SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amoxicillin 125mg/5ml Powder for Oral Suspension BP Sugar Free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 125mg Amoxicillin (as trihydrate)

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for Oral Suspension

Pale-yellow free flowing powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin is indicated in the treatment 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
- 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
- Gonorrhoea

Amoxicillin is also indicated for the prophylaxis of endocarditis.

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

It may also be used to treat susceptible organisms in upper respiratory tract infections, lobar and bronchopneumonia, urethritis, bacteriuria in pregnancy,

gynaecological infections including puerperal sepsis and septic abortion, peritonitis, intra-abdominal sepsis, septicaemia, bacterial endocarditis, skin and soft tissue infections and osteomyelitis.

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 (including the elderly)

Standard adult dosage

250mg three times daily, increasing to 500mg three times daily for more severe infections.

High dose therapy

3g twice daily is recommended in appropriate cases for the treatment of severe or recurrent purulent infection of the respiratory tract (max daily dose 6 g).

Short course therapy

Simple acute UTI: two 3g doses with 10-12 hours between the doses.

Gonorrhoea: Single 3g dose.

Adults and children ≥ 40kg

Indication*	**Dose***
Acute bacterial sinusitis	250mg to 500mg every 8 hours or 750mg to 1g every 12 hours For severe infections 750mg to 1g every 8 hours Acute cystitis may be treated with 3g twice daily for one day
Asymptomatic bacteriuria in pregnancy	
Acute pyelonephritis	
Dental abscess with spreading cellulitis	
Acute cystitis	
Acute otitis media	500mg every 8 hours, 750mg to 1g every 12 hours For severe infections 750mg to 1g every 8 hours for 10 days
Acute streptococcal tonsillitis and pharyngitis	
Acute otitis media	500mg every 8 hours, 750mg to 1g every 12 hours For severe infections 750mg to 1g every
Acute streptococcal tonsillitis and pharyngitis	

Acute exacerbations of chronic bronchitis	8 hours for 10 days
Community acquired pneumonia	500mg to 1g every 8 hours
Typhoid and paratyphoid fever	500mg to 2g every 8 hours
Prosthetic joint infections	500mg to 1g every 8 hours
Prophylaxis of endocarditis	2g orally, single dose 30 to 60 minutes before procedure
Helicobacter pylori eradication	750mg to 1g 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: 500mg to 1g 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): 500mg to 2g every 8 hours up to a maximum of 6g/day in divided doses for 10 to 30 days
*Consideration should be given to the official treatment guidelines for each indication	

Children < 40kg

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

Amoxicillin 125mg/5ml Suspension is recommended for children under six months of age.

The daily dosage for children is 40 - 90mg/kg/day in two to three divided doses* (not exceeding 3g/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.

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

Recommended doses:

Indication	**Dose**
Acute bacterial sinusitis	20 to 90mg/kg/day in divided doses* Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations.
Acute otitis media	
Community acquired pneumonia	
Acute cystitis	
Acute pyelonephritis	

Dental abscess with spreading cellulitis	
Acute streptococcal tonsillitis and pharyngitis	40 to 90mg/kg/day in divided doses*
Typhoid and paratyphoid fever	100mg/kg/day in three divided doses
Prophylaxis of endocarditis	50mg/kg orally, single dose 30 to 60 minutes before procedure
Lyme disease (see section 4.4)	Early stage: 25 to 50mg/kg/day in three divided doses for 10 to 21 days Late stage (systemic involvement): 100mg/kg/day in three divided doses for 10 to 30 days
+ 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

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

In patients receiving haemodialysis

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 30ml/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 in children under 40kg:

Creatinine clearance ml/min	Dose	Interval between administration
> 30	Usual dose	No adjustment necessary
10 - 30	Usual dose	12 h (corresponding to 2/3 of the dose)
< 10	Usual dose	24 h (corresponding to 1/3 of the dose)

Amoxicillin may be removed from the circulation by haemodialysis.

	Haemodialysis
Adults and children ≥ 40kg	15mg/kg/day given as a single daily dose. Prior to haemodialysis one additional dose of 15mg/kg should be administered. In order to restore circulating drug levels, another dose of 15mg/kg should be administered after haemodialysis.

In patients receiving peritoneal dialysis

Amoxicillin maximum 500mg/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. 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 (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals (see section 4.3). 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. Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

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 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 (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.

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

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

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 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.

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.

Important information about excipients

The medicine contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 in new born babies.

Use with caution in patients with acute and chronic lymphocytic leukaemia.

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.

Probenecid delays the excretion of Amoxicillin and dietary fibre can reduce the absorption of Amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. The incidence of skin rashes with amoxicillin is increased by concomitant allopurinol.

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).

