Public Assessment Report

Decentralised Procedure

Amoxicillin 250mg Capsules
Amoxicillin 500mg Capsules

UK/H/0979/001-2/DC
UK licence no: PL 20117/0030-1

Morningside Healthcare Ltd
LAY SUMMARY

On 11 March 2008, the MHRA granted Morningside Healthcare Ltd Marketing Authorisations (licences) for the medicinal products Amoxicillin 250mg Capsules (PL 20117/0030) and Amoxicillin 500mg Capsules (PL 20117/0031). These are prescription only medicines (POM) for the treatment and prevention of a wide range of infections.

The active ingredient, amoxicillin (as the trihydrate), is an antibacterial drug. It works by killing the bacteria that cause several types of infections.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amoxicillin 250mg and 500mg Capsules outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

Information About Initial Procedure

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<th>Amoxicillin 250mg and 500mg Capsules</th>
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<td>Type of Application</td>
<td>Article 10.1, Generic Application</td>
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<td>Active Substance</td>
<td>Amoxicillin trihydrate</td>
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<td>Form</td>
<td>Capsules</td>
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<td>Strength</td>
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<td>MA Holder</td>
<td>Morningside Healthcare Ltd</td>
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<td></td>
<td>115 Narborough Road</td>
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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

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.

**Dosage in impaired renal function**

The dose should be reduced in patients with severe renal function impairment. In patients with a renal clearance of less than 30 ml/min an increase in the dosage interval or a reduction in the subsequent doses is recommended (see section 4.4). 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:

Creatinine clearance>30ml / min: No adjustment necessary.
Creatinine clearance 10-30ml / min: 15 mg amoxicillin /kg body weight given b.i.d
Creatinine clearance <10ml / min: 15 mg amoxicillin /kg body weight given as a single daily dose

*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**
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, depending on the degree of impairment, it may be necessary to reduce the total daily dosage (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.

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.

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.

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.

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)

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
Common: Diarrhoea and nausea.
Uncommon: Vomiting.
Very rare: Mucocutaneous candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis).
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
Common: Skin rash
Uncommon: Urticaria and pruritus
Very rare: Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP)

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.

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.

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 : 24 months
For HDPE bulk pack : 24 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
Morningside Healthcare Ltd
115 Narborough Road,
Leicester, LE3 0PA
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/03/2008

10 DATE OF REVISION OF THE TEXT
11/03/2008
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 containing 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.

Dosage in impaired renal function

The dose should be reduced in patients with severe renal function impairment. In patients with a renal clearance of less than 30 ml/min an increase in the dosage interval or a reduction in the subsequent doses is recommended (see section 4.4). 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:

Creatinine clearance>30ml / min: No adjustment necessary.
Creatinine clearance 10-30ml / min: 15 mg amoxicillin /kg body weight given b.i.d
Creatinine clearance <10ml / min: 15 mg amoxicillin /kg body weight given as a single daily dose

*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
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, depending on the degree of impairment, it may be necessary to reduce the total daily dosage (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.

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.

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.

### 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 (>1/10000, <1/1000), very rare (<1/10000)

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.

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)

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
Common: Diarrhoea and nausea.
Uncommon: Vomiting.
Very rare: Mucocutaneous candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis).
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
Common: Skin rash
Uncommon: Urticaria and pruritus
Very rare: Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP)
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.

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 \( \leq 8 \text{ mg/L} \) amoxicillin.

From CLSI recommendations and using CLSI-specified methods:

- *M. catarrhalis* (β-lactamase negative) \( S \leq 0.25 \text{mg/L}; R \geq 0.5 \text{mg/L}; \)
- *H. influenzae* (β-lactamase negative) \( S \leq 1 \text{mg/L}; R \geq 4 \text{mg/L}; \)
- *S. pneumoniae* \( S \leq 0.5 \text{mg/L}; R \geq 2 \text{mg/L}; \)
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.

