TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>11</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td></td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>12</td>
</tr>
<tr>
<td>Patient Information Leaflet</td>
<td>33</td>
</tr>
<tr>
<td>Labelling</td>
<td>35</td>
</tr>
</tbody>
</table>
AMOXICILLIN 250 MG, 500 MG AND 1 G, POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 31745/0021-3

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ibigen Srl Marketing Authorisations for the medicinal products Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion (PL 31745/0021-3) on 25 May 2012. These are prescription-only medicines (POM) used to treat a wide range of bacterial infections which may include those affecting the:

- chest (bronchitis or pneumonia)
- tonsils (tonsillitis)
- ears (otitis media)
- sinuses (sinusitis)
- kidneys, bladder or the urethra (the tube which carries urine from the bladder)
- 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)
- teeth and gums
- skin (including animal bites).

Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion can also be used to treat gonorrhoea (a sexually transmitted infection), infections associated with pregnancy and typhoid and paratyphoid (fevers caused by a group of bacteria called Salmonella).

The active ingredient, amoxicillin (as amoxicillin sodium), is one of a group of medicines called ‘penicillins’. These medicines are also known as ‘antibiotics’ and they work by killing the bacteria that cause infections.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion outweigh the risks and Marketing Authorisations have been granted.
AMOXICILLIN 250 MG, 500 MG AND 1 G, POWDER FOR
SOLUTION FOR INJECTION OR INFUSION
PL 31745/0021-3

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk assessment Page 10
INTRODUCTION

On 25 May 2012, the MHRA granted Marketing Authorisations for the medicinal products Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion (PL 31745/0021-3) to Ibigen Srl. The products are prescription-only medicines (POM) 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.

Amoxicillin 250 mg, 500mg and 1 g, powder for solution for injection or infusion may also be used for the prevention of bacteraemia, associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.

The applications were submitted as abridged applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion (PL 24610/0010-12), which were granted Marketing Authorisations to Bowmed Limited on 26 March 2009.

Amoxicillin 250 mg, 500 mg and 1 g, Powder for solution for Injection or Infusion contain the active ingredient, amoxicillin (as amoxicillin sodium), which is a broad spectrum antibiotic.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 31745/0021-3

PROPRIETARY NAME: Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion

ACTIVE(S): Amoxicillin sodium

COMPANY NAME: Ibigen Srl

E.C. ARTICLE: Article 10c of Directive 2001/83/EC

LEGAL STATUS: POM

1. INTRODUCTION
These are abridged applications for Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion (PL 31745/0021-3), submitted under Article 10(c) of Directive 2001/83/EC, as amended. The proposed Marketing Authorisation Holder is Ibigen Srl, Via Fossignano 2, 04011 – Aprilia (LT), Italy.

The applications cross-refer to Amoxicillin 250 mg, 500 mg and 1 g, Powder for Solution for Injection or Infusion (PL 24610/0010-12, which were granted Marketing Authorisations to Bowmed Limited on 26 March 2009.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)
The proposed names of the products are Amoxicillin 250 mg, 500 mg and 1 g, powder for solution for injection or infusion. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
All strengths of the products are packaged in clear Type III glass vials with chlorobutyl rubber closures. Each clear Type III glass vial with chlorobutyl rubber closure contains a white or almost white powder for solution for injection or infusion containing 250 mg, 500 mg or 1g of amoxicillin (as amoxicillin sodium). The products are packed into cardboard cartons with Patient Information Leaflets, in pack sizes of 1, 5, 10, 20 or 50 vials.

Not all pack sizes may be marketed.

The proposed shelf-life (36 months for the unopened vials; opened vials are to be used immediately) and storage conditions (‘Store below 25°C.’) are consistent with the details registered for the cross-reference products.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
Ibigen Srl, Via Fossignano 2, 04011 – Aprilia (LT), Italy.

The Qualified Person (QP) responsible for pharmacovigilance is stated and his CV is included.
2.5 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.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

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

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
These products contain no excipients.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula and utilising the same process as the reference products Amoxicillin 250 mg, 500mg and 1 g, Powder for solution for Injection or Infusion (PL 24610/0010-12).

3. EXPERT REPORTS
The applicant cross-refers to the data for Amoxicillin 250 mg, 500 mg and 1 g, Powder for solution for Injection or Infusion (PL 24610/0010-12), to which it claims to be identical. This is acceptable.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to those for the cross-reference products.

5. SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs)
The proposed Summaries of Product Characteristics is consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
PIL
The approved PIL is satisfactory and in line with the approved SmPCs. It is consistent with the details registered for the cross-reference products.

