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Public Assessment Report

Scientific discussion

Forcid Solutab 875 mg/125 mg szájban diszpergálódó tabletta

Forcid Solutab 875 mg / 125 mg dispersible tablet
Amoxicillinum trihydricum, Kalii clavulanas

HU/H/0386/001
previously
FI/H/0171/001

Date: 26. 06. 2014

Scientific discussion
during the initial phase

This module reflects the scientific discussion for the approval of Forcid Solutab 875 mg/125 mg dispersible tablet. The procedure was finalised at 29. 10. 2002. For information on changes after this date please refer to the module 'Update'.

This report has been prepared by the original RMS, the Finnish Authority on 26. 06. 2014[S1][S2]**. There has been an RMS-transfer of the product on 27. 06. 2014. The PAR has been and will be updated by the new RMS Hungary.**

Content

I. INTRODUCTION

Marketing authorisation was applied for based on essential similarity with the innovator product. According to the application forms, the applications are made according to the provisions of Article 10(1) of Directive 2001/83/EC, as amended. 2001/83/EC. Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for this amoxicillin-clavulanic acid product.

After the initial approval the product information has been harmonized with the outcome of Augmentin article 30 referral (Ref. EMEA/CHMP/97898/2009).

The product is indicated for the treatment of bacterial infections as agreed in the above mentioned referral. A comprehensive description of the indications and posology is given in the SmPC.

II. QUALITY ASPECTS

II.1 Introduction

The Forcid 875 mg / 125 mg tablet is an immediate release tablet as well as dispersible tablet containing known active substances amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate). The basic formula is composed of typical pharmaceutical ingredients used in manufacture of compressed tablets: dispersible cellulose, microcrystalline cellulose, crospovidone, vanillin, mandarin flavour, lemon flavour, saccharin and magnesium stearate. The tablets are packed in double-sided aluminium laminate (PA/Alu/PVC//Alu) blister packages in an outer carton box.

II.2 Drug Substances

The active substances in Forcid tablets are amoxicillin trihydrate and potassium clavulanate, both well-known active substances described in the European Pharmacopoeia. Amoxicillin trihydrate is a semisynthetic product derived from a fermentation product. It is chemically described as (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. Amoxicillin trihydrate is white or almost white, crystalline powder. It is slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in fatty oils and it dissolves in dilute acids and dilute solutions of alkali hydroxides. The amoxicillin molecule possesses four chiral centers: three in the beta-lactam moiety and one in the side-chain.

Potassium clavulanate is the potassium salt of a clavulanic acid produced by the growth of certain strains of *Streptomyces clavuligerus.* Its chemical name is potassium (2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo-[3.2.0]heptane-2-carboxylate.

Potassium clavulanate is white or almost white, crystalline, hygroscopic powder. It is freely soluble in water, slightly soluble in ethanol (96%) and very slightly soluble in acetone. Potassium clavulanate has two chiral carbons (carbons 2 and 5).

Polymorphism phenomena are not known for amoxicillin trihydrate or potassium clavulanate.

Manufacture

The Certificates of Suitability of Monographs of the European Pharmacopoeia (CEP) have been issued to the manufacturers of amoxicillin trihydrate used in the manufacture of Forcid tablets. The EDQM has granted a CEP also for the manufacturer of potassium clavulanate. Appropriate information on the packaging materials for both active substances is provided.

Specification

Amoxicillin trihydrate and Potassium clavulanate are controlled according to the Ph. Eur. monographs and additional specifications laid down by the Certificates of Suitability and finished product manufacturer. The use or absence of use of material of human or animal origin in the manufacture of substance has been declared in the Certificates of Suitability of both active substances.

Batch analysis data on amoxicillin trihydrate and potassium clavulanate have been provided. All batches comply with the specifications set and conform batch-to-batch consistency.

Stability

In the Certificates of Suitability re-test periods of 5 / 6 years are granted for amoxicillin trihydrate. According to the CEP of potassium clavulanate the re-test period is 3 years if stored under nitrogen at a temperature between 2-8°C.

II.3 Medicinal Product

The strength of the proposed medicinal product is identical with the reference product Augmentin 875 mg /125 mg containing 875 mg amoxicillin and 125 mg clavulanic acid per tablet. The basic formula is composed of typical pharmaceutical ingredients used in the manufacture of compressed tablets: microcrystalline cellulose (diluent), dispersible cellulose (binder), crospovidone (disintegrant), vanillin, mandarin and lemon flavour (flavouring agents), saccharin (sweetening agent) and magnesium stearate (tablet lubricant). The flavouring agents comply with the food flavouring regulations of EU. Other excipients are of compendial quality. Magnesium stearate is of vegetable origin.
Clavulanate is a hygroscopic substance and sensitive to degradation under influence of moisture. As the tablets are not coated, special attention has to be paid to the moisture content of some ingredients.

