CBG MEB

Public Assessment Report

Scientific discussion

Amoxiclav Aristo 500 mg/125 mg and 875 mg/125 mg film-coated tablets

(amoxicillin trihydrate and potassium clavulanate)

NL/H/3468/001-002/DC

Date: 12 July 2016

This module reflects the scientific discussion for the approval of Amoxiclav Aristo 500 mg/125 mg and 875 mg/125 mg film-coated tablets. The procedure was finalised on 9 July 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Amoxiclav Aristo 500 mg/125 mg and 875 mg/125 mg film-coated tablets, from Aristo Pharma 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 and 875 mg/125 mg, film-coated tablets (NL License RVG 09840 and 18553) which were registered in the Netherlands by GlaxoSmithKline B.V. on respectively 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

Both Amoxiclav Aristo 500 mg/125 mg and 875 mg/125 mg are white to off white oblong film-coated tablets with a non-functional score line. This line is to facilitate breaking for the ease of swallowing and not to divide the tablet into two equal doses.
The 500 mg/125 mg strength tablet contains as active substances 574.0 mg of amoxicillin trihydrate (equivalent to 500 mg amoxicillin) and 297.6 mg potassium clavulanate diluted with microcrystalline cellulose in the ratio 1:1 (equivalent to 125 mg clavulanic acid).
The 875 mg/125 mg strength tablet contains as active substances 1004.5 mg of amoxicillin trihydrate (equivalent to 875 mg amoxicillin) and 297.6 mg potassium clavulanate diluted with microcrystalline cellulose in the ratio 1:1 (equivalent to 125 clavulanic acid).

The film-coated tablets are packed in OPA/Al/PVC-Al blisters.

The excipients are:
tablet core - cellulose, microcrystalline (E460), crospovidone type A (E1202), croscarmellose sodium (E468), silica, colloidal anhydrous (E551) and magnesium stearate (E470b)
tablet coating – basic butylated methacrylate copolymer, titanium dioxide (E171), talc (E553b) and macrogol 6000.

II.2 Drug Substances

The active substances are amoxicillin trihydrate and potassium clavulanate diluted with microcrystalline cellulose in the ratio 1:1. 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 crystalline powder, which is freely soluble in water. 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 Ph.Eur.

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

Quality control of drug substances
The drug substance specifications are in line with the Ph.Eur and additional requirements are laid down on the CEPs. The specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three batches for amoxicillin trihydrate. For potassium clavulanate sufficient data have been provided.

Stability of drug substances
The active substance amoxicillin trihydrate is stable for 6 years when stored under the stated conditions. Potassium clavulanate is stable for 48 months at 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained.
It has been explained that there is very limited impact of particle size of both actives on the performance of the product. This explanation – being a justification of absence of drug substance particle size specifications for both actives – is additionally supported by the tight dissolution specifications on both actives: NLT 85% (Q) in 30 min. It has been shown that the dissolution method has sufficiently discriminating ability. The two strengths for both the reference product and the test products are not dose-weight proportional, therefore bioequivalence studies have been performed for both strengths.

Manufacturing process
The manufacturing process consist of a repeating sequence of weighing, blending, compacting, sieving, final blending, compression and film-coating. It is considered a standard process. Full process validation will be performed on three consecutive batches of each strength of the product for commercial batch size.

Control of excipients
The specifications for the excipients are considered acceptable. For the tablet coating ingredient basic butylated methacrylate copolymer adequate specifications were proposed, for all other excipients Ph. Eur. monograph requirements are applicable and herewith acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, uniformity of dosage units (CU), dissolution, assay, degradation products, residual solvents (acetone, 2-propanol), water content and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 4 batches of the 500 mg/125 mg strength and 3 batches of

the 875/125 mg from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 2 batches of each strength in accordance with applicable European guidelines. The batches were stored for 24 months at 25°C/60% RH, 12 months at 30°C/65% RH and 3 or 6 months at 40°C/75% RH. Stability results in both the accelerated and intermediate studies were not satisfactory. The MAH improved the stability behaviour of the drug product by introducing new Alu-Alu blisters having thicker Aluminium layers. With the new stability batches (2 batches per strength) 12 months data at 25°C/60% RH and 30°C/65% RH, and 3 months at 40°C/75% RH have become available. On basis of the data submitted, a shelf life was granted of 24 months for both strengths when stored in the original package in order to protect from moisture. Protection from light is not necessary.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amoxiclav Aristo 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 Amoxiclav Aristo 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

These products are generic formulations 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 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH initially submitted two bioequivalence studies (one for each strength) under fasting conditions. However, as stated in the SmPC of Augmentin, the dose should be administered at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid. As stated in the EMA guideline on the investigation of Bioequivalence, for products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.