PIL user testing has been accepted for the ‘parent leaflet’ for Amoxicillin 250 mg, 500 mg and 1 g, Powder for Solution for Injection or Infusion (PL 24610/0010-12, Bowmed.
Limited, UK) based on bridging to the successful user-testing of the PILs for Flucloxacillin and Co-amoxiclav, powders for solution for injection or infusion (Bowmed Limited, UK).

As the text, layout and design of the ‘parent leaflet’ for Amoxicillin 250 mg, 500 mg and 1 g, Powder for Solution for Injection or Infusion (PL 24610/0010-12, Bowmed Limited, UK) and that of the leaflet Amoxicillin 250 mg, 500 mg and 1 g, Powder for Solution for Injection or Infusion (PL 31745/0021-3) are considered identical, no further user testing of the leaflet for these products is necessary.

Carton and blister label
The proposed artwork is consistent with the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation, the applicant has also included the names of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing labels.

7. CONCLUSION
The data submitted with these applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-Clinical Assessment

As these are abridged applications submitted under Article 10(c) of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the applications are for identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the marketing authorisations for the proposed products.

The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10(c) 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 Marketing Authorisation Holder has not submitted a Risk Management Plan (RMP). As the applications are for identical versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active ingredient is well-established.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for these applications.

EFFICACY
These applications are identical to previously granted applications for Amoxicillin 250 mg, 500 mg and 1 g, Powder for Solution for Injection or Infusion (PL 24610/0010-12). No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with that for Amoxicillin 250 mg, 500 mg and 1 g, Powder for Solution for Injection or Infusion (PL 24610/0010-12). The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amoxicillin sodium is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
AMOXICILLIN 250 MG, 500 MG AND 1G, POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 31745/0021-3

STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the Marketing Authorisation applications on 15 February 2012.
2  Following standard checks and communication with the applicant the MHRA considered the applications valid on 02 April 2012.
3  Following assessment, the applications were granted on 25 May 2012.
1 **NAME OF THE MEDICINAL PRODUCT**
Amoxicillin 250 mg, powder for solution for injection or infusion

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each 10ml vial contains 250 mg amoxicillin as amoxicillin sodium.
Each vial contains approximately 19 mg sodium.

3 **PHARMACEUTICAL FORM**
Powder for solution for injection or infusion.
Glass vial containing white or almost white powder.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
*Treatment of Infection:*
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

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

*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.

4.2 **Posology and method of administration**

**Adult dosage (including elderly patients):**
*Treatment of infection:*
Moderate infections: 500 mg via intramuscular injection every 8 hours (or more frequently if necessary).
This dose may be given by slow intravenous injection if more convenient.
Severe infections: 1 g via intravenous injection every 6 hours.
**Prophylaxis of endocarditis:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental procedures:</strong> prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues and who have not received a penicillin in the previous month. (N.B. Patients with prosthetic heart valves should be referred to hospital - see below).</td>
<td>Patient not having general anaesthetic</td>
<td>3 g Amoxicillin orally, 1 hour before procedure. A second dose may be given 6 hours later, if considered necessary. Initially 3 g Amoxicillin orally 4 hours prior to anaesthesia, followed by 3 g orally (or 1 g IV or IM if oral dose not tolerated) as soon as possible after the operation.</td>
</tr>
<tr>
<td>Patient having general anaesthetic: if oral antibiotics considered to be appropriate</td>
<td>Patient having general anaesthetic: if oral antibiotics not appropriate.</td>
<td>1 g Amoxicillin IV or IM immediately before induction; with 500 mg orally, 6 hours later.</td>
</tr>
<tr>
<td><strong>Dental procedures:</strong> patients for whom referral to hospital is recommended: a) Patients to be given a general anaesthetic who have been given a penicillin in the previous month. b) Patients to be given a general anaesthetic who have a prosthetic heart valve. c) Patients who have had one or more attacks of endocarditis.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM immediately prior to anaesthesia (if given) or 15 minutes prior to dental procedure. Followed by (6 hours later): 500 mg Amoxicillin orally</td>
<td>See Note 2. Note 3. Amoxicillin and gentamicin should not be mixed in the same syringe. Note 4. Please consult the appropriate data sheet for full prescribing information on gentamicin.</td>
</tr>
<tr>
<td><strong>Genitourinary Surgery or Instrumentation:</strong> prophyaxis for patients who have no urinary tract infection and who are to have genito-urinary surgery or instrumentation under general anaesthesia. In the case of Obstetric and Gynaecological Procedures and Gastrointestinal Procedures—routine prophylaxis is recommended only for patients with prosthetic heart valves.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction. Followed by (6 hours later): 500 mg Amoxicillin orally or IV or IM according to clinical condition.</td>
<td>See Notes 2, 3 and 4 above.</td>
</tr>
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</table>
### Condition

