1. **NAME OF THE MEDICINAL PRODUCT**

   Amoxicillin 250 mg Capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Each Filled capsule contains Amoxicillin Trihydrate BP/EP equivalent to Amoxicillin 250 mg.

   For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

   Capsules:

   *Amoxicillin 250 mg Capsules*: Red / Buff coloured size ‘2’ capsules containing white to off white powder printed with ‘AMOXY 250’ in black ink.

4. **CLINICAL PARTICULARS**

   **4.1 Therapeutic indications**

   Amoxicillin is indicated for the treatment of the following bacterial infections when caused by amoxicillin-sensitive gram-positive and gram-negative pathogens:

   - Infections of the upper respiratory tract, including infections of the ears, nose and throat: Acute otitis media, acute sinusitis and bacterial pharyngitis.
   - Infections of the kidneys and the genito-urinary tract: Cystitis, pyelonephritis.
   - Infections of the gastrointestinal tract: It may be necessary to use combination therapy when treating infections caused by anaerobic organisms.
   - 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. Amoxicillin may also be used for the treatment of endocarditis as an extension of parenteral therapy.

   Consideration should be given to official, local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents. Susceptibility of the causative organism to the treatment should be tested (if possible), although the therapy may be initiated before the results are available.
4.2 Posology and method of administration

Posology

The dosage depends on the susceptibility of the pathogens and the severity of the disease.

Adults and adolescents (>40kg body weight):

The usual dosage covers a range from 750 mg to 3 g amoxicillin daily in three divided doses. In some areas 1500 mg amoxicillin daily in three divided doses are recommended as the upper usual dose.

Short course treatment:

Uncomplicated urinary tract infections: two 3 g doses with 10-12 hours between the doses are recommended in some areas.

High dosage treatment (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.

Dosage for prevention of endocarditis:

For the prevention of endocarditis, in patients not having general anaesthetic, 3 g amoxicillin are given in the hour preceding the surgical procedure, followed by (6 hours later) a further 3 g dose, if considered necessary.

Children (up to 12 years of age):

For infants and children oral suspensions containing amoxicillin are recommended.

Children weighing < 40 kg

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.

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

Special dosage recommendation
Tonsillitis: 50 mg/kg/day in two 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.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14-21 days.

Prophylaxis for endocarditis: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.

**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). Short course treatments with a single dose of 3 g cannot be given in case of renal failure.

**Renal impairment in adults**

Creatinine clearance > 30 ml / min --- no adjustment necessary.
Creatinine clearance 10 - 30ml / min --- maximum dosage amoxicillin 500mg b.i.d
Creatinine clearance < 10 ml / min: --- maximum dosage amoxicillin 500mg/day

**Renal impairment in children under 40 kg:**

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<th>Interval between administration</th>
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<td>&lt; 10</td>
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</table>

**Duration of therapy:**

In general the therapy should be continued for 2 to 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.

**Method of administration:**

Amoxicillin capsules are administered orally

Amoxicillin capsules should be taken unchewed with liquid (e.g. a glass of water)
The absorption of amoxicillin is not reduced by food intake

4.3 Contraindications

Amoxicillin is contraindicated in patients with:

Hypersensitivity to penicillin; a cross-allergy to other beta-lactams such as cephalosporins should be taken into account.

Viral infections, acute lymphatic leukaemia, or infectious mononucleosis (due to an increased risk of erythematous skin rashes)

4.4 Special warnings and precautions for use:

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins.

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

Patients suffering from severe gastrointestinal disturbances with diarrhoea and vomiting should not be treated with amoxicillin, due to the risk of reduced absorption. In these cases a parenteral treatment with amoxicillin is advisable.

Amoxicillin should be used with caution in patients with an allergic diathesis and asthma.

In patients with renal function impairment, the excretion of amoxicillin will be delayed and reduced, depending on the degree of impairment, it may be necessary to reduce the total daily dosage accordingly (see section 4.2).

The prolonged use of amoxicillin may occasionally result in an overgrowth of non-susceptible organisms or yeasts. Patients should therefore carefully be watched for superinfections. 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 hypersensitivity to beta-lactam antibiotics (see 4.3).

