COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amoxiclav Elpen 875 mg/125 mg powder for oral suspension

(amoxicillin trihydrate and potassium clavulanate)

NL/H/4409/001/DC

Date: 30 October 2019

This module reflects the scientific discussion for the approval of Amoxiclav Elpen. The procedure was finalised at 17 September 2019. 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
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 Elpen 875 mg/125 mg powder for oral suspension from Elpen Pharmaceutical Co. Inc.

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 and 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 product Augmentin 875 mg/125 mg powder for oral suspension in sachet, which has been registered in Italy by GlaxoSmithKline S.p.A. since 27 April 1991.
In the Netherlands, Augmentin 875 mg/125 mg powder for oral suspension is not registered. Augmentin was however authorised as film-coated tablets in the same strength, 875 mg/125 mg (NL Licence RVG 18553); the strength is no longer registered.

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

Amoxiclav Elpen is a white to off-white powder for oral suspension.

The powder is packed in paper-aluminium-polyethylene foil sachets.

Each sachet contains as active substance 875 mg of amoxicillin and 125 mg clavulanic acid, as 1,004.31 mg of amoxicillin trihydrate and 148.91 mg potassium clavulanate.

The excipients are colloidal hydrated silica, aspartame, and orange flavour (glucose syrup dehydrated maize, modified corn starch (E1450), sucrose, alpha tocopherol (E307)).

II.2 Drug Substances

Amoxicillin trihydrate

The active substance is amoxicillin trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Amoxicillin trihydrate is a white or almost white, crystalline powder. It is slightly soluble in water, very slightly soluble in ethanol 96%, practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides. Amoxicillin trihydrate has a single crystal structure and does not exhibit polymorphism.

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 Ph.Eur.

Manufacturing process

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

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

The active substance is stable for six 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 potassium clavulanate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Potassium clavulanate is a white or almost white, hygroscopic powder. It is freely soluble in water. No polymorphism or isomerism is described. The CEP procedure is used for the active substance.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance
The active substance is stable for four years 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients, manufacturing process and packaging is sufficiently justified. The pharmaceutical development and optimization studies as well as the up-scaling studies are all considered acceptable.

One bioequivalence study has been performed. Batch analysis results for both reference bio-batches have been provided. The MAH performed comparative dissolution studies between development batch of the proposed product and corresponding innovator batch. At both pH 6.8, pH 4.5 and pH 1.2 amoxicillin was dissolved for more than 85% within 15 minutes. For clavulanic acid dissolution was over 85% in 15 minutes when dissolved at pH 4.5 and 6.8. At pH.1.2 clavulanic acid did not dissolve in either product. However, the paddle speed used was 75 rpm instead of the required 50 rpm. Since the dissolution studies are complementary to the bioequivalence study and bioequivalence has been demonstrated no further data are requested. The dissolution profiles are comparable.

Manufacturing process
A detailed flow chart for the manufacturing of the drug product is provided. The process consists of three stages: manufacturing the bulk blend, filling and sealing the sachets, and packaging. It can be considered as a standard process. The applied in-process controls are considered adequate. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines. The final drug products were tested in accordance with the final drug product specifications with additionally a leaker test. All batches complied.

Control of excipients
Aspartame, colloidal anhydrous silica, and nitrogen meet the specifications of the respective Ph.Eur. monographs. Orange flavour is adequately controlled according to the manufacturer's specifications. These specifications are 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 weight, water content, assay, related substances, any unspecified impurities and total impurities, clavulanate polymer and other fluorescent impurities, uniformity of dosage units 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 three laboratory and four production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Three laboratory scaled batches and three production scaled batches have been stored for up to 24 months at 25°C/60% RH, up to 24 months at 30°C/65% RH. No obvious trends were observed in any of the batches. An out of specification result in average weight was recorded during the 6th month of testing at 30˚C/65%RH. Since all the other parameters are well within the specifications, the out of specification (OOS) result can be considered as an individual fact which may be related to an analytical error not possible to be detected. Moreover, none of the following time points gave OOS result, either at average weight or at any other attribute tested. Only 6 month stability data for one batch stored at 40°C/75% RH are available, additional batches are included in the stability studies.

