Public Assessment Report

UKPAR

Amoxicillin 250mg and 500mg Capsules

(Amoxicillin trihydrate)

UK Licence No: PL 36722/0107-0108

Special Concept Development (UK) Limited t/a Rx farma
LAY SUMMARY
Amoxicillin 250mg and 500mg Capsules
(Amoxicillin trihydrate)

This is a summary of the Public Assessment Report (PAR) for Amoxicillin 250mg and 500mg Capsules (PL 36722/0107-0108). It explains how Amoxicillin 250mg and 500mg Capsules were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Amoxicillin Capsules in this lay summary for ease of reading.

For practical information about using Amoxicillin Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Amoxicillin Capsules and what are they used for?
This medicine is the same as Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020; Special Concept Development (UK) Limited), which are already authorised in the UK. The licence holder (Special Concept Development (UK) Limited) for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020) has agreed that its own scientific data can be used as a basis for the grant of identical licenses for Amoxicillin Capsules (PL 36722/0107-0108) (informed consent).

Amoxicillin capsules can treat a wide range of infections including those of the chest (bronchitis or pneumonia), tonsils (tonsillitis), ears (otitis media), the bladder or the urethra (the tube which carries urine from the bladder), kidneys, the female reproductive system including infections caused by difficulties during childbirth (puerperal sepsis and septic abortion), abdomen (intra-abdominal sepsis and peritonitis), heart (endocarditis), blood (septicaemia), skin, teeth and gum (abscesses).

They are also used to treat gonorrhoea (a sexually transmitted infection), infections associated with pregnancy & typhoid and paratyphoid fevers (caused by a group of bacteria called salmonella), inflammation of the bone and bone marrow (osteomyelitis) and inflammation of the membranes that cover the brain and spinal cord (meningitis).

How do Amoxicillin Capsules work?
This medicine contains the active ingredient amoxicillin (as amoxicillin trihydrate), which is an antibiotic that belongs to a group of medicines called penicillins. Amoxicillin works by killing the bacteria that cause the infection.

How are Amoxicillin Capsules used?
Amoxicillin Capsules are taken by mouth. The whole tablet should be swallowed with water, with or after food unless the label advises a specific time. Patients should drink several glasses of water each day of their treatment, unless told otherwise by a doctor.

Adults (including elderly patients):
The usual adult dosage for most infections is 250mg (one capsule every eight hours). This may be doubled in more severe infections.

Other dosages which may be given are:
For severe or recurrent respiratory tract infections - 3g twice daily.

For urinary tract infections – Two 3g doses with 10-12 hours between doses.

Gonorrhoea (a sexually transmitted infection) - A single 3g dose (combined with 1g of Probenecid)
Prevention of endocarditis– inflammation of the heart lining, heart muscles and heart valves (during dental procedures) – 3g orally given one hour before treatment followed by second dose six hours later, if necessary.

In patients with kidney problems lower dosage may be given than those listed above.

**Children:**

Children weighing less than 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.

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.

**Other dosages which may be given are:**

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.

Impaired renal function: The dose should be reduced. 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.

**Children (up to 10 years of age):**

Prevention of endocarditis – inflammation of the heart lining, heart muscles and heart valves (during dental procedures) – Same precautions apply as for adult dose.

- Children (5-10 years) – Half the adult dose
- Children (under 5 years) – Quarter the adult dose

**Children (under 10 years of age):**

For children under 10, it is recommended that the alternative liquid preparation is used.

This medicine can only be obtained with a prescription.

Please read Section 3 of the patient information leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

**How have Amoxicillin Capsules been studied?**

The applications for Amoxicillin Capsules (PL 36722/0107-0108) are considered to be identical to the previously authorised licenses for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020, with the same benefits and risks. So, no new studies have been provided for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0107-0108). However, reference is made to the studies for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020).

**What are the possible side effects of Amoxicillin Capsules?**

Like all medicines, Amoxicillin Capsules can cause side effects, although not everybody gets them.
For the full list of all side effects reported with Amoxicillin Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why are Amoxicillin Capsules approved?**
No new or unexpected safety concerns arose from these applications. The MHRA, therefore, considered that the benefits of Amoxicillin Capsules outweigh their risks; and the grant of Marketing Authorisations was recommended.

**What measures are being taken to ensure the safe and effective use of Amoxicillin Capsules?**
A risk management plan (RMP) has been developed to ensure that Amoxicillin Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the patient information leaflet for Amoxicillin Capsules including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Amoxicillin Capsules**
Marketing Authorisations were granted in the UK on 18 May 2017.

The full PAR for Amoxicillin Capsules follows this summary.