**Surgery or Instrumentation of the Upper Respiratory Tract**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients other than those with prosthetic heart valves.</td>
<td>1 g Amoxicillin IV or IM immediately before induction; 500 mg Amoxicillin IV or IM 6 hours later.</td>
<td>See Note 2 above. Note 5. The second dose of Amoxicillin may be administered orally.</td>
</tr>
</tbody>
</table>

| Patients with prosthetic heart valves. | Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction; followed by (6 hours later) 500 mg Amoxicillin IV or IM. | See Notes 2, 3, 4 and 5 above. |

### Children:

**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).

Renal impairment in children under 40 kg:

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min</th>
<th>Dose</th>
<th>Interval between administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>Usual dose</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>10 – 30</td>
<td>Usual dose</td>
<td>12 h (corresponding to 2/3 of the dose)</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Usual dose</td>
<td>24 h (corresponding to 1/3 of the dose)</td>
</tr>
</tbody>
</table>

**Administration:**

Intravenous injection, intravenous infusion, intramuscular injection:

See Section 6.6 for instructions for use and handling.

### 4.3 Contraindications

Amoxicillin is a penicillin and should not be given to patients with a history of hypersensitivity to penicillins or other beta-lactam antibiotics e.g. cephalosporins.
4.4 Special warnings and precautions for use

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 Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (See Section 4.9). Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

Dosage should be adjusted in patients with renal impairment (see section 4.2).

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

Amoxicillin injection contains approximately 3.3 mmol sodium per gram. This should be taken into consideration by patients on a sodium controlled diet.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with amoxicillin have shown no teratogenic effects. It 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.

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) and very rare (<1/10,000).

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

Hepato-biliary disorders
*Very rare:* Hepatitis and cholestatic jaundice; a moderate rise in AST and/or ALT (the significance of a rise in AST and/or ALT is unclear).

Skin and subcutaneous tissue disorders
*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) (See also Immune system disorders).

Renal and urinary disorders
*Very rare:* Interstitial nephritis, crystalluria (See Section 4.9).

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). Amoxicillin may be removed from the circulation by haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC code: J01CF05
Pharmacotherapeutic group: Beta-lactamase resistant penicillins

Amoxicillin is a broad spectrum antibiotic. It is rapidly bactericidal and possesses the safety profile of a penicillin. The wide range of organisms sensitive to the bactericidal action of Amoxicillin include:

- **Gram-positive**
  - *Streptococcus faecalis*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*
  - *Streptococcus viridans*
  - *Staphylococcus aureus* (penicillin-sensitive)
  - *Corynebacterium* species
  - *Bacillus anthracis*
  - *Listeria monocytogenes*

- **Gram-negative**
  - *Haemophilus influenzae*
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Salmonella* species
  - *Shigella* species
  - *Bordetella pertussis*
  - *Brucella* species
  - *Neisseria gonorrhoeae*
  - *Neisseria meningitidis*
  - *Vibrio cholerae*
  - *Pasteurella septica*

5.2 Pharmacokinetic properties
Amoxicillin is well absorbed by the oral and parenteral routes. Amoxicillin gives good penetration into bronchial secretions and high urinary concentrations of unchanged antibiotic.

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 inulin 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
There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

6.2 Incompatibilities
Amoxicillin should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates, or with intravenous lipid emulsions.

If Amoxicillin is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
Unopened vial: 36 months.
After opening: To be used immediately.
6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
Clear Type III glass vials with chlorobutyl rubber closure, in cartons of 1, 5, 10, 20 or 50 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Intravenous Injection:
Dissolve 250mg in 5 ml Water for Injections BP (final volume 5.2 ml).
Amoxicillin injection, suitably diluted, may be injected directly into a vein or the infusion line over a period of three to four minutes.

Intravenous Infusion:
Solutions may be prepared as described for intravenous injections and then added to an intravenous solution in a minibag or in-line burette and administered over a period of half to one hour. Alternatively, using a suitable reconstitution device, the appropriate volume of intravenous fluid may be transferred from the infusion bag into the vial and then drawn back into the bag after dissolution.

Intramuscular injection:
Add 1.5 ml Water for Injections BP and shake vigorously (final volume 1.7 ml).

