Public Assessment Report

Decentralised Procedure

Ampicillin 250 mg powder for solution for injection/infusion

Ampicillin 500 mg powder for solution for injection/infusion

Ampicillin 1 g powder for solution for injection/infusion

Ampicillin 2 g powder for solution for injection/infusion

PL 28176/0049
PL 28176/0050
PL 28176/0077
PL 28176/0078

UK/H/4323/001/DC
UK/H/4323/002/DC
UK/H/4323/003/DC
UK/H/4323/004/DC

Strides Arcolab International Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Strides Arcolab International Limited Marketing Authorisations for the medicinal products Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion (product licence numbers: PL 28176/0049-0050 and PL 28176/0077-0078) on 29 October 2012. These medicines are available on prescription only.

Ampicillin powder for solution for injection/infusion is a medicine for the treatment of bacterial infections (antibiotic) and works by killing the bacteria that cause infections. Ampicillin belongs to a group of medicines called the penicillins. Ampicillin powder for solution for injection/infusion is used to treat the following types of infection:

- complicated acute bacterial sinusitis
- meningitis caused by listeria
- infection of the heart
- kidney infections
- genital organ infections
- intra-abdominal infections
- urinary bladder infection

No new or unexpected safety concerns arose from this application. It was judged that the benefits of taking Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion outweigh the risks; hence Marketing Authorisations have been granted.
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Module 5: Scientific Discussion

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Module 1

Information about Decentralised Procedure

| Name of the products in the Reference Member State | Ampicillin 250 mg powder for solution for injection/infusion  
Ampicillin 500 mg powder for solution for injection/infusion  
Ampicillin 1 g powder for solution for injection/infusion  
Ampicillin 2 g powder for solution for injection/infusion |
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| Reference numbers for the Decentralised Procedure | UK/H/4323/001/DC  
UK/H/4323/002/DC  
UK/H/4323/003/DC  
UK/H/4323/004/DC |
| Reference Member State | United Kingdom |
| Member States concerned | AT, BE, ES, RO, FI, DE, IT, PL, NO, DK |
| Start date of the Decentralised Procedure | 19 January 2011 |
| End date of the Decentralised Procedure | 14 June 2012 |
| Marketing Authorisation numbers | PL 28176/0049  
PL 28176/0050  
PL 28176/0077  
PL 28176/0078 |
| Name and address of the authorisation holder | Strides Arcolab International Limited  
Unit 4, Metro Centre,  
Tolpits Lane,  
Watford, Hertfordshire,  
WD18 9SS United Kingdom |
Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

Product Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

Ampicillin 250 mg powder for solution for injection/infusion

Label:

![Ampicillin 250 mg label image]
Ampicillin 500 mg powder for solution for injection/infusion

Label:

For Intramuscular or Intravenous use only
Read the package leaflet before use
Each vial contains: Ampicillin Sodium equivalent to Ampicillin 500 mg.
Reconstituted/diluted solution should be used immediately.
Any unused portion must be discarded appropriately.
Do not store above 25 °C.
Keep out of the sight and reach of children.
Medicinal product subject to medical prescription.

PL 28176/0050
MA Holder: Strides Arcolab International Ltd.
Lot.: EXP.
Carton:

Ampicillin 500 mg powder for solution for Injection/Infusion
Ampicillin

For Intramuscular or Intravenous use only
1 Vial

Each vial contains:
Ampicillin Sodium equivalent to Ampicillin 500 mg.
Read the package leaflet before use.
Use as directed by thePhysician.
For single use.
Any unused portion must be discarded appropriately.
Reconstituted/diluted solution should be used immediately.
Unopened vial: Do not store above 25 °C.
Keep out of the sight and reach of children.

Medicinal product subject to medical prescription.

Barcode @ 80%

MHRA PAR; AMPICILLIN 250 MG, 500 MG, 1 G AND 2 G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 28176/0049-0050 AND PL 28176/0077-0078
Ampicillin 1 g powder for solution for injection/infusion

Label:
Carton:
Module 5

Scientific Discussion

1. Introduction

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion for the treatment of bacterial infections caused by susceptible organisms could be approved.

EXECUTIVE SUMMARY
Problem Statement
This Decentralised application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, a so-called generic application. The European reference product is Pentrexyl 500 mg powder for solution for injection or infusion, which was first authorised in Denmark on 17 October 1963. This reference product is licensed to Bristol-Myers Squibb AB (Marketing Authorisation number: 5638). The reference product has, been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

With the UK acting as RMS in this Decentralised Procedure (DCP), Strides Arcolab International Limited sought Marketing Authorisations for Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion in Austria, Belgium, Spain, Romania, Finland, Germany, Italy, Poland, Norway and Denmark.

