CBG MEB

# Public Assessment Report

# Scientific discussion

# Amoxicilline/Clavulaanzuur Devatis 500 mg/125 mg and 875 mg/125 mg film-coated tablets

# (amoxicillin trihydrate/clavulanic acid)

## NL/H/4029/001-002/DC

## Date: 24 May 2018

**This module reflects the scientific discussion for the approval of Amoxicilline/ Clavulaanzuur Devatis 500 mg/125 mg and 875 mg/125 mg film-coated tablets. The procedure was finalised on 16 February 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amoxicilline/Clavulaanzuur Devatis 500 mg/125 mg and 875 mg/125 mg film-coated tablets from Devatis GmbH.

The product is indicated for the treatment of the following infections in adults and children :

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Augmentin 500 mg/125 mg, registered in the UK, and Augmentan 875 mg/125 mg, film-coated tablets, registered in Germany.
In the Netherlands the innovator product Augmentin (NL License RVG 09840 and 18553) was registered by GlaxoSmithKline B.V. on 2 December 1983 (500 mg/125 mg strength) and 22 August 1996 (875 mg/125 mg strength). The higher strength is no longer registered in the Netherlands.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Amoxicilline/Clavulaanzuur Devatis 500 mg/125 mg is a white to off white, oval-shaped, biconvex film coated tablet, debossed with ‘500’ on one side and ‘D V’ on the other side. Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

Amoxicilline/Clavulaanzuur Devatis 875 mg/125 mg is a white to off white, capsule-shaped, biconvex film coated scored tablet, debossed with ‘875’ on one side and a score line in between ‘D’ and ‘V’ on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

The film-coated tablets are packed in desiccant laminated Al-Al blisters.

The excipients are:
*Tablet core* - croscarmellose sodium (E468), microcrystalline cellulose (E460), colloidal anhydrous silica (E551), magnesium stearate (E470b)
*Film-coating* - polyvinyl alcohol partially hydrolysed (E1203), titanium dioxide (E171), talc (E553b), macrogol 4000 (E1521), methylacrylic acid-ethyl acrylate copolymer 1:1, sodium hydrogen carbonate (E500)

## II.2 Drug Substances

The active substances are amoxicillin trihydrate and potassium clavulanate. Both are established active substances described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is a white or almost white crystalline powder, which is slightly soluble in water. Potassium clavulanate is a white or almost white hygroscopic powder, which is freely soluble in water, slightly soluble in ethanol and very soluble in acetone. No polymorphism or isomerism is described for either active substance.

The CEP procedure is used for both active substances. 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
CEPs have been submitted; therefore no details on the manufacturing process of the active substances have been included.

Quality control of drug substances
The active substance specifications are in line with the Ph.Eur. monographs and the CEPs ( additional requirements for related substances) and additional in-house tests for particle size, residual solvents (only potassium clavulanate, diluted) and microbial limits. The specifications are acceptable in view of the various EU guidelines.
Batch analytical data demonstrating compliance with the active substance specifications have been provided for three batches of each active substance.

Stability of drug substances
*Amoxicillin trihydrate*
The active substance is stable for 6 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

*Potassium clavulanate*
The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients are well known. The main development studies performed were comparative dissolution studies between the test and reference product used in the bioequivalence studies. The choices of the packaging and manufacturing process are justified. Bioequivalence studies have been performed with both tablet strengths against their respective reference product strengths. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a standard process of direct compression followed by film-coating. The manufacturing process has been adequately validated according to relevant European guidelines.
Process validation data on the product has been presented for six pilot scaled batches (three batches per strength). The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements, with some additional in-house controls on functionality related characteristics. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average tablet weight, thickness, length, width, identification, assay, dissolution, uniformity of dosage units, water, hardness, disintegration, related substances, clavulanate polymer and other fluorescent impurities, residual solvent and microbial purity. Except for the limits for assay and some impurities, the release and shelf life specifications are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot scaled batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot scaled batches per strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 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 blisters from OPA/PVC/PE-Copo coated with desiccant sealed with aluminium foils. Results of a photostability study have shown that the drug product is not sensitive to light exposure.
Based on the stability results provided, a shelf-life of 24 months has been granted with storage conditions 'Store below 25°C' and 'Store in the original package in order to protect from moisture'.

Specific measures for 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amoxicilline/Clavulaanzuur Devatis has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.
No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amoxicilline/Clavulaanzuur Devatis is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Augmentin, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 member states agreed that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Amoxicillin trihydrate and potassium clavulanate are well-known active substances 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

## IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Amoxicilline/Clavulaanzuur Devatis 500 mg/125 mg and 875 mg/125 mg (Devatis GmbH, Germany) is compared with the pharmacokinetic profile of the reference products Augmentin 500/125 mg (GSK, UK) and Augmentan 875/125 mg (GSK, Germany).,

The choice of the reference products in the bioequivalence studies has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Analytical/statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The bioequivalence studies were carried out under fasting conditions, which is acceptable. The SmPC states that the dose should be administered with a meal to minimise potential gastrointestinal intolerance.

Bioequivalence studies

***Bioequivalence study I – 500 mg/125 mg***
*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 19 - 44 years. Each subject received a single dose (500 mg amoxicillin, 125 mg clavulanic acid) of one of the 2 formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable.

