COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dipyridamol Glenmark 200 mg, hard modified release capsules

(dipyridamole)

NL/H/4294/001/DC

Date: 30 January 2020

This module reflects the scientific discussion for the approval of Dipyridamol Glenmark 200 mg, hard modified release capsules. The procedure was finalised at 17 January 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

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
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 Dipyridamol Glenmark 200 mg, hard modified release capsules, from Glenmark Arzneimittel GmbH.

The product is indicated:

- For secondary prevention of ischaemic stroke and transient ischaemic attacks in conjunction with acetylsalicylic acid, or as monotherapy if acetylsalicylic acid is contra-indicated.
- As an adjunct to coumarin anticoagulants for prophylaxis of thromboembolism associated with prosthetic heart valves.

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 Persantin Retard 200 mg, modified-release capsules, hard, which has been registered in the United Kingdom by Boehringer Ingelheim since 3 February 1997. Persantin Retard 200 mg, modified-release capsules have been registered in the Netherlands since 4 December 1990 through a national procedure (NL license RVG 14870)

The concerned member states (CMS) involved in this procedure were Denmark, Norway, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dipyridamol Glenmark is a hard gelatine capsule consisting of a red cap and an orange body imprinted with Glenmark Logo ‘G’ on the cap and ‘729’ on the body with black ink and filled with light yellow to yellow coloured pallets. Each modified release capsule contains 200 mg dipyridamole.

The capsules are packed in HDPE bottles with a polypropylene cap and heat seal liner (composed of Alu/Adhesive/PET/HS (product contact layer)). The bottles contain a 5 g molecular sieve pouch and a 5 g silica gel pouch as desiccant.

The excipients are:
Capsule content - tartaric acid, hypromellose, talc, acacia, povidone, hypromellose phthalate, methylacrylic acid - methyl methacrylate copolymer (1:2) and triacetin
Capsule shell - titanium dioxide (E171), iron oxide red (E172), sunset yellow (E110) and gelatin
Printing ink– shellac, iron oxide black (E172) and potassium hydroxide.

II.2 Drug Substance

The active substance is dipyridamole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Dipyridamole is a bright yellow, crystalline powder, practically insoluble in water, slightly soluble in acetone soluble in anhydrous ethanol and dissolves in diluted mineral acids. The solubility is pH dependent and it is freely soluble in acidic pH and very slightly soluble or insoluble in basic pH. Dipyridamole is classified as a BCS class II compound. Dipyridamole is non-hygroscopic and does not contain chiral centre and does therefore not exhibit isomerism. The active substance exhibits polymorphism and two forms are reported.

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 and meets the requirements of the monograph in the Ph.Eur with additional in-house tests for control of polymorphic form, particle size distribution and microbial quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 5 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 is justified and their functions explained. Risk assessment was used throughout development to identify potentially high risk formulation and process variables, and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Based on the risk assessment, attributes having medium/high impact on the drug product critical quality attributes were further investigated during formulation development. Assay, content uniformity, dissolution, residual solvent, water content and related substances were considered critical quality attributes.

Sufficient details are provided for both drug formulation and manufacturing process development. A total of three bioequivalence studies have been submitted; under fasting conditions, under fed conditions and steady state fed conditions. Sufficient information on the dissolution characteristics has been provided comparing the test product to the innovator product. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process is considered a non-standard process and consists of the coating of pallets followed by drug loading and enteric coating of the drug loaded pellets to control the drug release. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with their respective monographs in the Ph. Eur. Additionally, tartaric acid pellets, hypromellose, hypromellose phthalate and triacetin are controlled by additional in-house specifications which have all been validated. The 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 description, identification, average fill weight, dissolution, uniformity of dosage units, related substances, assay, residual solvents, water content and microbial quality. 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 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH (up to 12 months). Additionally, the MAH provides stability data for bulk packaging as well as photostability and in-use stability data. On basis of the

data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'This medicinal product does not require any special storage conditions. Store in the original package with desiccant in order to protect from moisture. Keep the bottle tightly closed.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The hard capsules used contain bovine gelatine. Suitable TSE/BSE statements CEPs are provided from each manufacturer/supplier. Triacetin is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dipyridamol Glenmark 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 Dipyridamol Glenmark 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 Persantin Retard 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

Dipyridamole is a well-known active substance 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 three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dipyridamol Glenmark 200 mg, hard modified release capsules (Glenmark Arzneimittel GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Persantin Retard 200 mg, modified-release capsules, hard (Boehringer Ingelheim, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Study I – single dose under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 31.07 years (mean) ± 5.53 (SD). Each subject received a single dose (200 mg) of one of the 2 dipyridamole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected at pre-dose and 0.00, 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 28, 30, 32, 36, 48 hours after administration of the products.

The design of the study is acceptable. A single dose study under fasted conditions is part of the assessment of modified released formulations. The wash-out period of 10 days is sufficient.