This summary was last updated in June 2017.
SCIENTIFIC DISCUSSION

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Special Concept Development (UK) Limited t/a Rx farma, Marketing Authorisations for the medicinal products Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0107-0108) on 18 May 2017. These products are prescription-only medicines (POM).

Amoxicillin is a broad spectrum antibiotic indicated for the treatment of commonly-occurring bacterial infections such as:

- Upper respiratory tract infections
- Otitis media
- Acute and chronic bronchitis
- Chronic bronchial sepsis
- Lobar and bronchopneumonia
- Cystitis, urethritis, pyelonephritis
- Bacteriuria in pregnancy
- Gynaecological infections including puerperal sepsis and septic abortion
- Gonorrhoea
- Peritonitis
- Intra abdominal sepsis
- Septicaemia
- Bacterial endocarditis
- Typhoid and paratyphoid fever
- Skin and soft tissue infections
- Osteomyelitis
- Dental abscess (as an adjunct to surgical management)
- Invasive Salmonellosis
- Meningitis

Prophylaxis of endocarditis: Amoxicillin may be used for the prevention of bacteraemia, associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.

In some of these infections initiation of treatment or indeed the whole course of treatment may need to be by the parenteral route.

In children with urinary tract infection, the need for further clinical investigation should be considered.

Amoxicillin is also indicated for the prophylaxis of endocarditis.

These applications were made under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Amoxicillin 250 mg and 500 mg Capsules. These reference licenses underwent a series of change of ownerships and were originally authorised to Eastern Pharmaceuticals Limited (PL 11382/0001-0002) on 30 July 1991 and then to LPC Medical (UK) Ltd (PL 19348/0065-6) on 07 February 2005, to Fourrts (UK) Pharmacare Limited (PL 39484/0005-6) on 13 June 2011, to Globegen Laboratories Limited (PL 41318/0006-0007) on 14 November 2012 and finally to the current Marketing Authorisation Holder (MAH), Special Concept Development (UK) Limited (PL 36722/0019-0020), on 01 May 2014.

No new data were submitted nor were necessary to be submitted for these applications, as the data are identical to those of the previously authorised cross-reference products.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in
place for these product types at all sites responsible for the manufacture and assembly of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0107-0108) outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 INTRODUCTION

These are informed consent applications for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0107-0108) submitted under Article 10c of Directive 2001/83/EC, as amended.

The applicant has cross-referred to Amoxicillin 250 mg and 500 mg Capsules. These reference licenses underwent a series of change of ownerships and were originally authorised to Eastern Pharmaceuticals Limited (PL 11382/0001-0002) on 30 July 1991 and then to LPC Medical (UK) Ltd (PL 19348/0065-6) on 07 February 2005, to Fourrts (UK) Pharmacare Limited (PL 39484/0005-6) on 13 June 2011, to Globegen Laboratories Limited (PL 41318/0006-0007) on 14 November 2012 and finally to the current Marketing Authorisation Holder (MAH), Special Concept Development (UK) Limited (PL 36722/0019-0020), on 01 May 2014. The applications are considered valid.

MARKETING AUTHORISATION APPLICATION FORM

Name(s)
The proposed names of the products are Amoxicillin 250mg and 500mg Capsules. The products have been named in-line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes
Each capsule contains amoxicillin trihydrate equivalent to 250mg or 500mg amoxicillin. The route of administration is oral.

The products are packaged either in a polypropylene tubular container with an open end equipped to accept a polyethylene closure, with a tamper-evident tear strip in pack sizes of 4, 100, 500 and 1000 capsules, in blister strips consisting of polyvinylchloride (PVC) aluminium or in blister packages of polyvinylidene chloride (PVDC) coated PVC/aluminium blisters in pack sizes of 12, 15 and 21 capsules.

The proposed shelf-life for the products is 3 years with the storage condition “Store below 25°C”.

The packaging and proposed shelf-life are consistent with the details registered for the cross-reference products.

Legal status
The products are available as prescription-only medicines (POM).

Marketing Authorisation Holder/Contact Persons/Company
Special Concept Development (UK) Limited t/a Rx farma, Unit 1-7 Colonial Way, Watford, Hertfordshire, WD24 4YR United Kingdom.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross reference products.
Manufacturing process
The proposed manufacturing processes are consistent with the details registered for the cross reference products.

Finished product/shelf-life specifications
The proposed finished product specifications are in line with the details registered for the cross-reference products.

Bioequivalence
No bioequivalence data are required to support these simple applications because the proposed products are manufactured to the same formula and utilise the same processes as the reference products Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020; Special Concept Development (UK) Limited).