Therefore the MAH submitted two additional bioequivalence studies, one for each strength conducted under fed conditions. The four studies are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Amoxiclav Aristo tablets (Aristo Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Augmentin tablets (GlaxoSmithKline S.A., Belgium):

- Study I - A bioequivalence study under fasting conditions with the 500 mg/125 mg strength
- Study II - A bioequivalence study under fasting conditions with the 875 mg/125 mg strength
- Study III - A bioequivalence study under fed conditions with the 500 mg/125 mg strength
- Study IV - A bioequivalence study under fed conditions with the 875 mg/125 mg strength

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

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

Bioequivalence studies

Bioequivalence study I - Amoxiclav Aristo 500 mg/125 mg vs Augmentin under fasted conditions
Design
A single-dose, randomised, balanced, open-label, two-period, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 19-42 years. After an overnight fast each subject received a single dose (500 mg amoxicillin/125 clavulanic acid mg) of one of the 2 formulations. The tablets were administered in solid form with 240 ml. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable.

Results
Four subjects did not return for the second period of the study. Therefore, 36 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 trihydrate under fasted conditions.

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	30307 ± 7286	30599 ± 7307	9026 ± 2350	1.83 (0.83 – 4.0)	1.6 ± 0.3
Reference	30923 ± 5864	31267 ± 5858	9049 ± 2449	1.92 (1.0 – 5.0)	1.8 ± 0.4
***Ratio (90% CI)**	0.97 (0.92 - 1.02)	--	0.99 (0.93 – 1.06)	--	--
CV (%)	13.9	--	16.6	--	--

$AUC_{0-\infty}$	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, t_{max} (median, range)) of clavulanic acid under fasted conditions.

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7886 ± 2627	8210 ± 2297	3136 ± 1221	1.5 (0.83 – 3.0)	1.1 ± 0.7
Reference	8310 ± 2987	8399 ± 2987	3382 ± 1451	1.42 (0.5 – 4.0)	1.2 ± 0.2
***Ratio (90% CI)**	0.98 (0.88 – 1.08)	--	0.96 (0.85 – 1.09)	--	--
CV (%)	25.8	--	32.2	--	--

$AUC_{0-\infty}$	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 – Amoxiclav Aristo 875 mg/125 mg vs Augmentin under fasted conditions

Design

A single-dose, randomised, balanced, open-label, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-43 years. After an overnight fast each subject received a single dose (875 amoxicillin/125 clavulanic acid mg) of one of the 2 formulations. The tablets were administered in solid form with 240 ml. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable.

Results

One subject did not return for the second period of the study. One subjects was excluded for pharmacokinetic analysis due to very low plasma concentrations for amoxicillin as well as for clavulanic acid. As the AUC_t value of this subject was below 5% of the geometric mean of the total population without this subject, it is acceptable to exclude the data of this subject from pharmacokinetic and statistical analysis. Therefore, 38 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 trihydrate under fasted conditions.

Treatment N=38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h

Test	40883 ± 9920	41319 ± 10019	11723 ± 2813	2.0 (1.0 – 4.5)	1.6 ± 0.3
Reference	43442 ± 8049	43808 ± 8136	12138 ± 2882	2.5 (1.0 – 4.55)	1.6 ± 0.2
***Ratio (90% CI)**	0.93 (0.86 – 1.00)	--	0.96 (0.89 – 1.03)	--	--
CV (%)	20.3	--	18.5	--	--

$AUC_{0-\infty}$ 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, t_{max} (median, range)) of Clavulanic acid under fed conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	8812 ± 3961	8898 ± 3938	3520 ± 1772	1.6 (0.83 – 1.6)	1.2 ± 0.8
Reference	8195 ± 3413	8283 ± 3412	3428 ± 1596	1.5 (0.67 – 3.0)	1.2 ± 0.2
***Ratio (90% CI)**	1.05 (0.89 – 1.22)	--	0.99 (0.84 – 1.15)	--	--
CV (%)	41.8	--	42.1	--	--

$AUC_{0-\infty}$ 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*

Bioequivalence study III - Amoxiclav Aristo 500 mg/125 mg vs Augmentin under conditions

Design

A single-dose, randomised, balanced, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 20-44 years. In each study period, subjects were fasted overnight for at least 10 hours prior to start of a high fat, high calorie, non-vegetarian breakfast (911 kcal). After 30 minutes each subject received a single dose (500 mg amoxicillin/125 clavulanic acid mg) of one of the 2 formulations. The tablets were administered in solid form with 240 ml. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable. Instead of at the start of a meal, the formulation was administered 30 min after the start of intake of a meal. Although not fully in accordance with the SmPC, it is considered acceptable.