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: 24 months
For HDPE bulk pack: 24 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
Morningside Healthcare Ltd
115 Narborough Road,
Leicester, LE3 0PA
United Kingdom
8  MARKETING AUTHORIZATION NUMBER(S)
   PL 20117/0031

9  DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
   11/03/2008

10 DATE OF REVISION OF THE TEXT
    11/03/2008
Module 3
Patient Information Leaflet

Amoxicillin 250mg & 500 mg Capsules
(Amoxicillin)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. They may harm themselves, even if their symptoms are the same as yours.
- If you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

In this leaflet:
1. What Amoxicillin capsules are and what this is used for
2. Before you take Amoxicillin capsules
3. How to take Amoxicillin capsules
4. Possible side effects
5. How to store Amoxicillin capsules
6. Further information

1. WHAT AMOXCILLIN CAPSULES ARE AND WHAT THIS IS USED FOR

Amoxicillin is an antibiotic (bacteriostatic medicine) for treating infections. It belongs to a group of antibiotics called "Penicillins". Amoxicillin works by killing the bacteria that cause infections. Amoxicillin can also be used to prevent infections.

Your doctor has prescribed Amoxicillin capsules because it can treat a wide range of infections including those of the:
- Ear, Nose and Throat
- Skin (including acne)
- Urethritis (urethritis)
- Bladder or Urinary (the tube which carries urine from the bladder)
- Bladder, Kidneys or Genital Tract Infections
- Heart (Endocarditis)

2. BEFORE YOU TAKE AMOXCILLIN CAPSULES

Do not take Amoxicillin if:
- you are allergic to penicillin or similar types of antibiotics such as cephalosporins. If you have had an allergic reaction (such as a rash) when taking an antibiotic, you should tell your doctor before you take Amoxicillin.
- you have ever had an allergic reaction to amoxicillin or any of the ingredients listed toward the end of this leaflet (see "ingredients")
- you have a viral infection, cancer of the white blood cells (leukemias and lymphomas), or glandular fever.
- the expiry date (EDP) printed on the pack has passed.

Take Special Care with Amoxicillin Capsules
Let your doctor know any of the following apply to you:
- If you are pregnant or breast-feeding.
- If you have been treated for kidney problems.
- If you are pregnant or breast-feeding.
- If you are taking blood thinners.

If any of the above apply to you, your doctor may decide that you need a different dose of amoxicillin or a different medicine instead of amoxicillin. If you have not told your doctor about any of these things, tell them before you take Amoxicillin.

Taking other medicines
Amoxicillin capsules may occasionally interact with other medicines, so it is important that you tell your doctor about all the medicines you are taking, including those obtained without a doctor's prescription. In particular, tell your doctor if you are taking any of the following:
- Morphine, codeine, or similar medicines
- Medicines used to prevent blood clots (anticoagulants) e.g. warfarin
- Any other medicines

If any of these apply to you, you should talk to your doctor before taking Amoxicillin capsules.

Taking Amoxicillin capsules with food and drink
Amoxicillin capsules may have no known interactions with any food or drink. Alcohol may be taken after Amoxicillin, so use it with moderation.

Pregnancy and breast-feeding
Ask your doctor or pharmacist before taking Amoxicillin capsules.

Driving and using machines
Amoxicillin capsules have not been shown to have any effect on ability to drive and use machines. Nevertheless, consideration should be given to the potential for amoxicillin to cause dizziness and confusion.

3. HOW TO TAKE AMOXCILLIN CAPSULES

Follow your doctor's instructions about how and when to take Amoxicillin. Your doctor will advise on dosage strength, number of capsules to be taken each day, and for how long you will need to take Amoxicillin.

Always take Amoxicillin capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Do not stop taking the medicine just because you feel well before the infection is cured.

Amoxicillin capsules should be swallowed whole with water.

Adults
For most infections you have to take one 250mg capsule three times a day. This can be increased to 500mg amoxicillin three times a day if the infection is severe.

For severe or frequent chest infections your doctor may recommend taking 3g amoxicillin twice a day.