The occurrence of anaphylactic shock and other severe allergic reactions is rare following oral administration of amoxicillin. However, if such reactions occur, appropriate emergency treatment measures must be taken: i.v. administration of epinephrine, followed by antihistaminic drugs, volume substitution and administration of glucocorticoids. Patients should be kept under close observation, and further therapeutic measures (artificial respiration, oxygen) should be administered as required.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. At high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to minimize the possibility of amoxicillin crystalluria.

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

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

In common with other broad spectrum antibiotics, amoxicillin may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

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

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

An increase in the absorption of digoxin may occur on concurrent administration with amoxicillin

The antibacterial action of amoxicillin may be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol

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.

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin may result in increased blood concentrations of amoxicillin and prolonged exposure.

4.6 Pregnancy and lactation

Pregnancy
Animal studies with Amoxicillin have shown no teratogenic effects. The product has been in extensive clinical use since 1972 and its suitability in human pregnancy has been well documented in clinical studies. When antibiotic therapy is required during pregnancy, Amoxicillin may be considered appropriate when the potential benefits outweigh the potential risks associated with treatment.

Lactation
Amoxicillin may be given during lactation. With the exception of the risk of sensitisation associated with the excretion of trace quantities of amoxicillin in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed. Nevertheless, consideration should be given to the potential for amoxicillin to cause dizziness and convulsions (see section 4.8).

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:-

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000)

Most side effects 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 or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.

Prolongation of bleeding time and prothrombin (see Section 4.5 and section 4.4 - Special Warnings and Precautions for Use)

Immune system disorders

Very rare: As with other antibiotics, severe allergic reactions, including angioneurotic oedema, anaphylaxis (see Section 4.4 - Special Warnings and Precautions for Use), serum sickness and hypersensitivity vasculitis.

If a hypersensitivity reaction is reported, the treatment must be discontinued. (See also Skin and subcutaneous tissue disorders).

Nervous system disorders

Very rare: Hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders

Clinical Trial Data

* Common: Diarrhoea and nausea.

* Uncommon: Vomiting.
Post-marketing Data
Very rare: Mucocutaneous candidiasis and antibiotic associated colitis (including pseudomembranous 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.

Hepatobiliary disorders
Very rare: Hepatitis and cholestatic jaundice. A moderate rise in serum activities of liver-derived enzymes such as AST and/or ALT. The significance of a rise in serum activities of 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 also Immune system disorders).

Renal and urinary tract disorders
Very rare: Interstitial nephritis.

Very rare: Crystalluria (see Section 4.9 Overdose)

Other undesirable effects
Prolonged and repeated use of the preparation can result in superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis. *The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.

4.9 Overdose
Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to the water/electrolyte balance. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use). Amoxicillin may be removed from the circulation by haemodialysis.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Penicillins with extended spectrum
ATC Code J01CA04

Mode of action

Amoxicillin is an aminopenicillin that exerts its bactericidal action by inhibition of the synthesis of the bacterial cell wall.

PK/PD relationship

Clinical efficacy of beta-lactams appears to be related to time that drug concentrations in the blood exceed the MIC for a specific micro-organism.

Mechanisms of resistance

Bacteria may be resistant to amoxicillin owing to:

- production of beta-lactamases that hydrolyse aminopenicillins
- alterations in penicillin-binding proteins
- impermeability of the bacteria to the drug
- drug efflux pumps.

One or more of these mechanisms may co-exist in the same organism leading to variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

Breakpoints

The MIC breakpoints for susceptible organisms vary according to species. S (sensitive) and R (resistant).

Enterobacteriaceae are considered susceptible when inhibited at ≤ 8 mg/L amoxicillin.

From CLSI recommendations and using CLSI-specified methods:

*M. catarrhalis* (β-lactamase negative) S ≤ 0.25mg/L; R ≥ 0.5mg/L;

*H. influenzae* (β-lactamase negative) S ≤1mg/L; R ≥4mg/L;

*S. pneumoniae* S≤ 0.5mg/L; R ≥ 2mg/L.