The aim of the development of Forcid dispersible tablets was to offer optimal patient comfort by using highest possible concentration of active substances while maintaining the desired tablet properties namely ability to be taken whole or after dispersion in some water. The tablet formulation has to comply with the Ph. Eur. requirements for non-coated tablets and in addition complying with specification in the monograph on dispersible tablet is needed. The equivalent bioavailability was confirmed in a bioequivalence study in healthy volunteers using Augmentin 875 mg / 125 mg tablets as reference. Comparative dissolution rates for test and reference product are presented in the dossier.

Manufacture

The manufacturing process is quite simple and commonly used process consisting out of wet granulation step, followed by drying and several mixing steps after which the mixture can be compressed to tablets. Because the clavulanate is sensitive for high levels of moisture, several stages of the manufacturing process will take place in a humidity controlled environment. A flow-chart of the manufacturing process has been provided in the dossier. All critical process parameters have been identified and controlled by appropriate in-process controls.
The manufacturing process has been validated with full-scale production batches using three different batches of amoxicillin trihydrate and three different batches of potassium clavulanate. Validation results have been provided. The data presented show that the production scale batches meet the acceptance criteria of in-process controls and product specification. The validation results demonstrate batch-to-batch consistency.

Product Specification

The specifications are adequately justified. The release and shelf life specification contain all relevant tests and limits for this dosage form. The limits are based on relevant guidelines and batch results. Tests include: colour, appearance, dimensions of tablet, disintegration time,

fineness of dispersion, pH, friability, free water content, uniformity of dosage, identification of active substances, dissolution, microbial purity, assay (HPLC) and related substances (HPLC). Analytical methods are adequately described and suitably validated. Batch analysis data on three batches have been provided. Batch analysis results indicate satisfactory product uniformity.

Stability

Stability tests on the finished product were performed under ICH stability conditions. Stability batches were tested at 25°C / 60% RH. In addition stability tests at intermediate condition of 30°C/ 65% and at accelerated condition of 40°C / 75% RH were conducted. Parameters tested are stability indicating. The stability data provided confirm the proposed shelf life of 24 months when stored below 25°C.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Forcid 875 mg / 125 mg dispersible tablets is adequately established.

Satisfactory chemical and pharmaceutical documentation has been submitted. There are no major deviations from EU and ICH requirements.

The active substances are well known and are described in Ph. Eur. monographs. The quality of the active substances is regarded to be suitable for the intended use and appropriately controlled by the applicant. The excipients are commonly used in these types of formulations. They are compendial or food grade quality. The packaging material is commonly used. The manufacturing process of the finished product is quite simple and has been adequately described. Because the clavulanate is sensitive for high levels of moisture, several stages of the manufacturing process will take place in humidity controlled environment. Appropriate in-process controls are set and the manufacturing process has been adequately validated. Batch analysis results indicate satisfactory product uniformity. Stability data indicate that the product is stable when stored at 25°C for the proposed shelf life.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new data were provided, as the scope of the applicant was to prove essential similarity with an already approved product. The non-clinical overview on the preclinical pharmacology, pharmacokinetics, and toxicology is adequate. There are no preclinical objections to granting the marketing authorisation.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since this amoxicillin-clavulanic acid product 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.3 Discussion on the non-clinical aspects

Abridged applications of products containing a known active ingredient avoid the need for repetitive tests on animals and humans. The marketing authorization application of the originator product contains the full documentation on amoxicillin-clavulanic acid combination.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is an abridged form for Marketing Authorisation for amoxicillin - clavulanic acid preparations which are essentially similar products to Augmentin (SmithKline Beecham) which is already marketed in more than 150 countries world-wide.

No new studies on the pharmacodynamics or clinical efficacy or safety of the product have been submitted except the bioequivalence study.

IV.2 Pharmacokinetics, the b**ioequivalence study**

Bioequivalence between Forcid Solutab 875/125 mg tablet and Augmentin 875 mg tablet, the originator, has been shown. The Applicant carried out one pharmacokinetic (PK) bioequivalence study which was a four way cross-over study with 48 healthy male and female volunteers (single oral dose of 875/125 mg). Forcid Solutab 875/125 mg tablet taken either intact or after prior dispersal was compared with Augmentin 875/125 and Co-Amoksiclav 1 g tablets. The study revealed that clavulanate had considerably higher intra-subject variability regarding both AUC and Cmax (CV = 34.6 % and 33.4 %, respectively) than amoxicillin (CV = 13.4 % and 18.1 %, respectively). For the present study it was assumed that the intra-subject variability of both amoxicillin and clavulanate for the new 875/125 mg tablet would be comparable. With respect to amoxicillin pharmacokinetics the usual bioequivalence range of 0.80 – 1.25 was applicable. Because of the high intra-subject variability, for clavulanate a wider bioequivalence range of 0.70 – 1.43 was considered appropriate. From each subject, plasma samples for assay of amoxicillin and clavulanate were taken upt to 7 hours post dosing. Area under the plasma concentration - time curve and the maximal plasma concentration (AUC0-inf and Cmax) were used as criteria for evaluation of bioequivalence. AUC0-last, Tmax, T½elim, CL/F, VD/F were used as secondary parameters. The PK-parameters were assessed both for amoxicillin and clavulanic acid.