Results
Two subjects withdrew by not showing up for the second period and one withdrew on his own accord. Therefore, a total of 37 subjects completed the study and were included in the statistical analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin trihydrate under fed conditions.

Treatment N=37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	28570 ± 5675	29008 ± 5843	9167 ± 2523	2.0 (1.33 – 5.5)	1.6 ± 0.4
Reference	28777 ± 5269	29097 ± 5328	9399 ± 2832	2.0 (1.33 – 4.0)	1.7 ± 0.4
***Ratio (90% CI)**	0.99 (0.96-1.02)	--	0.99 (0.91 – 1.07)	--	--
CV (%)	7.5	--	20.6	--	--

$AUC_{0-\infty}$ 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 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fed conditions.

Treatment N=37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5450 ± 2332	5528 ± 2335	2318 ± 1082	1.83 (1.33 – 4.0)	1.1 ± 0.2
Reference	5613 ± 2177	5695 ± 2184	2301 ± 1076	1.83 (1.0 – 4.0)	1.1 ± 0.2
***Ratio (90% CI)**	0.94 (0.81 – 1.09)	--	0.98 (0.82 – 1.18)	--	--
CV (%)	38.5	--	47.4	--	--

$AUC_{0-\infty}$ 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 IV – Amoxiclav Aristo 875 mg/125 mg vs Augmentin under fed conditions
Design
A single-dose, randomised, balanced, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 20-42 years. In each study period, subjects were fasted overnight for at least 10 hours prior to start of a high fat, high calorie, non-vegetarian breakfast (911 kcal). After 30 minutes each subject received a single dose (875 amoxicillin/125 clavulanic acid mg) of one of the 2 formulations. The tablets were administered in solid form with 240 ml. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.33, 1.67, 1.83, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0 and 12.0 hours after administration of the products.

The design of the study is acceptable. Instead of at the start of a meal, the formulation was administered 30 min after the start of intake of a meal. Although not fully in accordance with the SmPC, it is considered acceptable.

Results
One subject did not return to the facility without clarification. Therefore, a total of 39 subjects were eligible for pharmacokinetic analysis.

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin trihydrate under fed conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	44339 ± 8276	45063 ± 8146	12772 ± 4138	2.25 (1.5 – 6.0)	1.6 ± 0.3
Reference	45599 ± 8032	46193 ± 8287	13068 ± 2935	2.5 (1.33 – 5.5)	1.6 ± 0.3
***Ratio (90% CI)**	0.97 (0.92 – 1.01)	--	0.94 (0.86 – 1.03)	--	--
CV (%)	12.1	--	24.8	--	--

$AUC_{0-\infty}$ 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 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Clavulanic acid under fed conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5333 ± 2467	5436 ± 2473	2160 ± 1168	2.0 (1.33 – 5.0)	1.2 ± 0.3
Reference	5351 ± 2716	5433 ± 2713	2131 ± 1234	2.0 (1.33 – 4.5)	1.1 ± 0.2
***Ratio (90% CI)**	1.01 (0.87 – 1.18)	--	1.02 (0.85 – 1.22)	--	--
CV (%)	41.6	--	49.1	--	--

$AUC_{0-\infty}$ 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*

<u>Conclusion on bioequivalence studies</u>
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 Amoxiclav Aristo 500 mg/125 mg

and 875 mg/125 mg, film-coated tablets are considered bioequivalent with Augmentin 500 mg/125 mg and 875 mg/125 mg film-coated tablets under fed conditions.

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 Amoxiclav Aristo.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity • Hepatic impairment
Important potential risks	• Acute generalised exanthemous pustulosis • Antibiotic-associated colitis • Increased risk of neonatal necrotizing enterocolitis (when amoxicillin/clavulanic acid is used prophylactically in women with preterm, premature rupture of the foetal membrane) • Lack of efficacy due to resistance
Missing information	• Exposure during pregnancy • Exposure through human milk • Exposure in children under 2 years

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

For this authorisation, a full user testing report for the 875 mg/125 mg strength and a bridging report for the 500 mg/125 mg strength were provided for the package leaflet (PL). The user testing has been adequately performed and the overall readability/quality of the PL is acceptable. The final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively. Furthermore, there were no problems identified regarding comprehensibility and usefulness of information. The bridging report had been prepared in accordance with the guidance on readability testing and it is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxiclav Aristo 500 mg/125 mg and 875/125 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Augmentin 500 mg/125 mg and 875/125 mg 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, both under fasting and fed conditions.

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 Amoxiclav Aristo 500 mg/125 mg and 875 mg/125 mg film-coated tables with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 July 2015.

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