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

**Commonly susceptible species**

Gram-positive aerobes

*Enterococcus faecalis*
**Streptococcus agalactiae**  
**Streptococcus pyogenes**

**Gram-negative aerobes**  
**Neisseria meningitidis**

**Anaerobes**  
**Clostridium perfringens**  
**Peptostreptococci**

**Species for which acquired resistance may be a problem**

**Aerobes**  
**Staphylococcus aureus**  
**Streptococcus pneumoniae**  
**Streptococcus viridans**  
**Escherichia coli**  
**Haemophilus influenzae**  
**Haemophilus parainfluenzae**  
**Klebsiella spp**  
**Moraxella catarrhalis**  
**Neisseria gonorrhoeae**  
**Proteus mirabilis**  
**Proteus spp (indole positive)**  
**Proteus vulgaris**  
**Providencia spp**

**Anaerobes**  
**Bacteroides spp.**  
**Fusobacterium spp**

**Inherently resistant organisms**

**Gram-negative aerobes**  
**Acinetobacter spp**  
**Citrobacter spp**  
**Enterobacter spp**  
**Pseudomonas spp**  
**Serratia spp**

**Others**  
**Chlamydia**  
**Mycoplasma**  
**Rickettsia**

$ In some instances and in some regions almost all strains of certain species are now resistant to aminopenicillins. Therefore it is recommended that amoxicillin should not be used to treat any of the following unless laboratory test results have confirmed susceptibility.

### 5.2 Pharmacokinetic properties

**Absorption:**
The absolute bioavailability of amoxicillin varies between 75 and 90%. Bioavailability (as assessed by pharmacokinetic parameters AUC and/or recovery in urine) is linearly proportional to the dose of amoxicillin between 250 mg and 750 mg. The extent of absorption of amoxicillin decreases at higher doses. Absorption of amoxicillin is not affected by concomitant food intake. Oral administration of a single dose of 500 mg amoxicillin results in plasma concentrations of 6 - 11 mg/l. After administration of a single dose of 3 g amoxicillin, the plasma concentrations reach 27 mg/l. Peak plasma concentrations are present about 1-2 hours after administration.

**Distribution:**

Protein binding for amoxicillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. Amoxicillin can penetrate inflamed meninges and enter the cerebrospinal fluid. Amoxicillin crosses the placenta and a small percentage is excreted into the breast milk.

**Biotransformation and elimination:**

Amoxicillin is mainly excreted via the kidney. About 60-80% of an oral dose of amoxicillin is excreted in the urine in unchanged form within 6 hours of administration. A small percentage is excreted in the bile. About 7 - 25% of the administered dose is metabolised to inactive penicilloic acid. The serum half-life in patients with normal renal function is about 1 – 1.5 hour. The serum half-life of amoxicillin in patients with end-stage renal failure is between 5 to 20 hours. Amoxicillin may be removed from the circulation by haemodialysis.

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 to 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.

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains:

Croscarmellose Sodium, Magnesium stearate.

**Capsule shell components:**

**Cap:**

Brilliant blue E133

Carmoisine E122

Sunset yellow E110
Titanium dioxide E171

**Body:**
Quinoline yellow E104  
Sunset yellow E110  
Titanium dioxide E171

**Shell composition:**
Purified Water  
Methyl Parahydroxybenzoate E218  
Propyl Parahydroxybenzoate E216  
Gelatin (TSE Free)  
Sodium lauryl sulphate

**Printing ink components:**
Absolute alcohol  
Isopropyl alcohol  
Shellac  
Black iron oxide  
Butyl alcohol  
Propylene glycol

6.2 **Incompatibilities**

Not applicable
6.3 Shelf life

For blister packs: 36 months
For HDPE bulk pack: 18 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

21 capsules packed in a blister pack containing PVC with a backing of Aluminium foil.