*Results*
One subject withdrew his consent before dosing in Period II. A total of 71 subjects completed the study and were included in the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of amoxicillin under fasted conditions.

| **Treatment N=71** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** µg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 29.0 ± 6.1 | 29.1 ± 6.2 | 9.1 ± 2.6 | 1.78 (0.75 – 5.0) | 1.4 ± 0.2 |
| **Reference** | 28.8 ± 6.0 | 29.0 ± 6.1 | 9.2 ± 2.5 | 1.75 (0.75 – 4.0) | 1.5 ± 0.3 |
| ***Ratio (90% CI)** | 1.00 (0.98 – 1.03) | -- | 0.99 (0.95 – 1.03) | -- | -- |
| **CV (%)** | 10.2 | -- | 13.6 | -- | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | area under the plasma concentration-time curve from time zero to t hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |
| **CV** | coefficient of variation |

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of clavulanic acid under fasted conditions.

| **Treatment N=71** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** µg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 8.0 ± 2.6 | 8.1 ± 2.6 | 3.3 ± 1.2 | 1.25 (0.75 – 3.33) | 1.2 ± 0.1 |
| **Reference** | 7.6 ± 2.4 | 7.6 ± 2.4 | 3.0 ± 1.1 | 1.25 (1.0 – 3.0) | 1.2 ± 0.2 |
| ***Ratio (90% CI)** | 1.06 (0.97 – 1.15) | -- | 1.08 (0.99 – 1.18) | -- | -- |
| **CV (%)** | 30.3 | -- | 31.9 | -- | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | area under the plasma concentration-time curve from time zero to t hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |
| **CV** | coefficient of variation |

**ln-transformed values*

***Bioequivalence study II – 875 mg/125 mg***

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 90 healthy male subjects, aged 18 – 43 years. Each subject received a single dose (875 mg amoxicillin, 125 mg clavulanic acid) of one of the 2 formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable.

*Results*

One subject was withdrawn at check-in for Period II due to protocol violation (drug abuse). Another subject withdrew his consent before dosing in Period II. The remaining 88 subjects completed the study and were included in the statistical analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of amoxicillin under fasted conditions.

| **Treatment N=88** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** µg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 43.3 ± 9.8 | 43.6 ± 9.9 | 12.6 ± 3.0 | 2.175 (1.0 – 5.0) | 1.5 ± 0.2 |
| **Reference** | 43.7 ± 10.9 | 44.0 ± 11.0 | 13.1 ± 3.3 | 2.0 (1.0 – 6.0) | 1.5 ± 0.2 |
| ***Ratio (90% CI)** | 1.00 (0.96 – 1.04) | -- | 0.96 (0.93 – 1.00) | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| **CV (%)** | 16.9 | -- | 15.8 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**CV** coefficient of variation
**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of clavulanic acid under fasted conditions.

| **Treatment N=88** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** µg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 7.2 ± 2.8 | 7.3 ± 2.8 | 3.0 ± 1.2 | 1.33 (0.67 – 2.67) | 1.2 ± 0.1 |
| **Reference** | 7.4 ± 2.1 | 7.4 ± 2.1 | 3.0 ± 1.0 | 1.33 (1.0 – 3.0) | 1.2 ± 0.2 |
| ***Ratio (90% CI)** | 0.94 (0.88 – 1.01) | -- | 0.96 (0.89 – 1.04) | -- | -- |
| **CV (%)** | 28.0 | -- | 32.1 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**CV** coefficient of variation
**ln-transformed values*

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for $AUC_{0-t}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Amoxicilline/ Clavulaanzuur Devatis 500 mg/125 mg and 875 mg/125 mg is considered bioequivalent with Augmentin 500/125 mg and Augmentan 875/125 mg film-coated tablets.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

## IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Amoxicilline/Clavulaanzuur Devatis.

- Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | • hypersensitivity reactions<br>• Severe skin reactions (e.g. morbilliform rash, acute generalized exanthemous pustulosis (AGEP))<br>• Renal disorders<br>• Hepatic impairment<br>• Antibiotic-associated colitis |

| | |
|---|---|
| Important potential risks | • Overgrowth of non-susceptible organisms<br>• Increased risk of necrotising enterocolitis in neonates |
| Missing information | • Use during pregnancy/lactation<br>• Doses >40 mg/10 mg/kg/day in children <2 years<br>• Use in patients with creatinine clearance less than 30 ml/min |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Augmentin. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH has submitted a bridging report. The PL for Amoxicillin/Clavulaanzuur Devatis film-coated tablets (daughter PL) is predominantly identical in both content and lay out to the approved and successfully user tested package leaflet of Amoxicillin/Clavulaanzuur oral suspension (parent PL, approved in procedure NL/H/3561/001-002/DC). The medicine described in the Daughter PL is presented in a different pharmaceutical form, film-coated tablets instead of an oral solution. This leads to differences between daughter and parent PL in section 3 of the PL. The impact of the differences in section 3 are due to a different way of taking the medicinal product and considered acceptable and not to affect the readability. In addition, the PL text is in line with that of the innovator product Augmentin.
The bridging report submitted has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxicilline/Clavulaanzuur Devatis 500 mg/125 mg and 875 mg/125 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Augmentin film-coated tablets. Augmentin 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 Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amoxicilline/Clavulaanzuur Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 February 2018.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number | Scope | Product Information affected | Date of end of the procedure | Approval/ non approval | Summary/ Justification for refuse |
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| | | | | | |