**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Pyranistole 200 mg prolonged release capsules
Dipyridamole
PA22865/001/001

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.

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## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Pyranistole 200 mg Prolonged-release Capsules, from Renata Pharmaceuticals (Ireland) Limited, on <date of authorisation> for secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin; an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves.

The applications were submitted under a mutual recognition repeat use procedure with Ireland as the reference member state and Denmark (DK) and Sweden (SE) as the concerned member states.

The original decentralised procedure was submitted in January 2017 under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal product of Persantin Retard 200 mg Modified Release Capsules, with the UK as reference member state and Ireland as concerned member state in the following procedure UK/H/6311/001/DC. The product has been authorised in Ireland since 18th May 2018.

The RMS was transferred from the UK to Ireland on <date>. The current procedure number is IE/H/0830/001/DC.

Pyranistole 200 mg Prolonged-release Capsules is subject to prescription only.

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

| | |
|---|---|
| Name of the product | Pyranistole 200 mg Prolonged-release Capsules |
| Name(s) of the active substance(s) (INN) | Dipyridamole |
| Pharmacotherapeutic classification (ATC code) | B01AC07 |
| Pharmaceutical form and strength(s) | 200 mg Prolonged-release Capsules |
| Marketing Authorisation Number(s) in Ireland (PA) | |
| Marketing Authorisation Holder | Renata Pharmaceuticals (Ireland) Limited |
| MRP/DCP No. | IE/H/0830/001/E/001 |
| Reference Member State | IE |
| Concerned Member State | DK, SE |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Pyranistole 200 mg Prolonged-release Capsules**.**

### 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 prolonged-release capsule contains 200 mg 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/*Ancillary Substances*)

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 Capsules/modified release capsules, 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 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 Pyranistole 200 mg Prolonged-release Capsules.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance is a generic formulation of Persantin 200 mg prolonged-release capsules. 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.

**III.2 Pharmacology**

Not applicable for this product type. Refer to section III.1 'Introduction' detailed above.

**III.3 Pharmacokinetics**

Not applicable for this product type. Refer to section III.1 'Introduction' detailed above.

**III.4 Toxicology**

Not applicable for this product type. Refer to section III.1 'Introduction' detailed above.

**III.5 Ecotoxicity/environmental risk assessment**

Since Pyranistole 200 mg Prolonged-release Capsules is intended for generic substitution. This will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary**.**

**III.6 Discussion on the non-clinical aspects**

There are no objections to the approval of this application from a non-clinical viewpoint.

**IV. CLINICAL ASPECTS**

**IV.1 Introduction**

The pharmacodynamic, pharmacokinetics, clinical efficacy and safety properties of dipyridamole are well known. A comprehensive review of the published literature has been provided by the MAH. The clinical overview has been written by an appropriately qualified person and is considered acceptable.

In support of this application the MAH submitted one pilot and three pivotal bioequivalence studies (one in fasted state, one in feel state and a multi-close steady state study). The study designs of single dose studies under fasting and fed conditions plus a multiple-dose study were appropriate according to the Guideline on pharmacokinetic and clinical evaluation of modified release dosage form (EMA/CPMP/EWP/280/96 Corr1 ).

Overall Conclusion
From the data presented by the MAH for 4 studies (1 pilot and 3 pivotal studies) the 90% confidence interval of the test/reference ratio for AUC and $C_{max}$ values for dipyridamole lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence. (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the test product Dipyridamole 200 mg prolonged-release capsules (Renata (UK) Limited) is bioequivalent to the reference product Persantin Retard 200 mg Modified Release Capsules, Hard (Boehringer Ingelheim Limited, UK).

**IV.2 Pharmacokinetics**

Absorption

Peak plasma concentrations are reached about 2 - 3 hours after administration. Mean peak concentrations at steady state conditions with 150 mg b.d. are 1.43 µg/mL (range 0.705 - 2.75 µg/mL), trough levels are 0.351 µg/mL (range 0.200 - 0.741 µg/mL). With a daily dose of 400 mg, the corresponding peak concentrations are 1.98 µg/mL (range 1.01 - 3.99 µg/mL); trough concentrations are 0.53 µg/mL (range 0.18 - l.01 µg/mL). There is no clinically relevant effect of food on the pharmacokinetics of dipyridamole. The absolute bioavailability is about 70%.

As first pass removes approx. 1/3 of the dose administered, near to complete absorption of dipyridamole prolonged-release capsules can be assumed.

Various kinetic studies at steady state showed, that all pharmacokinetic parameters which are appropriate to characterise the pharmacokinetic properties of prolonged-release preparations are either equivalent or somewhat improved with dipyridamole prolonged-release capsules given b.i.d. compared to dipyridamole tablets administered t.d.s. /q.d.s.: Bioavailability is slightly greater, peak concentrations are similar; trough concentrations are considerably higher and peak trough fluctuation is reduced

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.

Biotransformation
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.

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin, ATC code: B01AC07.

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 thefinal version of the European Union Reference Dates (EURD) list.

### IV.6 Discussion on the clinical aspects

The grant of a Marketing Authorization is recommended for Pyranistole 200 mg Prolonged-release Capsules application from a clinical viewpoint.

## V. OVERALL CONCLUSIONS

Pyranistole 200 mg Prolonged-release Capsules is a generic form of Persantin 200 mg prolonged-release capsules (Boehringer Ingelheim Limited UK), 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Pyranistole 200 mg Prolonged-release Capsules demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The EU reference product used in the initial marketing authorisation application for IE/H/0830/001/DC (i.e., Persantin Retard 200 mg Capsules, PL 00015/0206, MAH = Boehringer Ingelheim Limited) is no longer authorised in the UK. The applicant has not been able to identify a suitable alternative EU reference product on which to base its product information.

In the absence of a suitable authorised EU reference product, the applicant commits to maintaining its product information up-to-date by performing periodic (annual) bibliographical reviews, as well as implementing any recommendations by PRAC or CMDh on an ongoing basis.