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Methotrexate

The excretion of methotrexate can be markedly reduced by concurrent use of penicillins. There is considerable risk of methotrexate toxicity.

Very infrequently and unpredictably concurrent use with oral contraceptives may result in contraceptive failure.

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.

When antibiotic therapy is required during pregnancy, amoxicillin may be considered appropriate.

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 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.

There are no modern clinical studies available that can be used to determine the frequency of undesirable effects.

The following terminologies have been used for the classification of undesirable effects:

Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1000 and <1/100)
Rare (≥1/10000 and <1/1000)
Very rare (<1/10000)
Not known (cannot be estimated from the available data)

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

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. (See Section 4.4).
Immune system disorders	
Very Rare	As with other antibiotics, severe allergic reactions, including angioneurotic oedema, anaphylaxis (see section 4.4), serum sickness and hypersensitivity vasculitis. If a hypersensitivity reaction is reported, 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. Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.4).
Gastrointestinal disorders	
Clinical Trial Data	
*Common	Diarrhoea, indigestion, nausea.
*Uncommon	Vomiting
Post-Marketing Data	
Very rare	Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis). Black hairy tongue. 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.
Hepato-biliary disorders	
Very rare	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT. The significance of a rise in AST and/or ALT 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)
Renal & urinary tract disorders	
Very rare	Interstitial nephritis. Crystalluria (see sections 4.4 and 4.9 Overdose)
* 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.

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. Over dosage is unlikely but gross overdosage will result in very high urinary concentrations. Problems occurring as a result of this are unlikely if adequate fluid intake and urinary output are maintained, however, crystalluria is a possibility. More specific measures may be necessary in patients with impaired renal function. 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: J01C

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 bactericidal and is effective against the same range of organisms as ampicillin and has a similar mode of action.

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. Amoxicillin has been reported to be slightly more active than ampicillin against some streptococci and salmonella sp. but less active against shigella sp.

Pharmacokinetic/pharmacodynamic relationship

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

Amoxicillin is more rapidly and completely absorbed from the GI tract than ampicillin and peak plasma levels are 2-2.5 times greater for amoxicillin after oral administration of the same dose. Food does not interfere with absorption. MIC's ranging from 0.01 to 5µg/ml have been reported.

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 $\leq$ 0.5mg/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 2g/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

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 which is different in small children to that of adults. The time to peak plasma concentration (Tmax) is approximately one hour.

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

C_{max}	T_{max} *	AUC $_{(0\text{-}24h)}$	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 250 to 3000mg the bioavailability is linear in proportion to dose (measured as Cmax and AUC). The absorption is not influenced by simultaneous food intake.

Oral bioavailability of Amoxicillin = 93 ±10%
Half-life 1 hour (increased in uremia)

The bioavailability of amoxicillin capsules 250mg and 500mg was compared against that of Amoxil capsules 250mg and 500mg (manufactured by Smithkline Beecham). The results showed that Amoxicillin Capsules 250mg and 500mg were bio equivalent to Amoxil 250mg and 500mg respectively.

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.

Plasma binding 18%

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. Haemodialysis can be used for elimination of amoxicillin.

Urinary excretion of Amoxicillin = 52 ±15%

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 250mg or 500mg 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 - 2ml/min, very similar to the inuline clearance (GFR) in this population. 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

Sodium Benzoate (E211)
Disodium Edetate
Sodium Citrate
Citric acid anhydrous

Colloidal anhydrous silica
Sorbitol (E420)
Saccharin sodium
Banana flavour (containing Gum Arabic, Amyl acetate, Amyl and Ethyl butyrates, Euginol, Acetaldehyde, Citral, Ethyl heptanoate, Amyl valerianate, Allyl heptanoate and Orange oil)
Quinoline Yellow (E104)
Xanthan gum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Dry powder: 3 years

Reconstituted suspension: 7 days

Reconstituted suspension: Do not store above 25ºC

6.4 Special precautions for storage

Dry granules: Do not store above 25ºC. Keep the bottle tightly closed. Store in the original package.

After reconstitution: Store in a refrigerator (2-8ºC). Do not freeze. Keep the bottle tightly closed. Use within 1 week of reconstitution.

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

6.5 Nature and contents of container

150ml high density polyethylene bottle with high density polyethylene cap with induction seal wad (providing tamper-evidence), in pack size of 100ml.

6.6 Special precautions for disposal

To reconstitute the granules, add 84ml of water and shake well until all the powder is dissolved to form a Yellow-coloured suspension.

7 MARKETING AUTHORISATION HOLDER

Special Concept Development (UK) Ltd
Units 1-7 Colonial Way
Watford
Hertfordshire
WD24 4YR

8 MARKETING AUTHORISATION NUMBER(S)

PL 36722/0003

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10 DATE OF REVISION OF THE TEXT

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