A transient pink colouration or slight opalescence may appear during reconstitution. Reconstituted solutions are normally a pale straw colour. Amoxicillin injection may be added to the following intravenous fluids and used immediately.
• Water for Injections BP
• Sodium Chloride Intravenous Infusion (0.9%)
• Potassium Chloride (0.3%) and Sodium Chloride (0.9%) Intravenous Infusion
• Glucose Intravenous Infusion
• Sodium Chloride (0.18%) and Glucose (4%) Intravenous Infusion
• Dextran 40 Intravenous Infusion (10%) in Sodium Chloride Intravenous Infusion (0.9%)
• Dextran 40 Intravenous Infusion (10%) in Glucose Intravenous Infusion (5%)
• Sodium Lactate Intravenous Infusion (M/6)
• Compound Sodium Lactate Intravenous Infusions (Ringer-Lactate: Hartmann’s Solution)

7 MARKETING AUTHORISATION HOLDER
Ibigen Srl,
Via Fossignano 2
04011 – Aprilia (LT)
Italy

8 MARKETING AUTHORISATION NUMBER(S)
PL 31745/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/05/2012

10 DATE OF REVISION OF THE TEXT
25/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Amoxicillin 500 mg, powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 10ml vial contains 500 mg amoxicillin as amoxicillin sodium.

Each vial contains approximately 38 mg sodium.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion.

Glass vial containing white or almost white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Treatment of Infection:
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

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

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.

4.2 Posology and method of administration

Adult dosage (including elderly patients):

Treatment of infection:
Moderate infections: 500 mg via intramuscular injection every 8 hours (or more frequently if necessary). This dose may be given by slow intravenous injection if more convenient.
Severe infections: 1 g via intravenous injection every 6 hours.
### Prophylaxis of endocarditis:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental procedures:</strong> prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues and who have not received a penicillin in the previous month. (N.B. Patients with prosthetic heart valves should be referred to hospital - see below).</td>
<td>3 g Amoxicillin orally, 1 hour before procedure. A second dose may be given 6 hours later, if considered necessary.</td>
<td>Note 1. If prophylaxis with Amoxicillin' is given twice within one month, emergence of resistant streptococci is unlikely to be a problem. Alternative antibiotics are recommended if more frequent prophylaxis is required, or if the patient has received a course of treatment with a penicillin during the previous month.</td>
</tr>
<tr>
<td>Patient not having general anaesthetic</td>
<td>Initially 3 g Amoxicillin orally 4 hours prior to anaesthesia, followed by 3 g orally (or 1 g IV or IM if oral dose not tolerated) as soon as possible after the operation.</td>
<td></td>
</tr>
<tr>
<td>Patient having general anaesthetic: if oral antibiotics considered to be appropriate</td>
<td>1 g Amoxicillin IV or IM immediately before induction; with 500 mg orally, 6 hours later.</td>
<td></td>
</tr>
</tbody>
</table>

**Note 1.**
If prophylaxis with Amoxicillin' is given twice within one month, emergence of resistant streptococci is unlikely to be a problem. Alternative antibiotics are recommended if more frequent prophylaxis is required, or if the patient has received a course of treatment with a penicillin during the previous month.

**Note 2.**
To minimise pain on injection, Amoxicillin may be given as two injections of 500 mg dissolved in sterile 1% lidocaine solution (see *Administration*).

<table>
<thead>
<tr>
<th>Condition</th>
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<th>Notes</th>
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<tbody>
<tr>
<td><strong>Dental procedures</strong> : patients for whom referral to hospital is recommended: a) Patients to be given a general anaesthetic who have been given a penicillin in the previous month. b) Patients to be given a general anaesthetic who have a prosthetic heart valve. c) Patients who have had one or more attacks of endocarditis.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM immediately prior to anaesthesia (if given) or 15 minutes prior to dental procedure. Followed by (6 hours later): 500 mg Amoxicillin orally</td>
<td>See Note 2. Note 3. Amoxicillin and gentamicin should not be mixed in the same syringe. Note 4. Please consult the appropriate data sheet for full prescribing information on gentamicin.</td>
</tr>
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<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genitourinary Surgery or Instrumentation:</strong> prophylaxis for patients who have no urinary tract infection and who are to have genito-urinary surgery or instrumentation under general anaesthesia. In the case of Obstetric and Gynaecological Procedures and Gastrointestinal Procedures – routine prophylaxis is recommended only for patients with prosthetic heart valves.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction. Followed by (6 hours later): 500 mg Amoxicillin orally or IV or IM according to clinical condition.</td>
<td>See Notes 2, 3 and 4 above.</td>
</tr>
</tbody>
</table>
### Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery or Instrumentation of the Upper Respiratory Tract</td>
<td>Patients other than those with prosthetic heart valves.</td>
<td>1 g Amoxicillin IV or IM immediately before induction; 500 mg Amoxicillin IV or IM 6 hours later.</td>
</tr>
<tr>
<td></td>
<td>Patients with prosthetic heart valves.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction; followed by (6 hours later) 500 mg Amoxicillin IV or IM.</td>
</tr>
</tbody>
</table>

### Children:

**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).

Renal impairment in children under 40 kg:

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min</th>
<th>Dose</th>
<th>Interval between administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>Usual dose</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>10 – 30</td>
<td>Usual dose</td>
<td>12 h (corresponding to 2/3 of the dose)</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Usual dose</td>
<td>24 h (corresponding to 1/3 of the dose)</td>
</tr>
</tbody>
</table>

**Administration:**
Intravenous injection, intravenous infusion, intramuscular injection:
See Section 6.6 for instructions for use and handling.

