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. 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. 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: penicillins with extended spectrum; ATC Code: JO1CA04.

Mechanism of action

Amoxicillin is a semi-synthetic 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, which is acid-resistant and has a similar antibacterial spectrum to ampicillin.

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.

Mechanism 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.

Amoxicillin is better absorbed after oral administration, yielding blood levels approximately twice as high as those obtained with similar doses of ampicillin.

Amoxicillin is used for the same purposes as ampicillin and is especially suitable for the treatment of infections of the urinary and respiratory tracts by ampicillin-sensitive organisms. It is rapidly bactericidal and possesses the safety profile of a penicillin.

Bacteria may be resistant to amoxicillin due to production of beta-lactamases which hydrolyse aminopenicillins, due to alteration in penicillin-binding proteins, due to impermeability to the drug, or due to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to a variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

Breakpoints

MIC breakpoints for amoxicillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 11.0.

Organism	Susceptibility Breakpoints (μg/ml)	
	Susceptible	Resistant
Haemophilus influenzae[1]	≤ 0.001	> 2
Moraxella catarrhalis	Note [2]	Note [2]
Staphylococcus spp.	Note [3, 4, 5]	Note [3, 4, 5]
Enterococcus spp.[6]	≤ 4 [7]	> 8[7]
Streptococcus groups A, B, C, G (indications other than meningitis)	Note [8]	Note [8]
Streptococcus pneumoniae[9]	≤ 0.5	> 1
Enterobacterales [10]	≤ 8	> 8
Gram-negative Anaerobes [11]	≤ 0.5	> 2
Gram-positive Anaerobes [11] (except *Clostridioides difficile*)	≤ 4	> 8

Non-species related breakpoints	≤ 2	> 8
Viridans group streptococci	≤0.5	>2
Pasteurella multocida	≤1	>1
Helicobacter pylori	≤0.125	>0.125
Neisseria meningitidis (indications other than meningitis)	≤0.125	>1

[1] 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.

[2] 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.

[3] 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 isoxazolylpenicillins (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.

[4] 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.

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

[6] Aminopenicillin breakpoints in enterococci are based on intravenous administration. For oral administration the breakpoints are relevant for urinary tract infections only.

[7] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta- lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

[8] 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 isoxazolylpenicillins for streptococcus group B.

[9] 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.

[10] 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.

[11] Susceptibility to ampicillin, amoxicillin, piperacillin and ticarcillin can be inferred from susceptibility to benzylpenicillin.

Susceptibility:
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

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.

Cmax	Tmax *	AUC (0-24h)	T ½
(µg/ml)	(h)	((µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

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

Haemodialysis can be used for elimination of amoxicillin.
Peak plasma amoxicillin concentrations of about 5µg per ml have been observed 1 to 2 hours after a dose of 250mg with detectable amounts present for up to 8 hours. Doubling the dose can produce double the concentrations. The presence of food in the stomach does not appear to diminish absorption significantly.
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).
Amoxicillin gives good penetration into bronchial secretions and high urinary concentrations of unchanged antibiotic.Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. In healthy meninges amoxicillin diffuses badly in liquor cerebrospinalis. Amoxicillin crosses the placenta and a small percentage is excreted into the breast milk.

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 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.

In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inuline clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different from that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

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

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

Saccharin Sodium,

Sodium Benzoate (E211)

Sodium Citrate Anhydrous

Lime Flavour

Microcrystalline Cellulose

Carboxymethylcellulose Sodium

Disodium Edetate

Sorbitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Dry Powder: 2 years

Reconstituted Suspension: 14 days

Reconstituted Suspensions: Do not store above 25°C.

6.4 Special precautions for storage

Do not store above 25°C.

Protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1. White polyethylene bottle with child resistant cap.

2. Clear glass bottle with white polypropylene cap.

Pack sizes: 60 ml and 100 ml

6.6 Special precautions for disposal

Check cap seal is intact before use.
Invert and shake bottle to loosen powder.
Fill the bottle with water to just below the mark on the bottle label. Invert and shake well, then top up with water to the mark. Invert and shake again.
Shake well before taking each dose.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited, 2nd Floor,
Connect 38, 1, Dover Place,
Ashford, Kent,
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8 MARKETING AUTHORISATION NUMBER(S)

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