About the Products
Ampicillin is a beta-lactam antibiotic that has been used extensively to treat bacterial infections since 1961, the ATC code for the product is J01CA01. Ampicillin is active against gram positive and some gram negative bacteria. Ampicillin acts as a competitive inhibitor of the enzyme transpeptidase, which is needed by bacteria to make their cell walls. It inhibits the third and final stage of bacterial cell wall synthesis in binary fission, which ultimately leads to cell lysis. The following bacteria have been shown in in vitro studies to be susceptible to ampicillin:

- Gram-positive organisms: hemolytic and nonhemolytic streptococci, D. pneumoniae, nonpenicillinase-producing staphylococci, Clostridia spp., B. anthracis, Listeria monocytogenes, and most strains of enterococci
- Gram-negative organisms: H. influenzae, N. gonorrhoeae, N. meningitidis, Proteus mirabilis, and many strains of Salmonella, Shigella, and E. coli.

General Comments on the Submitted Dossier
The submitted documentation in relation to the proposed products is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.
General Comments on Compliance with GMP, GLP, GCP and Agreed Ethical Principles

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GLP
Since a literature review has been presented for the non-clinical aspects of this application, it cannot be verified whether the studies cited were in compliance with the GLP regulations; however, it is assumed that the studies described in the review would have been conducted in compliance with the standards prevailing at the time.

GCP
No clinical studies have been conducted in support of the application. According to the regulatory requirements, CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence, a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted any.

SCIENTIFIC OVERVIEW AND DISCUSSION

2. Quality Aspects

Drug Substance  

Nomenclature
PhEur: Ampicillin sodium
Systematic: Sodium (2S,5R,6R)-6-[(2R)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate
CAS: 69-52-3

Structure
Mr: 371.4
Formula: C₁₆H₁₈N₃NaO₄S
Structure:

General Properties
Physical form: White or almost white powder, hygroscopic
Solubility: Freely soluble in water, practically insoluble in acetone, in fatty acid and in liquid paraffin

All aspects of the manufacture and control of the active substance ampicillin sodium are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Drug Product

Description and Composition
The products are white to off white crystalline powders for solution for injection/infusion containing 250 mg, 500 mg, 1 g or 2g ampicillin. The products contain no pharmaceutical excipients.

Pharmaceutical Development
Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic powders for solution for injection/infusion formulations bioequivalent and pharmaceutically equivalent to the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies have been conducted on exhibit batches and results were acceptable. A process validation scheme for commercial scale batches is also presented in accordance with CPMP/QWP/848/96 and is acceptable.

Finished Product Specification
Finished product specifications are provided and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided; the data demonstrate that the batches are compliant with the proposed release specifications.

Container Closure System
The finished products are licensed for marketing in packs containing one glass vial with a dark grey bromobutyl rubber stopper and flip off aluminium seal.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU
legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been approved when the storage precaution “Do not store above 25°C” is applied.

**Quality Overall Summary**
A satisfactory Quality Overall Summary prepared by an appropriately qualified expert has been provided. The CV of the expert has also been supplied.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and product labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) Form**
The MAA form is satisfactory.

**Quality Conclusion**
There are no objections to approval of Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion from a pharmaceutical point of view.

**3. Preclinical Aspects**

**Preclinical Overview**
The pharmacological, pharmacokinetic and toxicological properties of ampicillin are well known. As ampicillin is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The preclinical overview has been written by a suitably qualified expert. The overview, dated 26 November 2010, refers to 10 references from the published literature dated up to 2003. In view of the fact that the pharmaco-toxicological properties of ampicillin are well known, the overview is acceptable.

**Environmental Risk Assessment**
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all ampicillin-containing products, which, in turn, is unlikely to increase exposure of the environment to ampicillin.
Product Literature
The product literature is acceptable from a preclinical point of view.

Preclinical Conclusion
There are no objections to the approval of Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion from a preclinical point of view.

4. Clinical Aspects

Therapeutic Indications
The applicant has proposed the following in the SmPC:

“Ampicillin powder for solution for injection/infusion is indicated in the treatment of infections caused by ampicillin- sensitive organisms (see section 4.4 and 5.1). As needed, ampicillin should be administered after initial broad spectrum coverage with a third generation cephalosporin.

• Complicated acute bacterial sinusitis
• Endocarditis
• Pyelonephritis
• Cystitis (see section 4.4)
• Intra-abdominal infections
• Female genital infections
• Listeria Meningitis when used in conjunction with an aminoglycoside

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

The indications are consistent with those for the reference product and are satisfactory.

Posology and Method of Administration
The applicant has proposed the following in the SmPC:

“Posology
The dose level of ampicillin is dependent on the patient’s age, weight and renal function, the severity and site of infection and the presumed or identified etiologic agents.