### 4.3 Contraindications
Amoxicillin is a penicillin and should not be given to patients with a history of hypersensitivity to penicillins or other beta-lactam antibiotics e.g. cephalosporins.
4.4 **Special warnings and precautions for use**

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 Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (See Section 4.9). Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

Dosage should be adjusted in patients with renal impairment (see section 4.2).

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

Amoxicillin injection contains approximately 3.3 mmol sodium per gram. This should be taken into consideration by patients on a sodium controlled diet.

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.

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

4.6 **Fertility, pregnancy and lactation**

**Pregnancy**

Animal studies with amoxicillin have shown no teratogenic effects. It 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.

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) and very rare (<1/10,000).

The majority of side effects listed below are not unique to amoxicillin and may occur when using other penicillins.
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 - Interaction with other Medicaments and other Forms of Interaction)

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).

Hepato-biliary disorders

*Very rare:* Hepatitis and cholestatic jaundice; a moderate rise in AST and/or ALT (the significance of a rise in AST and/or ALT is unclear).

Skin and subcutaneous tissue disorders

*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) (See also Immune system disorders).

Renal and urinary disorders

*Very rare:* Interstitial nephritis, crystalluria (See Section 4.9 Overdose).

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).

Amoxicillin may be removed from the circulation by haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC code: J01CF05
Pharmacotherapeutic group: Beta-lactamase resistant penicillins

Amoxicillin is a broad spectrum antibiotic. It is rapidly bactericidal and possesses the safety profile of a penicillin. The wide range of organisms sensitive to the bactericidal action of Amoxicillin include:

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus faecalis</em></td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td><em>Salmonella species</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>Shigella species</em></td>
</tr>
<tr>
<td>(penicillin-sensitive)</td>
<td><em>Bordetella pertussis</em></td>
</tr>
<tr>
<td><em>Clostridium species</em></td>
<td><em>Brucella species</em></td>
</tr>
<tr>
<td><em>Corynebacterium species</em></td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td></td>
<td><em>Pasteurella septica</em></td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties
Amoxicillin is well absorbed by the oral and parenteral routes. Amoxicillin gives good penetration into bronchial secretions and high urinary concentrations of unchanged antibiotic.

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
There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

6.2 Incompatibilities
Amoxicillin should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates, or with intravenous lipid emulsions.

If Amoxicillin is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

6.3 Shelf life
Unopened vial: 36 months.
After opening: To be used immediately.
6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
Clear Type III glass vials with chlorobutyl rubber closure, in cartons of 1, 5, 10, 20 or 50 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Intravenous Injection:
Dissolve 500mg in 10 ml Water for Injections BP (final volume 10.4 ml).
Amoxicillin injection, suitably diluted, may be injected directly into a vein or the infusion line over a period of three to four minutes.

Intravenous Infusion:
Solutions may be prepared as described for intravenous injections and then added to an intravenous solution in a minibag or in-line burette and administered over a period of half to one hour. Alternatively, using a suitable reconstitution device, the appropriate volume of intravenous fluid may be transferred from the infusion bag into the vial and then drawn back into the bag after dissolution.

Intramuscular injection:
Add 2.5 ml Water for Injections BP and shake vigorously (final volume 2.9 ml).

A transient pink colouration or slight opalescence may appear during reconstitution. Reconstituted solutions are normally a pale straw colour.

Amoxicillin injection may be added to the following intravenous fluids and used immediately.
- Water for Injections BP
- Sodium Chloride Intravenous Infusion (0.9%)
- Potassium Chloride (0.3%) and Sodium Chloride (0.9%) Intravenous Infusion
- Glucose Intravenous Infusion
- Sodium Chloride (0.18%) and Glucose (4%) Intravenous Infusion
- Dextran 40 Intravenous Infusion (10%) in Sodium Chloride Intravenous Infusion (0.9%)
- Dextran 40 Intravenous Infusion (10%) in Glucose Intravenous Infusion (5%)
- Sodium Lactate Intravenous Infusion (M/6)
- Compound Sodium Lactate Intravenous Infusions (Ringer-Lactate: Hartmann’s Solution)

7 MARKETING AUTHORISATION HOLDER
Ibigen Srl,
Via Fossignano 2
04011 – Aprilia (LT)
Italy

8 MARKETING AUTHORISATION NUMBER(S)
PL 31745/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/05/2012

10 DATE OF REVISION OF THE TEXT
25/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Amoxicillin 1g, Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 20ml vial contains 1g Amoxicillin as Amoxicillin Sodium.