Infections of the bladder or urethra (urine infections) can be treated with 2 or 3 doses taken with 10-12 hours between doses.

People who have had heart problems may need an antibiotic when they go to a dentist or if they have to go into hospital for surgery to prevent them from getting a heart infection (endocarditis). Patients who are not having general anaesthetic, 3g amoxicillin are given in the hour preceding the surgical procedure, followed by 250mg every 6 hours if necessary.
Doses may be lower than those listed above in patients with kidney problems.

**Children (under 12 years)**
For infants and children oral suspensions containing amoxicillin are recommended.

If you take more Amoxicillin Capsules than you should
Never take more than the recommended dose each day. If you or someone else swallows more of these capsules all together, contact your doctor, pharmacist or hospital emergency department immediately. Always take any capsule left over with you and ask the doctor, as this will allow easier identification of the capsules.

If you forget to take Amoxicillin Capsules
If you miss a dose, just carry on with the next one as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking Amoxicillin capsules
If you stop taking Amoxicillin capsules without medical advice then discuss what to do with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Amoxicillin capsules can cause side effects, although not everybody gets them.

The more common side effects of Amoxicillin that have been reported in more than 1 in 10 people taking it include:
- **Nausea** (feeling of sickness) or diarrhoea
- **Skin rash**

**Uncommon side effects that have been reported in between 1 in 100 and 1 in 1,000 people taking amoxicillin include:**
- **Vomiting**
- Allergic skin reactions with itching. If you start to itch or get a rash, STOP taking Amoxicillin and tell your doctor at once.

**Very rare side effects that have been reported in less than 1 in 10,000 people taking Amoxicillin includes:**
- Hypersensitivity or severe allergic reaction including swollen face or breathing problems. Tell your doctor straight away if you notice any of these symptoms and STOP taking Amoxicillin.
- **Thrush (a yeast infection of the vagina, mouth or skin folds). You can get treatment for thrush from your doctor or pharmacist**
- **Tooth discoloration. The colour usually returns to normal with brushing**

Tell your doctor that you are taking Amoxicillin
- Excessive body movements (hypermobility), dizziness or convulsions. People who are on high doses of Amoxicillin or whose kidneys do not work properly may experience convulsions.
- A reversible reduction in the number of cells circulating in the blood. This may cause anaemia (a reduction in the number of circulating red blood cells that result in feeling weak or light-headed) or a longer time taken for blood to clot and wounds or cuts to stop bleeding.
- **Crystals, forming of crystals in the urine.**

See your doctor straight away if you experience any of the following very rare side effects:
- **Severe diarrhoea with bleeding**
- **Notice your urine becoming darker or your faeces (body waste) becoming paler**
- **Notice your skin or the white of your eyes turning yellow (jaundice)**
- **Clostridium**
- **Difficulty or discomfort in passing urine or passing urine that is cloudy.**

Many of the side effects go away as your body gets used to them, but if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. HOW TO STORE AMOXICILLIN CAPSULES**

Store below 30°C, keep all medicines well out of the reach and sight of children. It's best to keep them in a cupboard or medicine cabinet.

If your doctor tells you to stop taking this medicine, or if for any other reason you have some capsules left over, please return them to the pharmacist.

Remember, this medicine is just for you. Do not give it to anyone else. It may not be suitable for them, even if their symptoms seem to be the same as yours.

**6. FURTHER INFORMATION**

What Amoxicillin Capsules contain
The active substance is Amoxicillin Trihydrate. The other ingredients are: Lactose, Magnesium stearate, Sunset yellow F110, Carmine E122, Brilliant blue E133, Quinoline Yellow E 104, Titanium dioxide E171, Methylparaben and Propylparaben.

What Amoxicillin Capsules looks like and content of the pack
Red/buff coloured capsules printed with "AMOX 250" in black ink.
Red/buff coloured capsules printed with "AMOX 500" in black ink.
Amoxicillin 250mg and 500mg are supplied in pack sizes of 21, 100 & 500. Not all packs sizes may be marketed.