EXPERT REPORT
The applicant cross-references the data for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020), to which these applications are claimed to be identical. This is acceptable. The applicant has included expert reports of the applications. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The quality data for these applications are consistent with those approved for Amoxicillin 250 mg and 500 mg Capsules (PL 36722/0019-0020) and, as such, have been judged to be satisfactory. The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS
As these are abridged simple applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data has been supplied and none are required.

A suitable justification has been provided for not submitting an environmental risk assessment.

The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS
As these are abridged simple applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The grant of Marketing Authorisations is recommended.

Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Amoxicillin 250mg and 500mg Capsules.
A summary of safety concerns and routine risk minimisation as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity and anaphylaxis</td>
<td>Warning is provided in section 4.3 and 4.4 for the use in patients with history of severe immediate hypersensitivity reaction (e.g. anaphylaxis) or other beta-lactam agents. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Prescription only medicine.</td>
<td>None</td>
</tr>
<tr>
<td>Severe skin reactions (e.g. AGEP)</td>
<td>Warning is provided in section 4.4 of SmPC for the occurrence of severe skin reactions at the treatment</td>
<td>None</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Caution</td>
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<tr>
<td>Hepatitis and cholestatic jaundice</td>
<td>Listed in section 4.8 of SmPC as very rare occurrence of hepatitis and cholestatic jaundice.</td>
<td>None</td>
</tr>
<tr>
<td>Interaction with laboratory tests</td>
<td>Warning is provided in section 4.4 of SmPC for the interaction of amoxicillin with certain laboratory tests. Care should be taken for testing the presence of glucose in urine in patients and oestriol test in pregnant women during treatment with amoxicillin.</td>
<td>None</td>
</tr>
<tr>
<td>Severe neutropenia or agranulocytosis</td>
<td>Listed in section 4.8 of SmPC for the very rare occurrence of reversible leucopenia including severe neutropenia or agranulocytosis.</td>
<td>None</td>
</tr>
<tr>
<td>Antibiotic-associated colitis</td>
<td>Warning is provided in section 4.4 of SmPC to consider the diagnosis of antibiotic associated colitis in patients who present with diarrhoea during, or subsequent to the administration of antibiotics.</td>
<td>None</td>
</tr>
<tr>
<td>Overgrowth of non-susceptible with prolonged use</td>
<td>Warning is provided in section 4.4 for the prolonged use of amoxicillin which may occasionally result in overgrowth of non-susceptible organisms.</td>
<td>None</td>
</tr>
<tr>
<td>Methotrexate toxicity</td>
<td>Warning is provided in section 4.5 on SmPC for the interaction of penicillin and methotrexate causing reduced excretion and increased risk of toxicity methotrexate.</td>
<td>None</td>
</tr>
</tbody>
</table>

Prescription only medicine.
Routine risk minimisation is provided through the Summaries of Product Characteristics and the Patient Information Leaflet and this is sufficient.

The grant of Marketing Authorisations is recommended.

V USER CONSULTATION
A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to the leaflet for Amoxicillin 250 mg and 500 mg Capsules (Special Concept Development (UK) Limited). The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s product is identical to the cross-reference products. Extensive clinical
experience with amoxicillin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics, Patient Information Leaflet & Labels

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

The current approved labelling is listed below:
UKPAR Amoxicillin 250mg and 500mg Capsules  PL 36722/0107-0108

Amoxicillin 250mg Capsules

Keep out of the sight and reach of children.

Storage:
Store below 25°C.

Usage:
Read the package leaflet before use.
Use as directed by the physician.
Each hard capsule contains amoxicillin trihydrate equivalent to 250mg Amoxicillin.

Take ONE capsule THREE times a day for ... days. Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop.

Name
Date
Dispensed by

PL36722/0107
MA Holding Special Concept Development (UK) Limited,
Unit 17, Colonnade Way, Watford,
Hertfordshire, WD24 4YR
POM 5034188 14 3193
UKPAR Amoxicillin 250mg and 500mg Capsules

Amoxicillin 250mg Capsules

Each hard capsule contains amoxicillin trihydrate equivalent to 250mg Amoxicillin.

- Use as directed by the physician.
- Read the package leaflet before use.
- Store below 25°C.
- Keep out of the sight and reach of children

MA Holder:
Special Concept Development (UK) Limited, Unit 1-7
Colonial Way, Watford, Hertfordshire, WD24 4YR

PL 36722/0107 POM
UKPAR Amoxicillin 250mg and 500mg Capsules

For oral administration

21 Capsules

PL 36722/0108
MA Holder: Special Concept Development (UK) Limited,
Unit 1-7 Cootenall Way, Watford,
Hertfordshire, WD24 4YR

POM
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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