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Irish Medicines Board
PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Dipyridamole 50 mg/5 ml Oral Suspension
Dipyridamole
PA0281/149/001

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB 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 IMB has granted a marketing authorisation for Dipyridamole 50mg/5ml Oral Suspension, from Pinewood Laboratories Ltd on 2nd May 2014. Dipyridamole 50mg/5ml Oral Suspension is indicated in adults as an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves.

With Ireland as the Reference Member State in this Decentralized Procedure, Pinewood Laboratories Limited is applying for the Marketing Authorisations for Dipyridamole 50mg/5ml Oral Suspension in Ireland and the UK.

This is a prescription-only medicinal product.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product Dipyridamole 50 mg /5ml Oral Suspension Name(s) of the active substance(s) (INN) Dipyridamole Pharmacotherapeutic classification (ATC code) B01AC07 Pharmaceutical form and strength(s) Oral Suspension 50 mg / 5 ml Marketing Authorisation Number(s) in Ireland (PA) PA 281/149/1

Marketing Authorisation Holder Pinewood Laboratories Limited
MRP/DCP No. IE/H/247/01/DC
Reference Member State Ireland
Concerned Member State UK

II QUALITY ASPECTS

II.1. Introduction

This application is for Dipyridamole 50 mg/5 ml Oral Suspension,

II.2 Drug substance

The active substance is Dipyridamole, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification 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
Each 5 ml of oral suspension contains 50mg of dipyridamole.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.

A visual description of the product is included in section 3 of the SmPC.

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)
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer’s 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 have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

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 and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

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 Dipyridamole 50mg/5ml Oral Suspension.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Persantin 100 mg tablets (Boehringer Ingelheim Limited UK) 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

IV.1 Introduction

Dipyridamole is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Persantin 100 mg tablets marketed by Boehringer Ingelheim Limited UK

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product.

To support this application, the applicant originally submitted a study performed under fed conditions:
A single-dose, randomised, cross over, replicated design study was carried out to study the bioavailability and to compare the pharmacokinetic profiles of Dipyridamole 50mg/5ml Oral Suspension (Pinewood Product) with the reference product - Persantin® Dipyridamole 100mg Tablet (Boehringer Ingelheim, Ltd, UK) in healthy male and female volunteers under fed conditions.

However, it was considered that a fed study is insufficient to claim bioequivalence between test and reference product.

As requested, an additional bioequivalence study has been performed by the applicant:
A randomized, single dose, open-label, two-treatment, four-period, two sequence, crossover, replicate, comparative bioavailability study on a new formulation of Dipyridamole 2 x (50mg/5mL) Oral Suspension of Pinewood Healthcare Ltd., Ireland compared with Persantin® 100mg tablet of Boehringer Inge1heim Ltd., UK in 36 healthy, adult, human subjects under fasting condition.

Based on the submitted bioequivalence studies Dipyridamole (50mg/5mL) Oral Suspension, manufactured by Pinewood Healthcare Ltd., Ireland is considered bioequivalent with Persantin 100 mg tablets (Boehringer Ingelheim Limited), according to the Guidance on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. *1*

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Distribution

Owing to its high lipophilicity, log P 3.92 (n-octanol/0.1 N, NaOH), dipyridamole distributes to many organs.
Non-clinical studies indicate that, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart, it does not cross the blood-brain barrier to a significant extent and shows a very low placental transfer. Non-clinical data have also shown that dipyridamole can be excreted in breast milk.
Protein binding of dipyridamole is about 97-99%, primarily it is bound to alpha 1-acid glycoprotein and albumin.
Metabolism

Metabolism of dipyridamole occurs in the liver. Dipyridamole is metabolized by conjugation with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide. In plasma about 80% of the total amount is parent compound, 20% of the total amount is monoglucuronide with oral administration.

Elimination
Dominant half-lives ranging from 2.2 to 3 hours have been calculated after the administration of dipyridamole. A prolonged terminal elimination half-life of approximately 15 h is observed. This terminal elimination phase is of relatively minor importance in that it represents a small proportion of the total AUC, as evidenced by the fact that steady-state is achieved within 2 days with both t.d.s. and q.d.s., regimens. There is no significant accumulation of the drug with repeated dosing. Renal excretion of parent compound is negligible (< 0.5%). Urinary excretion of the glucuronide metabolite is low (5%), the metabolites are mostly (about 95%) excreted via the bile into the faeces, with some evidence of entero-hepatic recirculation. Total clearance is approx. 250 mL/min and mean residence time is approx. 8 h (resulting from an intrinsic MRT of approx. 6.4 h and a mean time of absorption of 1.4 h).

IV.3 Pharmacodynamics

No new studies have been performed and none is required for this type of application.

Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells in vitro and in vivo; the inhibition amounts to 80% at its maximum and occurs dose-dependently at therapeutic concentrations (0.5-2 µg/mL). Consequently, there is an increased concentration of adenosine locally to act on the platelet A_2-receptor, stimulating platelet adenylate cyclase, thereby increasing platelet cAMP levels. Thus, platelet aggregation in response to various stimuli such as PAF, collagen and ADP is inhibited. Reduced platelet aggregation reduces platelet consumption towards normal levels. In addition, adenosine has a vasodilator effect and this is one of the mechanisms by which dipyridamole produces vasodilation.

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. Whilst the inhibition of cAMP-PDE is weak, therapeutic levels inhibit cGMP-PDE, thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as NO).

Dipyridamole also stimulates the biosynthesis and release of prostacyclin by the endothelium.

Dipyridamole reduces the thrombogenicity of subendothelial structures by increasing the concentration of the protective mediator 13-HODE (13-hydroxyoctadecadienic acid)

IV.4 Clinical Efficacy

No new studies have been performed and none is required for this type of application.

IV.5 Clinical Safety

The clinical efficacy of dipyridamole is well established. The bioequivalence study has raised no new or unexpected safety concerns.

A Risk Management Plan is not proposed at this time in line with the known safety profile of the active substance.

The schedule for Periodic Safety Update Reports (PSUR) submission has been addressed in line with this being a generic product. The applicant should follow the **PSUR submission cycle** as adopted in the final version of the European Union Reference Dates (EURD) list.

V OVERALL CONCLUSIONS

Dipyridamole 50mg/5ml Oral Suspension is a generic form of Persantin 100 mg tablets(Boehringer Ingelheim Limited UK). Persantin 100 mg tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted considered that Dipyridamole 50mg/5ml Oral Suspension demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.