Marketing Authorisation Holder
Morningside Healthcare Ltd
115 Norborough Road,
Leicester, LE3 2PA
United Kingdom

Batches are released by batch release number:
Morningside Pharmaceuticals Ltd
DPavilion Way, Castle Business Park,
Leightonbuzzard,
Luton, LU1 5GW
United Kingdom
Module 4
Labelling
Each capsule contains amoxicillin 250mg (as trihydrate), Brilliant Blue E133, Carmoisine E122.

For oral administration.

See leaflet for further information.

Store below 30°C. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

PL21/12030

Product Licence Holder:
Morningside HealthCare Ltd, 115 Harborough Road
Leicester, LE2 5BA, United Kingdom

Code: KRN0400/MA/20/03/2003

Exp: MM/YYY
Batch: AJTDEXXX
Module 5

Scientific Discussion During Initial Procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Amoxicillin 250mg Capsules (PL 20117/0030) and Amoxicillin 500mg Capsules (PL 20117/0031) on 11 March 2008. The products are prescription only medicines.

These applications were submitted as generic applications under Article 10.1 of 2001/83 EC, as amended, referring to Amoxil Capsules 250mg and 500mg (Beecham Group plc, trading as GlaxoSmithKline UK, Bencard or SmithKline Beecham Pharmaceuticals), which were granted licences in the UK in April 1972.

The products contain the active ingredient amoxicillin (as the trihydrate) and are 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 lower respiratory tract (acute exacerbation of chronic bronchitis, community-acquired pneumonia); infections of the kidneys and the genitor-urinary tract (cystitis, pyelonephritis); infections of the gastrointestinal tract (it may be necessary to use combination therapy when treating infections caused by anaerobic organisms) and 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).

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

No new preclinical studies were conducted, which is acceptable given that the applications referred to products that have been licensed for over 10 years.

A single bioequivalence study was submitted by the applicant. The study was conducted under Good Clinical Practice (GCP) guidelines.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 195 (30 July 2007), with the RMS and the CMS agreeing that the licence was approvable. The national phase of the decentralised procedure was completed in the UK on 11 March 2008.
## ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Amoxicillin 250mg and 500mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Amoxicillin trihydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Penicillins with extended spectrum (J01CA04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Capsules; 250mg and 500mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/0979/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20117/0030&lt;br&gt;PL 20117/0031</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Morningside Healthcare Ltd&lt;br&gt;115 Narborough Road&lt;br&gt;Leicester&lt;br&gt;LE3 0PA&lt;br&gt;United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

All aspects of the manufacture and control of amoxicillin trihydrate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of amoxicillin trihydrate for inclusion in these medicinal products.

Appropriate stability data have been provided to support a retest period of 5 years when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

The excipients present are croscarmellose sodium and magnesium stearate. Brilliant blue (E133), carmoisine (E122), sunset yellow (E110), titanium dioxide (E171), quinoline yellow (E104), purified water, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), gelatin and sodium lauryl sulphate are present in the capsule shell. Absolute alcohol, isopropyl alcohol, shellac, black iron oxide, butyl alcohol and propylene glycol are present in the printing ink.

The excipients and contents of the printing ink used in the manufacture of the capsules are routinely tested for compliance with current relevant international standards. The contents of the capsule shell comply with suitable in house specifications. Satisfactory certificates of analysis have been provided.

None of the excipients used contain material of animal or human origin.

Pharmaceutical Development

The applicant has provided suitable product development rationale and data.

Dissolution profiles

Dissolution profiles for the drug products were found to be similar to the reference products.

Impurity profiles

The impurity profiles for batches of the drug product and reference product were comparable.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the products along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the products.

The manufacturing process has been validated and the results are satisfactory.
Control of Drug Product
The proposed finished product specifications are acceptable and provide assurance of the quality of the finished products. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specifications.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the Drug Product
The stability data provided support a shelf-life of 24 months, storage conditions “Store below 30°C.”