Pack sizes of 100 and 500 capsules are available in HDPE screw-top containers with an aluminium tagger

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BROWN & BURK UK LIMITED,
5 Marryat Close, Hounslow West,
Middlesex, TW4 5DQ, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 25298/0088

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/03/2008

10. DATE OF REVISION OF THE TEXT

12/10/2012
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amoxicillin 500 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Filled capsule contains Amoxicillin Trihydrate BP/EP equivalent to Amoxicillin 500 mg.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules:

Amoxicillin 500 mg Capsules: Red / Buff Coloured size ‘0’ Capsules containg white to off white powder printed with ‘AMOXY 500 ‘ in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin is indicated for the treatment of the following bacterial infections when caused by amoxicillin-sensitive gram-positive and gram-negative pathogens:

- Infections of the upper respiratory tract, including infections of the ears, nose and throat: Acute otitis media, acute sinusitis and bacterial pharyngitis.
- Infections of the kidneys and the genito-urinary tract: Cystitis, pyelonephritis.
- Infections of the gastrointestinal tract: It may be necessary to use combination therapy when treating infections caused by anaerobic organisms.
- 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. Amoxicillin may also be used for the treatment of endocarditis as an extension of parenteral therapy.

Consideration should be given to official, local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents. Susceptibility of the causative organism to the treatment should be tested (if possible), although the therapy may be initiated before the results are available.

4.2 Posology and method of administration

Posology

The dosage depends on the susceptibility of the pathogens and the severity of the disease.
Adults and adolescents (>40kg body weight):

The usual dosage covers a range from 750 mg to 3 g amoxicillin daily in three divided doses. In some areas 1500 mg amoxicillin daily in three divided doses are recommended as the upper usual dose.

*Short course treatment:*

Uncomplicated urinary tract infections: two 3 g doses with 10-12 hours between the doses are recommended in some areas.

High dosage treatment (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.

Dosage for prevention of endocarditis:

For the prevention of endocarditis, in patients not having general anaesthetic, 3 g amoxicillin are given in the hour preceding the surgical procedure, followed by (6 hours later) a further 3 g dose, if considered necessary.

Children (up to 12 years of age):

For infants and children oral suspensions containing amoxicillin are recommended.

Children weighing < 40 kg

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.

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

Special dosage recommendation

Tonsillitis: 50 mg/kg/day in two 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.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14-21 days.

Prophylaxis for endocarditis: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.

*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). Short course treatments with a single dose of 3 g cannot be given in case of renal failure.

Renal impairment in adults

Creatinine clearance > 30 ml / min --- no adjustment necessary.
Creatinine clearance 10 - 30ml / min --- maximum dosage amoxicillin 500mg b.i.d
Creatinine clearance < 10 ml / min: --- maximum dosage amoxicillin 500mg/day

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Duration of therapy:

In general the therapy should be continued for 2 to 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.

Method of administration:

Amoxicillin capsules are administered orally

Amoxicillin capsules should be taken unchewed with liquid (e.g. a glass of water)

The absorption of amoxicillin is not reduced by food intake

4.3 Contraindications

Amoxicillin is contraindicated in patients with:

Hypersensitivity to penicillin; a cross-allergy to other beta-lactams such as cephalosporins should be taken into account.

Viral infections, acute lymphatic leukaemia, or infectious mononucleosis (due to an increased risk of erythematous skin rashes)
4.4 Special warnings and precautions for use:

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins.

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

Patients suffering from severe gastrointestinal disturbances with diarrhoea and vomiting should not be treated with amoxicillin, due to the risk of reduced absorption. In these cases a parenteral treatment with amoxicillin is advisable.

Amoxicillin should be used with caution in patients with an allergic diathesis and asthma.

In patients with renal function impairment, the excretion of amoxicillin will be delayed and reduced, depending on the degree of impairment, it may be necessary to reduce the total daily dosage accordingly (see section 4.2).

The prolonged use of amoxicillin may occasionally result in an overgrowth of non-susceptible organisms or yeasts. Patients should therefore carefully be watched for superinfections.

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 hypersensitivity to beta-lactam antibiotics (see 4.3).

