CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amoxicilline Aurobindo 250 mg, 500 mg, 1000 mg, powder for solution for injection or infusion
Amoxicilline Aurobindo 2000 mg, powder for solution for infusion
Aurobindo Pharma B.V., the Netherlands

amoxicillin (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 106883-106886

24 January 2013

Pharmacotherapeutic group:	penicillins with extended spectrum
ATC code:	J01CA04
Route of administration:	intravenous, intramuscular
Therapeutic indication:	bacterial infections caused by amoxicillin sensitive microorganisms (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	4 August 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Amoxicilline Aurobindo 250 mg, 500 mg, 1000 mg, powder for solution for injection or infusion and Amoxicilline Aurobindo 2000 mg, powder for solution for infusion from Aurobindo Pharma B.V. The date of authorisation was on 4 August 2011 in the Netherlands.

The product is indicated for bacterial infections caused by amoxicillin sensitive microorganisms:

- lower respiratory tract infections: acute exacerbation of chronic bronchitis, mild to moderate community-acquired pneumonia
- endocarditis prophylaxis
- acute bacterial meningitis caused by *L. monocytogenes*
- complicated urinary tract infections: pyelonephritis
- biliary tract infections as part of combination therapy

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

A comprehensive description of the indications and posology is given in the SPC.

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.
Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

This national procedure concerns a generic application claiming essential similarity with the innovator product is Clamoxyl powder for solution for injection (NL License RVG 07435) which was registered in the Netherlands by GlaxoSmithKline B.V. in 1977 (original product). As the product was withdrawn from the Dutch market in 2005, reference is made to Clamoxyl IV/IM 1 G powder for solution for injection, which has been registered in Belgium since 1978.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Amoxicilline Aurobindo is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is amoxicillin sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, very hygroscopic crystalline powder, which is freely soluble in water, slightly soluble in ethanol and practically insoluble in acetone.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for related substances, residual solvents, particle size, sterility and density. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Amoxicilline Aurobindo contains 250, 500, 1000 or 2000 mg amoxicillin (as amoxicillin sodium). It is a white to off white powder.

The powder for injection and/or infusion is packed in 10 ml (250 and 500 mg), 20 ml (1000 mg) or 100 ml (2000 mg) type-I, clear glass vials with grey bromobutyl rubber stoppers sealed with aluminium seals having an orange (250 mg), light blue (500 mg), grey (1000 mg) or lime green (2000 mg) coloured polypropylene disc.

The product does not contain excipients.

Pharmaceutical development
The development of the product has been described. Bioequivalence studies have not been performed, which is acceptable for this parenteral product. The pharmaceutical development of the product has been adequately performed. The choice of aseptic filling as a sterilization method is considered justified.

No overage is used in the formulation. The compatibility of rubber stoppers with drug product is demonstrated by conducting the stability studies on samples placed in inverted position. Sterility and bacterial endotoxins are tested as part of the finished product specification. They should meet the Ph.Eur. requirements.
The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process for amoxicillin for injection consists of sterilization, vial washing, vial filling and stoppering, vial sealing and inspection. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three smallest production-scale batches of each strength. Process validation for three maximum production-scale batches of each strength will be performed post authorization.

Control of excipients
Nitrogen is used as headspace gas and the specification is according to the Ph.Eur. This is acceptable.

Quality control of drug product
The product specification includes tests for description, identity, water, pH, average fill weight, uniformity of dosage units, related substances, assay, bacterial endotoxins, sterility, particulate matter, reconstitution time and constituted solution. Release and shelf-life requirements are identical, with the exception of assay. The analytical methods have been adequately described and validated. Batch analytical data have been provided on three minimum production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three minimum production-scale batches for each strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Type I clear glass vials closed with grey rubber stoppers, sealed with aluminium seals and a polypropylene disc. No significant changes in the drug product were observed. A photostability study has been carried out on one batch of each strength. There was no significant change. The proposed shelf-life of 2 years with no specific storage conditions is justified.

For i.m. injection, the powder has to be reconstituted with water for injections. The solvents which can be used to reconstitute the product in order to obtain a solution for i.v. injection or i.v. infusion have been justified. Upon reconstitution the solution for injection should be used immediately. Solution intended for infusion should be added to the fluid for infusion immediately. The in-use periods of the infusion (depending on the infusion liquid) have been determined and are included in the approved SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Clamoxyl, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of amoxicillin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Amoxicillin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

Amoxicilline Aurobindo powder for injection and/or infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Amoxicilline Aurobindo 250 mg, 500 mg, 1000 mg and 2000 mg is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan
Amoxicillin was first approved in 1977, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amoxicillin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for another amoxicillin generic, which was approved through an MRP. The indications correspond to the ones accepted for this procedure, but limited to those infections that may require parenteral therapy, and with recent treatment guidelines.

Readability test
The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PIL for Ampicillin/Sulbactam powder for solution for infusion. Both products contain active substances of the same pharmacotherapeutic group: penicillin antibiotics. The leaflets therefore contain the same key messages for safe use. Both PILs have the same layout and design. Separate user testing for the leaflet of Amoxicilline Aurobindo is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amoxicilline Aurobindo 250 mg, 500 mg, 1000 mg, powder for solution for injection or infusion and Amoxicilline Aurobindo 2000 mg, powder for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Clamoxyl. Clamoxyl is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other amoxicillin containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Amoxicilline Aurobindo 250 mg, 500 mg, 1000 mg, powder for solution for injection or infusion and Amoxicilline Aurobindo 2000 mg, powder for solution for infusion were authorised in the Netherlands on 4 August 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of the marketing authorisation.	--	MA transfer	19-9-2011	3-10-2011	Approval	N
replacement of Ph.Eur. Certificate of Suitability (CEP) for Amoxicillin Sodium (Sterile) drug substance with an updated Ph. Eur. CEP.	--	IA	13-8-2012	29-8-2012	Approval	N
Amendment of the batch size range (minimum-maximum) for Amoxicillin for Injection considering the varying commercial/demand requirements of the product.	--	IB	18-10-2012	5-11-2012	Approval	N
Minor changes in the manufacturing process of the finished product with respect to the area classification during sealing of the vials.	--	IB	18-10-2012	5-11-2012	Approval	N