Each vial contains approximately 76 mg sodium.

3 PHARMACEUTICAL FORM
Powder for Solution for Injection or Infusion.
Glass vial containing white or almost white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of Infection:
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

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

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.

4.2 Posology and method of administration
Adult dosage (including elderly patients):
Treatment of infection:
Moderate infections: 500 mg via intramuscular injection every 8 hours (or more frequently if necessary).
This dose may be given by slow intravenous injection if more convenient.
Severe infections: 1 g via intravenous injection every 6 hours.
Prophylaxis of endocarditis:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental procedures:</strong> prophylaxis for patients undergoing extraction, scaling or surgery involving gingival tissues and who have not received a penicillin in the previous month. (N.B. Patients with prosthetic heart valves should be referred to hospital - see below).</td>
<td>Patient not having general anaesthetic</td>
<td>Note 1. If prophylaxis with Amoxicillin' is given twice within one month, emergence of resistant streptococci is unlikely to be a problem. Alternative antibiotics are recommended if more frequent prophylaxis is required, or if the patient has received a course of treatment with a penicillin during the previous month. Note 2 To minimise pain on injection, Amoxicillin may be given as two injections of 500 mg dissolved in sterile 1% lidocaine solution (see Administration).</td>
</tr>
<tr>
<td>Patient having general anaesthetic: if oral antibiotics considered to be appropriate</td>
<td>3 g Amoxicillin orally, 1 hour before procedure. A second dose may be given 6 hours later, if considered necessary.</td>
<td></td>
</tr>
<tr>
<td>Patient having general anaesthetic: if oral antibiotics not appropriate.</td>
<td>Initially 3 g Amoxicillin orally 4 hours prior to anaesthesia, followed by 3 g orally (or 1 g IV or IM if oral dose not tolerated) as soon as possible after the operation.</td>
<td></td>
</tr>
<tr>
<td>Patient having general anaesthetic: if oral antibiotics not appropriate.</td>
<td>1 g Amoxicillin IV or IM immediately before induction; with 500 mg orally, 6 hours later.</td>
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<tr>
<td><strong>Dental procedures:</strong> patients for whom referral to hospital is recommended: a) Patients to be given a general anaesthetic who have been given a penicillin in the previous month. b) Patients to be given a general anaesthetic who have a prosthetic heart valve. c) Patients who have had one or more attacks of endocarditis.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM immediately prior to anaesthesia (if given) or 15 minutes prior to dental procedure. Followed by (6 hours later): 500 mg Amoxicillin orally</td>
<td>See Note 2. Note 3. Amoxicillin and gentamicin should not be mixed in the same syringe. Note 4. Please consult the appropriate data sheet for full prescribing information on gentamicin.</td>
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<tr>
<td><strong>Genitourinary Surgery or Instrumentation:</strong> prophylaxis for patients who have no urinary tract infection and who are to have genitourinary surgery or instrumentation under general anaesthesia. In the case of Obstetric and Gynaecological Procedures and Gastrointestinal Procedures—routine prophylaxis is recommended only for patients with prosthetic heart valves.</td>
<td>Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction. Followed by (6 hours later): 500 mg Amoxicillin orally or IV or IM according to clinical condition.</td>
<td>See Notes 2, 3 and 4 above.</td>
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</tbody>
</table>
**Condition** | **Dosage** | **Notes**
---|---|---
*Surgery or Instrumentation of the Upper Respiratory Tract*
Patients other than those with prosthetic heart valves. | 1 g Amoxicillin IV or IM immediately before induction; 500 mg Amoxicillin IV or IM 6 hours later. | See Note 2 above. Note 5. The second dose of Amoxicillin may be administered orally. |
Patients with prosthetic heart valves. | Initially: 1 g Amoxicillin IV or IM with 120 mg gentamicin IV or IM, immediately before induction; followed by (6 hours later) 500 mg Amoxicillin IV or IM. | See Notes 2, 3, 4 and 5 above. |

**Children:**

**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).

Renal impairment in children under 40 kg:

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<tr>
<th>Creatinine clearance ml/min</th>
<th>Dose</th>
<th>Interval between administration</th>
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<td>&gt; 30</td>
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<tr>
<td>10 – 30</td>
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<tr>
<td>&lt; 10</td>
<td>Usual dose</td>
<td>24 h (corresponding to 1/3 of the dose)</td>
</tr>
</tbody>
</table>

**Administration:**

Intravenous injection, intravenous infusion, intramuscular injection: See Section 6.6, Instructions for use and handling.