On the basis of the data submitted a shelf life was granted of 24 months. The labelled storage conditions are "Store below 30°C. Store in the original package in order to protect from moisture."

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 Elpen has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amoxiclav Elpen 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 and clavulanic acid 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Amoxiclav Elpen 875 mg/125 mg powder for oral suspension (Elpen Pharmaceutical Co. Inc., Greece) is compared with the pharmacokinetic profile of the reference product Augmentin 875 mg/125 mg powder for oral suspension (GlaxoSmithKline S.p.A., Italy).

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

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects, with an average age of 40 years. Each subject received a single dose (875 mg/125 mg) of one of the two formulations.

The sachet was orally administered after an overnight fast of at least ten hours. Prior to administration, the content of the sachet was suspended in a glass with about 50 ml of water and the subjects drank it. The glass was rinsed thoroughly with water and the subjects drank the content again. The total amount of water used for the formulations suspending and administration was 200 ml. Immediately after administration, the subject's oral cavity was checked to confirm complete medication and fluid intake.

A high-fat breakfast immediately followed the administration. The composition of the high-fat breakfast was in accordance with the recommendations given in the CHMP Guideline on the Investigation of Bioequivalence: a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800-1000 kcal) meal. This test meal derived approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4, 5, 6, 7, 8, 10, and 12 hours after administration of the products.

A single dose, crossover study under fed conditions to assess bioequivalence is considered adequate. According to the SmPC of the reference product, the dose should be administered at the start of a meal to minimise potential gastrointestinal intolerance. The bioequivalence study may therefore either be performed under fasted or under fed conditions.

The washout period of 21 days should be sufficient, considering the mean elimination half-lives for amoxicillin and clavulanic acid.

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.

Results

Three subjects were withdrawn from the study during the washout: one subject for personal reasons and two subjects due to adverse events. Therefore, 33 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=33	AUC_{0-t} (mg.h/L)	$AUC_{0-\infty}$ (mg.h/L)	C_{max} (mg/L)	t_{max} (h)	$t_{1/2}$ (h)
Test	33.6 ± 7.2	33.8 ± 7.3	11.5 ± 3.1	1.50 (1.0 – 2.0)	1.47 ± 0.35
Reference	32.7 ± 5.8	33.0 ± 5.8	11.4 ± 2.3	1.25 (0.75 – 2.0)	1.56 ± 0.60
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	--	1.00 (0.95 – 1.06)	--	--
Intra-subject CV (%)	9.6	--	13.3	--	--

$AUC_{0-\infty}$ 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 fed conditions.

Treatment N=33	AUC_{0-t} (mg.h/L)	$AUC_{0-\infty}$ (mg.h/L)	C_{max} (mg/L)	t_{max} (h)	$t_{1/2}$ (h)
Test	5.54 ± 1.72	5.60 ± 1.72	2.32 ± 0.81	1.25 (0.50 – 1.75)	1.08 ± 0.14
Reference	5.71 ± 1.65	5.77 ± 1.66	2.44 ± 0.80	1.25 (0.75 – 3.0)	1.14 ± 0.26
***Ratio (90% CI)**	0.97 (0.93 – 1.01)	--	0.95 (0.91 – 1.00)	--	--
Intra-subject CV (%)	9.6	--	12.3	--	--

$AUC_{0-\infty}$ 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 study</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 study Amoxiclav Elpen is considered bioequivalent with Augmentin.

The MEB has been assured that the bioequivalence study has 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 Elpen.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	N/A
Important potential risks	Bacterial resistance development
Missing information	N/A

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 a bioequivalence study 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 been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amoxiclav Elpen 875 mg/125 mg powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Augmentin 875 mg/125 mg powder for oral suspension. 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 Amoxiclav Elpen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 September 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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