The occurrence of anaphylactic shock and other severe allergic reactions is rare following oral administration of amoxicillin. However, if such reactions occur, appropriate emergency treatment measures must be taken: i.v. administration of epinephrine, followed by antihistaminic drugs, volume substitution and administration of glucocorticoids. Patients should be kept under close observation, and further therapeutic measures (artificial respiration, oxygen) should be administered as required.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. At high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to minimize the possibility of amoxicillin crystalluria.

Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored. Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the
dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

In common with other broad spectrum antibiotics, amoxicillin may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

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

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

An increase in the absorption of digoxin may occur on concurrent administration with amoxicillin.

The antibacterial action of amoxicillin may be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

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.

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin may result in increased blood concentrations of amoxicillin and prolonged exposure.

4.6 Pregnancy and lactation

Pregnancy
Animal studies with Amoxicillin have shown no teratogenic effects. The product has been in extensive clinical use since 1972 and its suitability in human pregnancy has been well documented in clinical studies. When antibiotic therapy is required during pregnancy, Amoxicillin may be considered appropriate when the potential benefits outweigh the potential risks associated with treatment.

Lactation
Amoxicillin may be given during lactation. With the exception of the risk of sensitisation associated with the excretion of trace quantities of amoxicillin in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed. Nevertheless, consideration should be given to the potential for amoxicillin to cause dizziness and convulsions (see section 4.8).

4.8 Undesirable effects
The following convention has been utilised for the classification of undesirable effects:-
Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare
(>1/10,000, <1/1000), very rare (<1/10,000)

Most side effects listed below are not unique to amoxicillin and may occur when using
other pencillins.

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 or agranulocytosis),
reversible thrombocytopenia and haemolytic anaemia.

Prolongation of bleeding time and prothrombin (see Section 4.5 and section 4.4 -
Special Warnings and Precautions for Use)

Immune system disorders

**Very rare:** As with other antibiotics, severe allergic reactions, including angioneurotic
oedema, anaphylaxis (see Section 4.4 - Special Warnings and Precautions for Use),
serum sickness and hypersensitivity vasculitis.

If a hypersensitivity reaction is reported, the treatment must be discontinued. (See also
Skin and subcutaneous tissue disorders).

Nervous system disorders

**Very rare:** Hyperkinesia, dizziness and convulsions. Convulsions may occur in patients
with impaired renal function or in those receiving high doses.

Gastrointestinal disorders

Clinical Trial Data

* **Common:** Diarrhoea and nausea.
* **Uncommon:** Vomiting.

Post-marketing Data

**Very rare:** Mucocutaneous candidiasis and antibiotic associated colitis (including
pseudomembranous 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.
Hepatobiliary disorders
Very rare: Hepatitis and cholestatic jaundice. A moderate rise in serum activities of liver-derived enzymes such as AST and/or ALT. The significance of a rise in serum activities of 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 also Immune system disorders).

Renal and urinary tract disorders
Very rare: Interstitial nephritis.
Very rare: Crystalluria (see Section 4.9 Overdose)

Other undesirable effects
Prolonged and repeated use of the preparation can result in superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis.
*The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.

4.9 Overdose
Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to the water/electrolyte balance. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use). Amoxicillin may be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Penicillins with extended spectrum
ATC Code J01CA04

Mode of action
Amoxicillin is an aminopenicillin that exerts its bactericidal action by inhibition of the synthesis of the bacterial cell wall.
PK/PD relationship

Clinical efficacy of beta-lactams appears to be related to time that drug concentrations in the blood exceed the MIC for a specific micro-organism.

Mechanisms of resistance

Bacteria may be resistant to amoxicillin owing to:

- production of beta-lactamases that hydrolyse aminopenicillins
- alterations in penicillin-binding proteins
- impermeability of the bacteria to the drug
- drug efflux pumps.

One or more of these mechanisms may co-exist in the same organism leading to variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

Breakpoints

The MIC breakpoints for susceptible organisms vary according to species. S (sensitive) and R (resistant).

Enterobacteriaceae are considered susceptible when inhibited at ≤ 8 mg/L amoxicillin.