**4.3 Contraindications**

Amoxicillin is a penicillin and should not be given to patients with a history of hypersensitivity to penicillins or other beta-lactam antibiotics e.g. cephalosporins.
4.4 Special warnings and precautions for use

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 Section 4.3).

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

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Section 4.9). Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

Dosage should be adjusted in patients with renal impairment (see section 4.2).

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

Amoxicillin injection contains approximately 3.3 mmol sodium per gram. This should be taken into consideration by patients on a sodium controlled diet.

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.

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

4.6 Pregnancy and lactation

Pregnancy

Animal studies with amoxicillin have shown no teratogenic effects. It 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.

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) and very rare (<1/10,000).
The majority of side effects listed below are not unique to amoxicillin and may occur when using other penicillins.

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 - Interaction with other Medicaments and other Forms of Interaction)

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 pseudomembraneous colitis and haemorrhagic colitis).

Hepato-biliary disorders
Very rare: Hepatitis and cholestatic jaundice; a moderate rise in AST and/or ALT (the significance of a rise in AST and/or ALT is unclear).

Skin and subcutaneous tissue disorders
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) (See also Immune system disorders).

Renal and urinary disorders
Very rare: Interstitial nephritis, crystalluria (See Section 4.9 Overdose).

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

ATC code: J01CF05
Pharmacotherapeutic group: Beta-lactamase resistant penicillins

Amoxicillin is a broad spectrum antibiotic. It is rapidly bactericidal and possesses the safety profile of a penicillin. The wide range of organisms sensitive to the bactericidal action of Amoxicillin include:

- **Gram-positive**
  - *Streptococcus faecalis*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*
  - *Streptococcus viridans*
  - *Staphylococcus aureus* (penicillin-sensitive)
  - *Clostridium species*
  - *Corynebacterium species*
  - *Bacillus anthracis*
  - *Listeria monocytogenes*

- **Gram-negative**
  - *Haemophilus influenzae*
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Salmonella species*
  - *Shigella species*
  - *Bordetella pertussis*
  - *Brucella species*
  - *Neisseria gonorrhoeae*
  - *Neisseria meningitidis*
  - *Vibrio cholerae*
  - *Pasteurella septica*

5.2 Pharmacokinetic properties

Amoxicillin is well absorbed by the oral and parenteral routes. Amoxicillin gives good penetration into bronchial secretions and high urinary concentrations of unchanged antibiotic.

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

No further information of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Amoxicillin should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates, or with intravenous lipid emulsions.

If Amoxicillin is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 36 months.

After opening: To be used immediately.
6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Clear Type III glass vials with chlorobutyl rubber closure, in cartons of 1, 5, 10, 20 or 50 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Intravenous Injection:
Dissolve 1g in 20ml Water for Injections BP (final volume 20.8 ml).

Amoxicillin injection, suitably diluted, may be injected directly into a vein or the infusion line over a period of three to four minutes.

Intravenous Infusion:
Solutions may be prepared as described for intravenous injections and then added to an intravenous solution in a minibag or in-line burette and administered over a period of half to one hour. Alternatively, using a suitable reconstitution device, the appropriate volume of intravenous fluid may be transferred from the infusion bag into the vial and then drawn back into the bag after dissolution.

Intramuscular injection:
Add 2.5 ml Water for Injections BP and shake vigorously (final volume 3.3 ml).

A transient pink colouration or slight opalescence may appear during reconstitution. Reconstituted solutions are normally a pale straw colour.

Amoxicillin injection may be added to the following intravenous fluids and used immediately.

- Water for Injections BP
- Sodium Chloride Intravenous Infusion (0.9%)
- Potassium Chloride (0.3%) and Sodium Chloride (0.9%) Intravenous Infusion
- Glucose Intravenous Infusion
- Sodium Chloride (0.18%) and Glucose (4%) Intravenous Infusion
- Dextran 40 Intravenous Infusion (10%) in Sodium Chloride Intravenous Infusion (0.9%)
- Dextran 40 Intravenous Infusion (10%) in Glucose Intravenous Infusion (5%)
- Sodium Lactate Intravenous Infusion (M/6)
- Compound Sodium Lactate Intravenous Infusions (Ringer-Lactate: Hartmann’s Solution)

7 MARKETING AUTHORISATION HOLDER
Bowmed Limited
Unit 2, Eastman Way
Stevenage
Herts SG1 4SZ
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24610/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
17/12/2010
PATIENT INFORMATION LEAFLET

Amoxicillin 250mg, 500mg or 1g, Powder for Solution for Injection or Infusion
Amoxicillin as Amoxicillin Sodium

Before you are given Amoxicillin Injection
Before you are given Amoxicillin Injection, your doctor must check that it is safe for you to have this medicine.