10 ml of the reconstituted 10 % solution for intramuscular and intravenous injection or infusion contains 1.063 g of ampicillin sodium (equivalent to 1.0 g ampicillin and 65.8 mg or 2.86 mmol sodium).

Intravenous or intra-muscular injection
Adults and adolescents
500mg every 4 to 6 hours (the daily dose can be rised up to 6 g in case of severe infection)

Intravenous injection or infusion
Child 1 month – 12 years
25-50mg/kg (max 1g) every 6 hours (the dose can be doubled in case of severe infection)

**Neonate 21 – 28 days**
30mg/kg every 6 hours (the dose can be doubled in case of severe infection)

**Neonate 7 – 21 days**
30mg/kg every 8 hours (the dose can be doubled in case of severe infection)

**Neonate under 7 days**
30mg/kg every 12 hours (the dose can be doubled in case of severe infection)

**Special dosage and use recommendations**

**Impaired renal function**

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

For severely impaired renal function with a glomerular filtration rate of 30 ml/min and less, a reduction in the dose is recommended, since an accumulation of ampicillin is to be expected:
- at a creatinine clearance of 20 to 30 ml/min, the normal dose should be reduced to \( \frac{2}{3} \),
- at a creatinine clearance below 20 ml/min, the normal dose should be reduced to \( \frac{1}{3} \).

As a general rule, a dose of 1 g ampicillin in 8 hours should not be exceeded in patients with severe renal insufficiency.

For intramuscular administration, the usual limit of the injection volume must be complied with.

**Duration of use**
The duration of use depends on the course of the disease. As a general rule, ampicillin is used for 7 to 10 days, but for at least another 2 to 3 days after the signs of disease have subsided.

For the treatment of infections with beta-hemolytic streptococci, for safety reasons it is recommended to extend the treatment to at least 10 days to prevent late complications (e.g. rheumatic fever, glomerulonephritis)."

The posology is consistent with that for the reference product and is satisfactory.

**Clinical Efficacy**
No new efficacy data are presented for this application and none is required. However the applicant has provided a review of clinical trials published in the literature regarding the efficacy of ampicillin.
Clinical Safety
No new safety data are presented for this application and none is required. However the applicant has provided a review of clinical trials published in the literature regarding the safety of ampicillin.

Pharmacokinetic Properties
Distribution
Ampicillin is extensively distributed to tissues, crosses the placental barrier and diffuses into breast milk. Only 5% of the ampicillin concentration in plasma diffuses into cerebrospinal fluid (CSF) with intact meninges. With inflamed meninges, the ampicillin concentration in CSF can increase to 50% of the ampicillin concentration in plasma. The serum protein binding is 17-20%. The apparent volume of distribution is about 15 l.

Serum level
After oral administration of 1000 mg ampicillin, peak plasma levels of about 5 mg/l are reached after 90 to 120 min. After intramuscular injection, peak plasma levels are reached after 30 to 60 min.

Metabolism
Ampicillin is partly metabolised to microbiologically inactive penicilloates.

Elimination
Ampicillin is eliminated intact mainly by the renal route, but also through bile and faeces. After oral administration, about 40% of a dose is recovered unchanged in the urine. After parenteral administration, about 73 +/- 10% of an administered dose is excreted as unchanged substance in the 0- to 12-hour urine. Up to 10% of a dose is eliminated in the form of biotransformation products. The elimination half-life is about 50 to 60 min. In oliguria, the half-life may be prolonged to 8 to 20 hours. The half-life is also prolonged in newborns (2 to 4 hours). The renal clearance of ampicillin is about 194 ml/min after intravenous administration.

Pharmacovigilance System
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory summary of the clinical part of the dossier.

Product Literature
All product literature (SmPC, PIL and labelling) is medically satisfactory.

Clinical Conclusion
MHRA PAR; AMPICILLIN 250 MG, 500 MG, 1 G AND 2 G POWDER FOR SOLUTION FOR INJECTION/INFUSION, PL 28176/0049-0050 AND 0077-0078
There are no objections to the approval of Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion from a clinical point of view.

5. **Overall Conclusion and Benefit-Risk Assessment**

**QUALITY**
The important quality characteristics of Ampicillin 250 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

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

**EFFICACY AND SAFETY**
No new clinical data were submitted and none are required for an application of this type.
No new or unexpected safety concerns arise from this application.
The SmPCs and PIL are satisfactory and consistent with those of the reference products. Satisfactory product labelling has also been submitted.

**BENEFIT: RISK ASSESSMENT**
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ampicillin is considered to have demonstrated the therapeutic value of the compound. The benefit: risk balance is, therefore, considered to be acceptable. Marketing Authorisations should be granted.