There were no marked differences in the test and reference preparations considering AUC. The 90% confidence intervals (CI) for AUC $_{0\text{-last}}$ as well as AUC $_{0\text{-inf}}$ were within 80–125% range for both active ingredients, and compared to both comparators. The 90% confidence interval for C_{max} for clavulanic acid was within 80–125% range compared to Augmentin. Cmax of clavulanate of Co-Amoksiclav was slightly lower, and the 90% CI fits in the broader interval (0.70 - 1.43) range. The broader interval range can be accepted here with C_{max}, because the products are formally bioequivalent according to AUC, and due to nature of the active ingredient. In general, with antimicrobial agents it essential that concentrations in plasma (and tissue) are above certain minimal level individual for each pathogen. It is not essential from efficacy point of view, how much the maximal concentration is above the minimal inhibitory concentration (MIC). Clinically more relevant is the duration when the concentration is above the MIC. However, this duration (with some more or less artificial MIC) or mean retention time have not been reported.

The wider ranges for the C_{max} were supported also by the fact that there is more variability in the C_{max} values than in the AUC values.

Conclusion on the bioequivalence study: based on the submitted bioequivalence study Forcid Solutab is considered bioequivalent with Augmentin.

IV.3 Risk Management Plan

This is a generic version of amoxicillin-clavulanic acid which is a well-known combination of active substances marketed in the EU for more than 10 years. No safety concerns requiring additional risk minimisation activities have been identified so far. It is the opinion of the RMS that routine pharmacovigilance activities are sufficient and additional risk management plan is not required.

IV.4 Discussion on the clinical aspects

Abridged applications of products containing a known active ingredient avoid the need for repetitive tests on animals and humans. The marketing authorization application of the originator product contains the full documentation on amoxicillin-clavulanic acid. For generic products the bioequivalence studies are pivotal and have been described above in section IV 1.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

It may be concluded that the benefit/risk-ratio of this product is positive and marketing authorisation may be granted.

V.2 Package leaflet and user consultation

The package leaflet 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 during the renewal process. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Modul 6

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
Change in the test procedure	FI/H/071/001/007	IA	25. 01. 2005	08. 02. 2005	approval	no
SmPC update after FI/H/171/01/E01	FI/H/071/001/008	II	24. 02. 2005	21. 07. 2005	approval	no
Submission of new CEP	FI/H/071/001/009	IA	25. 01. 2005	08. 02. 2005	approval	no
Change of the marketing authorisation holder (Yamanouchi to Astellas)	FI/H/071/001/010	IA	15. 09. 205	14. 10. 2005	approval	no
Change in the name of the medicinal product	FI/H/071/001/011	IB	15. 09. 2005	25. 10. 2005	approval	no
Submission of new CEP	FI/H/071/001/012 FI/H/071/001/014	IA	08. 12. 2005	20.12.2005	approval	no
Change of the active substance specification	FI/H/071/001/013	IB	08. 12. 2005	28. 12. 2005	approval	no
Change in the primary packaging material	FI/H/071/001/015	IA	02. 04. 2007	17. 04. 2007	approval	no
Change in the test method and specification	FI/H/071/001/016	II	14. 08. 2007	12. 10. 2007	approval	no
Submission of new CEP	FI/H/071/001/017 FI/H/071/001/018	IA	02. 04. 2007	17. 04. 2007	approval	no
Change of the active substance specification	FI/H/071/001/019	IB	04. 09. 2004	04. 10. 2004	approval	no
Submission of new CEP	FI/H/071/001/020	IA	04. 09. 2007	04. 10. 2007	approval	no
Change in the name/address of the marketing authorisation holder	FI/H/071/001/021	IA	30. 04. 2009	14. 05. 2009	approval	no
Deletion of a manufacturing site	FI/H/071/001/022	IA	30. 04. 2009	14. 05. 2009	approval	no
Change in the SmPC and PIL	FI/H/071/001/024	IB	11. 01. 2011	02. 02. 2011	approval	no
Change in the name/address of the marketing authorisation holder	FI/H/071/001/026	IA	25. 05. 2012	24. 06. 2012	approval	no
Change in the name/address of the marketing authorisation holder	FI/H/071/001/027	IA	01.11.2012	01.12.2012	approval	no
Submission of new CEP	FI/H/071/001/028	IA	16. 01. 2013	15. 02. 2013	approval	no
Change in the name/address of the marketing authorisation holder	FI/H/071/001/029	IA	21. 01. 2013	20. 02. 2013	approval	no