From CLSI recommendations and using CLSI-specified methods:

- *M. catarrhalis* (β-lactamase negative) S ≤ 0.25mg/L; R ≥ 0.5mg/L;
- *H. influenzae* (β-lactamase negative) S ≤1mg/L; R ≥4mg/L;
- *S. pneumoniae* S≤ 0.5mg/L; R ≥2mg/L.

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Gram-positive aerobes

- *Enterococcus faecalis*
- *Streptococcus agalactiae*
- *Streptococcus pyogenes*

Gram-negative aerobes

- *Neisseria meningitidis*

Anaerobes

- *Clostridium perfringens*
- Peptostreptococci
Species for which acquired resistance may be a problem

Aerobes
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus viridans*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella spp*
- *Moraxella catarrhalis*
- *Neisseria gonorrhoeae*
- *Proteus mirabilis*
- *Proteus spp* (indole positive)
- *Proteus vulgaris*
- *Providencia spp*

Anaerobes
- *Bacteroides spp.*
- *Fusobacterium spp*

Inherently resistant organisms

Gram-negative aerobes
- *Acinetobacter spp*
- *Citrobacter spp*
- *Enterobacter spp*
- *Pseudomonas spp*
- *Serratia spp*

Others
- *Chlamydia*
- *Mycoplasma*
- *Rickettsia*

$ In some instances and in some regions almost all strains of certain species are now resistant to aminopenicillins. Therefore it is recommended that amoxicillin should not be used to treat any of the following unless laboratory test results have confirmed susceptibility.

5.2 Pharmacokinetic properties

Absorption:

The absolute bioavailability of amoxicillin varies between 75 and 90%. Bioavailability (as assessed by pharmacokinetic parameters AUC and/or recovery in urine) is linearly proportional to the dose of amoxicillin between 250 mg and 750 mg. The extent of absorption of amoxicillin decreases at higher doses. Absorption of amoxicillin is not affected by concomitant food intake. Oral administration of a single dose of 500 mg amoxicillin results in plasma concentrations of 6 - 11 mg/l. After administration of a single dose of 3 g amoxicillin, the plasma concentrations reach 27 mg/l. Peak plasma concentrations are present about 1-2 hours after administration.

Distribution:
Protein binding for amoxicillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. Amoxicillin can penetrate inflamed meninges and enter the cerebrospinal fluid. Amoxicillin crosses the placenta and a small percentage is excreted into the breast milk.

Biotransformation and elimination:

Amoxicillin is mainly excreted via the kidney. About 60-80% of an oral dose of amoxicillin is excreted in the urine in unchanged form within 6 hours of administration. A small percentage is excreted in the bile. About 7 - 25% of the administered dose is metabolised to inactive penicilloic acid. The serum half-life in patients with normal renal function is about 1 – 1.5 hour. The serum half-life of amoxicillin in patients with end-stage renal failure is between 5 to 20 hours. Amoxicillin may be removed from the circulation by haemodialysis.

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 to 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.

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains:

Croscarmellose Sodium, Magnesium stearate.

Capsule shell components:

Cap:
 Brilliant blue E133
 Carmoisine E122
 Sunset yellow E110
 Titanium dioxide E171

Body:
 Quinoline yellow E104
 Sunset yellow E110
 Titanium dioxide E171
Shell composition:
Purified Water
Methyl Parahydroxybenzoate  E218
Propyl Parahydroxybenzoate  E216
Gelatin (TSE Free)
Sodium lauryl sulphate

Printing ink components:
Absolute alcohol
Isopropyl alcohol
Shellac
Black iron oxide
Butyl alcohol
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
For blister packs : 36 months
For HDPE bulk pack : 18 months

6.4 Special precautions for storage
Store below 30°C

6.5 Nature and contents of container
21 capsules packed in a blister pack containing PVC with a backing of Aluminium foil.
Pack sizes of 100 and 500 capsules are available in HDPE screw-top containers with an aluminium tagger

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

BROWN & BURK UK LIMITED,
5 Marryat Close, Hounslow West,
Middlesex, TW4 5DQ, United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

PL 25298/0089

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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