IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension
AMOXICILLIN /CLAVULANIC ACID
PA281/145/2

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IHPRA has granted a marketing authorisation for Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension from Pinewood Laboratories Ltd on 7th December 2012 for the treatement of acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, community acquired pneumonia, cystitis, pyelonephritis, skin and soft tissue infections and bone and joint inections in adults and children .

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Augmentin 125mg/31.25mg per 5ml, Powder for Oral Suspesnion, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for amoxicillin trihydrate and clavulanic acid. Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as Augmentin Paediatric 125mg/31.25mg per 5ml, Powder for Oral Suspension.

The Summary of Product Characteristic (SPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Pinaclav
Name(s) of the active substance(s) (INN)	AMOXICILLIN TRIHYDRATE CLAVULANIC ACID
Pharmacotherapeutic classification (ATC code)	J01CR02

Pharmaceutical form and strength(s)	Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Supsension
Marketing Authorisation Number(s) in Ireland (PA)	PA281/145/2
Marketing Authorisation Holder	Pinewood Laboratories Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension.

II.2 Drug substance

The active substances are amoxicillin trihydrate and potassium clavulanate, established active substances described in the European Pharmacopoeia, and manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification for each active substance is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Pinaclav 125mg/31.25mg per 5ml, Powder for oral suspension is a white to off-white, powder for reconstitution with water. Each 5ml of reconstituted suspension contains amoxicillin trihydrate equivalent to 125mg amoxicillin and potassium clavulanate equivalent to 31.25mg of clavulanic acid. The other ingredients are xanthan gum (E415), hypromellose (E464), aspartame (E951), silicon dioxide, silica colloidal anhydrous, succinic acid, raspberry dry flavour, dry orange flavour 1&2 (contains maltodextrin) and golden syrup dry flavour.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

The ingredients comply with Ph. Eur. or in-house standards and are therefore adequately controlled by the agreed specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for liquid preparations for oral use and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as glass bottles with aluminium screw caps or a ROPP, internally lacquered closure, containing a flowed-in PVC liner.

Evidence has been provided that the packaging complies with relevant Ph. Eur. requirements and EU legislation for use with foodstuffs requirements, where applicable.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored below 25°C. Store in the original container to protect from moisture. Following reconstitution according to the directions the suspension should be stored between 2°C and 8°C and used within 7 days. Do not freeze.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension.

III NON-CLINICAL ASPECTS

This active substance is the same as that present in Augmentin Paediatric 125mg/31.25mg per 5ml, Powder for Oral Suspension on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV CLINICAL ASPECTS

Amoxicillin and potassium clavulanate is a well known active substance with established efficacy and tolerability. This medicinal product is the same as Augmentin Paediatric 125mg/31.25mg per 5ml, Powder for Oral Suspension on the European market.

As this is an “informed consent” procedure, no new clinical information has been supplied, and this is acceptable for this type of procedure.
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Augmentin Paediatric 125mg/31.25mg per 5ml, Powder for Oral Suspension marketed by GlaxoSmithKline (Ireland) Limited.

IV.2 Pharmacokinetics

Absorption
Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent

volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid. Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and nonrenal mechanisms.

IV.3 Pharmacodynamics

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.
Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

IV.4 Clinical Efficacy

As this is an “informed consent” procedure, no new clinical information has been supplied, and this is acceptable for this type of procedure.

IV.5 Clinical Safety

As this is an “informed consent” procedure, no new clinical information has been supplied, and this is acceptable for this type of procedure.

The PSUR cycle will follow the PSUR synchronisation scheme agreed for amoxicillin and potassium clavulanate and PSURs will be submitted every 3 years.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a third country.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation

From a quality and clinical perspective the overall assessment outcome of Pinaclav 125mg/31.25mg per 5ml, Powder for Oral suspension is positive.

Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension is the same as Augmentin Paediatric 125mg/31.25mg per 5ml Powder for Oral Suspension. Augmentin Paediatric 125mg/31.25mg per 5ml Powder for Oral Suspension is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The HPRA, on the basis of the data submitted considered that Pinaclav 125mg/31.25mg per 5ml, Powder for Oral Suspension was the same as the reference product and therefore granted a marketing authorisation.