You should not be given this medicine if:

- You know that you are allergic to penicillin or any other antibiotics.
- You have ever had a skin rash or swelling of the face or neck when taking any antibiotics.

1. WHAT AMOXICILLIN INJECTION IS AND WHAT IT IS USED FOR

Your medicine contains the active substance amoxicillin (as amoxicillin sodium), which is one of a group of medicines called "penicillins". These medicines are also known as "antibiotics" and they work by killing the bacteria that cause infections.

Amoxicillin injection is used to treat a wide range of bacterial infections which may include those affecting the:

- Chest (bronchitis or pneumonia)
- Tonsillitis (inflammation of the tonsils)
- Ear (otitis media)
- Sinusitis (inflammation of the sinuses)
- Kidneys, bladder or the urethra (the tube which carries urine from the bladder)
- Female reproductive system including infections caused by difficulties during childbirth (puerperal sepse and postpartum abortion)
- Abdominal (appendicular) abscess and peritonitis
- Heart (endocarditis)
- Blood (septicemia)
- Teeth and gums
- Skin (including animal bites)

Amoxicillin injection can also be used to treat gonorrhoea (sexually transmitted infection) infections associated with pregnancy and typhoid and paratyphoid fever caused by a group of bacteria called Salmonella.

2. BEFORE YOU ARE GIVEN AMOXICILLIN INJECTION

You should not be given this medicine if:

- You know that you are allergic to penicillin or any other antibiotics.
- You have ever had a skin rash or swelling of the face or neck when taking any antibiotics.

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INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only.

Special precautions for storage
Store below 25°C.

Instructions for use and handling
Intravenous injection:
- Discontinue 250mg or 5 ml into the intravenous injection volume, 500mg or 10 ml into the intravenous injection volume, 1 g or 20 ml into the intravenous injection volume. Amoxicillin injection, suitably diluted, may be injected directly into a vein or the infusion line over a period of three to five minutes.
3. HOW AMOXICILLIN INJECTION IS GIVEN

Your doctor or nurse will prepare your injection in the form of a liquid. They will inject this into a muscle intramuscularly or into a vein intravenously. Your doctor will decide how much you need and how often the injection should be given.

Adults including the elderly.

Treatment of infection:
The usual dose is 500mg given every 8 hours for most infections. Doses may be increased for certain infections, e.g. severe infections. This is to prevent you from getting a heart infection.
The usual dose is 1g given before you are given a general anaesthetic (if one is to be given).
You may be given another antibiotic (garamycin) at the same time.

You need a second injection of 500mg or 1g to be given in 6 hours later, or twice according to the general anaesthetic if you are unable to take amoxillin by mouth.

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

Children weighing < 40 kg
The daily dosage is 40 mg/kg/day in two to three divided doses not exceeding 2 g/day, except in the following cases, where your doctor may prescribe a different dose:
Tonsillitis, ear infection, prevention of heart infection in scarlet fever, and severe pneumonia. Doses may also be reduced or given less frequently in patients with kidney problems.

If you think you have missed an injection:
Speak to your doctor or nurse.

If you are given more of this medicine than you should:
This is unlikely to happen but if it does, the doctor will treat any symptoms that follow.

4. POSSIBLE SIDE EFFECTS

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

If you get any of the following side effects after receiving this medicine, tell your doctor or nurse immediately. If you get them, you may have had a serious allergic reaction or one of other types or reaction to this medicine:
• stomach pain or diarrhea (possibly with vomiting)
• your skin or the whites of your eyes start turning yellow
• any unexplained bleeding, bruising or skin discoloration
• skin rash and itching
• blistering of the skin, mouth, eyes, or genitalia
• any swollen lid or lips, difficulty in breathing or dizziness
• any swelling of the face, neck or tongue
• your urine becomes darker or your feces becomes paler
• convulsions (fits)

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE AMOXICILLIN INJECTION

Keep out of the reach and sight of children. Store in an area below 30°C. Your doctor or pharmacist will know how to store Amoxicillin Injection properly.

Do not use after the expiry date which is printed on the label and carton, or if the pack shows signs of deterioration.

Medicines should be disposed of via a manufacturer or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Amoxicillin Injection contains
Each vial contains 250mg, 500mg or 1g of amoxicillin (as amoxicillin sodium). There are no other ingredients.

What Amoxicillin Injection looks like and contents of the pack
Amoxicillin Injection is a white or almost white powder in a glass vial. Each carton contains 1, 5, 10 or 50 glass vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Igencia Srl
04014, Avro, Vicenza, Italy
Manufacturer:
Igencia Srl
04014, Avro, Vicenza, Italy

The leaflet is for information only. The latest version of this leaflet is available from your doctor or pharmacist.