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

A total of 43 subjects completed the study successfully as one subject was discontinued from the study. This subject discontinued from the study due to adverse event (vomiting) during period I after dosing. Three subjects were excluded from the pharmacokinetic and statistical

analysis due to the fact that they had experienced emesis within dosing interval. Therefore, a total of 40 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=40	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	12626 ± 4887	12836 ± 5000	2162 ± 630	2.67 (1 - 4)	6.11 ± 2.82
Reference	14571 ± 5809	14841 ± 5868	2299 ± 728	2.17 (1.3 - 4)	6.70 ± 2.53
***Ratio (90% CI)**	0.88 (0.82-0.95)	0.88 (0.82- 0.94)	0.95 (0.89- 1.00)	--	--
CV (%)	19.3	18.9	15.6	--	--

$AUC_{0-\infty}$ 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*

Study II – single dose under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 33.42 years (mean) ± 5.96 (SD). Each subject received a single dose (200 mg) of one of the 2 dipyridamole formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours followed by a standard high calorie, high fat breakfast which they entirely consumed within the next thirty minutes. The high fat breakfast consisted of omelette, toast, chicken cutlet and milk. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected at pre-dose and 0.00, 0.33, 0.67, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6, 7, 8, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours after administration of the products.

The design of the study is acceptable. A single dose study under fed conditions is part of the assessment of modified released formulations. The wash-out period of 10 days is sufficient.

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

All subjects completed the study. Two subjects were excluded from the pharmacokinetic and statistical analysis due to the fact that they had experienced emesis within dosing interval. Therefore, a total of 34 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dipyridamole under fed conditions.

Treatment N=34	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	13487 ± 6900	13766 ± 7188	1649.5 ± 597	4.5 (3 - 7)	6.3 ± 1.9
Reference	134514 ± 4679	13625 ± 4706	1539 ± 454	5 (3 - 8)	6.02 ± 1.6
***Ratio (90% CI)**	0.96 (0.89- 1.04)	0.97 (0.89- 1.05)	1.06 (0.97-1.15)	--	--
CV (%)	19.8	19.9	20.2	--	--

$AUC_{0-\infty}$ 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*

Study III – steady state under fed conditions

Design

A open-label, multiple-dose, randomised, balanced, two-treatment, two-period, two-sequence, crossover study, steady-state bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 33.7 years (mean) ± 9.9 (SD). Each subject received a single dose (200 mg) of one of the 2 dipyridamole formulations every 12 hours for 5 days (9 total dose administrations). Treatments were administered according to a two-treatment, two-period, two sequence randomisation schedule (AB or BA). The tablets were orally administered with 240 ml water after a normal-caloric meal provided 30 minutes before dosing. There were 2 dosing periods and the interval between the first dose in Period I and the first dose in Period II was 12 days.

Blood samples were collected before each morning and evening dose on Days 1 through 4, then on Day 5 at pre-dose (0-hour; within 5 minutes before dosing) and 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, and 12.00 hours after administration of the products.

The design of the study is acceptable. A single dose study under steady state and fed conditions is part of the assessment of modified released formulations. The wash-out period of 10 days is sufficient.

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
A total of 17 subjects discontinued the study: 7 subjects experienced emesis, 1 subject was discontinued due to headache and 9 subjects withdrew by their own will. Therefore, a total of 27 completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dipyridamole under fed conditions.

Treatment N=27	$AUC_{0-\tau}$ (ng.h/ml)	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	$t_{max,ss}$ h	$C_{\tau,ss}$ (ng/mL)
Test	15917.5 ± 6363.5	2020 ± 806	833 ± 383	3.5 ± 1.1	919 ± 401
Reference	16562 ± 6347	2098 ± 799	893 ± 426.5	3.05 ± 1.5	979 ± 476
***Ratio (90% CI)**	0.96 (0.91-1.01)	0.96 (0.91-1.02)	-	-	0.93 (0.86-1.01)

$AUC_{0-\tau}$ area under the plasma concentration curve during a dosage interval at steady state
$C_{max,ss}$ maximum plasma concentration at steady state
$C_{min,ss}$ maximum plasma concentration at steady state
$t_{max,ss}$ time for maximum concentration at steady state
$C_{\tau,ss}$ Observed plasma concentration at the end of the dosing interval at steady state

**ln-transformed values*

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\tau}$, $AUC_{0-\infty}$, C_{max} and $C_{\tau,ss}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Dipyridamol Glenmark is considered bioequivalent with Persantin.

The MEB has been assured that the bioequivalence studies have 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 Dipyridamol Glenmark.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	- Vasodilator effect in patients at risk (e.g.

	patients with hypotension, severe coronary artery disease, decompensated heart failure) - Use in patients with coagulation disorders
Important potential risks	None
Missing information	None

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 Persantin. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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 6 participants, followed by two rounds with 10 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dipyridamol Glenmark 200 mg, hard modified release capsules has a proven chemical-pharmaceutical quality and is a generic form of Persantin Retard 200 mg, modified-release capsules, hard. Persantin 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 Dipyridamol Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 January 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