Bioequivalence/Bioavailability
Refer to III.3 Clinical Aspects.

SPC, PIL, Labels
The SPC and labels are pharmaceutically acceptable.

The Patient Information Leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION
It is recommended that Marketing Authorisations are granted for these applications.

III.2 NON-CLINICAL ASPECTS
No new non-clinical data are required and the applicant has not provided any.

III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacokinetics
Amoxicillin is a well known substance. It is well absorbed by the oral and parenteral routes. Oral availability is about 77% and there is no first pass metabolism. Amoxicillin is rapidly and widely distributed in most body fluids with the exception of the eye and the prostate gland.

Amoxicillin is primarily excreted unchanged in the urine, but there is limited metabolism into Penicillic acid which is also excreted in the urine. Its half-life is approximately 1
hour. Probenecid inhibits its renal secretion and doses must also be adjusted in renal insufficiency.

**Bioequivalence**

A randomized, open label, two treatment, two period, two sequence crossover comparative study was used to compare the bioavailability of a single oral dose of Amoxicillin 500mg Capsules with Amoxil 500mg Capsules (GlaxoSmithKline, UK) in healthy, adult male, human subjects under fasting conditions.

Blood samples for drug plasma concentrations were drawn at 1 hour pre-dosing and at subsequent intervals until 12 hours post administration. Plasma drug concentrations were calculated using an LC-MS method. The analysis of the variance and calculation of 90%CI were done according to current guidelines. The pre-specified values to declare bioequivalence were also in accordance with the guidelines.

**Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amoxicillin 500mg</th>
<th>Amoxil 500mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference product</td>
<td>Test product</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>6.56±1.80</td>
<td>6.83±3.04</td>
</tr>
<tr>
<td>AUC (0-t) (µg.hr/ml)</td>
<td>19.90±6.49</td>
<td>18.60±5.57</td>
</tr>
<tr>
<td>AUC (0-∞) (µg.hr/ml)</td>
<td>20.24±6.52</td>
<td>18.94±5.58</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.97±0.68</td>
<td>1.79±0.58</td>
</tr>
<tr>
<td>t1/2</td>
<td>1.30±0.26</td>
<td>1.28±0.18</td>
</tr>
<tr>
<td>Kel (1/hr)</td>
<td>0.55±0.09</td>
<td>0.55±0.08</td>
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</table>

Summary of 90% confidence intervals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amoxicillin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>85.66-111.60</td>
</tr>
<tr>
<td>AUC (0-t) (µg.hr/ml)</td>
<td>80.51-102.83</td>
</tr>
<tr>
<td>AUC (0-∞) (µg.hr/ml)</td>
<td>81.04-102.74</td>
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</tbody>
</table>

The results indicate that the products are bioequivalent. The absence of a study using the 250mg product is acceptable, given that both the strengths are manufactured by the same manufacturer, the formulations are directly proportional and they have similar dissolution profiles.

**Pharmacodynamics**

Amoxicillin is a beta-lactam antibiotic with similar action to ampicillin. It acts through the inhibition of the biosynthesis of the cell wall mucopeptide.

**Efficacy**

No new efficacy data have been provided and none are required for applications of this type. The efficacy claims within the SPC are consistent with the innovator product.

**Safety**

No new safety data have been provided and none are required for applications of this type. The safety claims within the SPC are appropriate and consistent with the innovator product.
EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are satisfactory and consistent with the SPCs for the reference products.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
There are no clinical objections to the grant of Marketing Authorisations for these applications.

No new or unexpected safety concerns arose from these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amoxicillin 250mg and 500mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Amoxicillin 500mg Capsules and Amoxil 500mg Capsules (GlaxoSmithKline, UK). Given that linear kinetics apply between the 250mg and 500mg Capsules, that proportional formulae for the tablets have been used, the method of manufacture is the same and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 250mg Capsule is not considered necessary.

No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Clinical experience with amoxicillin trihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

Steps Taken After Initial Procedure - Summary

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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