Public Assessment Report

Scientific discussion

Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard

(dipyridamole)

NL/H/2913/001/DC

Date: 9 July 2014

This module reflects the scientific discussion for the approval of Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard. The procedure was finalised on 16 February 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 10-12.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard from Sandoz B.V.

The product is indicated:

- For secondary prevention of ischaemic stroke and transient ischaemic attacks.
  Treatment should be combined with acetylsalicylic acid. Dipyridamol Sandoz may be used as monotherapy in patients in whom the use of acetylsalicylic acid is contraindicated.
- As an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralized 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 UK 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 state (CMS) involved in this procedure was Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Dipyridamol Sandoz retard 200 mg is a hard gelatine capsules consisting of a red cap and an orange body. The capsule contains yellow coloured pellets.

The capsules are packed in a HDPE container (white polyethylene bottle) with PP (polypropylene) closure containing 2 desiccants.

The excipients are:
Capsule content - tartaric acid, sucrose, hypromellose, talc, acacia, triacetin, povidone, simethicone, cetostearyl alcohol, cetostearyl ethoxylate, sodium benzoate, methacrylic acid - ethyl acrylate copolymer, hypromellose phthalate
Capsule shell – gelatine, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172)

II.2 Drug Substance

The active substance is dipyrimadole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a bright yellow, crystalline powder, which is practically insoluble in water, freely soluble in acetone and soluble in anhydrous ethanol.

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 European Pharmacopoeia.

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 Ph.Eur., USP and additional standards. Batch analytical data demonstrating compliance with this specification have been provided. The MAH provided data on one batch and committed to include more batch analysis data in the dossier.

Stability of drug substance
The active substance is stable for 60 months 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 MAH mimicked the qualitative composition of the innovator product and the main principles of the gastro-resistant core formulation in gelatin capsules with tartaric acid cores, a hydrophilic acacia barrier layer, a drug layer and modified release coating.
With the selected dissolution method, the core formulation with the various functional layers has been fine-tuned in such way, that the proposed test product and the chosen innovator product show comparable dissolution profiles. Satisfactory data on the discriminating ability of the dissolution method, and the control on particle size distribution of all pellet stages.
Three bioequivalence studies have been performed between the test product of Dipyridamol Sandoz retard 200 mg and the reference product Persantin Retard 200 mg modified-release capsules, in fasting, fed and steady state. The comparative dissolution data between test and reference bio-batches, testing in 3 different media are considered appropriate. All dissolution profiles in the same test medium between test and reference product were similar.
The pharmaceutical development has been sufficiently described and explained.

Manufacturing process
The description of the manufacturing process is sufficiently detailed; sieve and sifting sizes for all pellet stages are listed as well as drying timers and temperatures, and the % limit of detection. Three batches have been validated. Adequate process validation data have been provided for this non-standard manufacturing process. All batch analysis results of the 3 validation batches meet the set drug product specifications.

Control of excipients
The excipients comply with the applicable Ph. Eur. or USP monographs. The specifications are considered acceptable. The orange opaque capsule specification is also appropriate.

Quality control of drug product
The drug product manufacturer has adopted the British Pharmacopoeia (BP) monograph of dipyridamole modified-release capsules. The finished product specification and standard test procedure are in line with the BP. The tests include identification, average weight of capsules, filled contents, uniformity of dosage units by mass variation, locking length, water content, dissolution, related substances, assay, residual solvents and microbial contamination.
Batch analysis results are provided for 3 batches have been provided. All drug product specifications were met.

Stability of drug product
Three batches of capsules have been stored for 24 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH, packed in a HDPE container.
The available photostability data ensures that the drug product is not sensitive to light. Based on the provided data, a shelf life of 24 months if stored not above 25°C can be granted, with the storage condition ‘Keep the container tightly closed in order to protect from moisture’.
The MAH provided in-use stability results in order to substantiate the in-use shelf-life claim in the SmPC, confirming that during the 6 weeks in-use period the BP requirements are met. The approvable in-use stability statement in the SmPC is ‘discard any capsules remaining 6 weeks after first opening’.

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

For gelatin is based on TSE certificates have been provided. For all excipients statements have been provided from suppliers that the materials do not represent a TSE risk. Triacetin is of non-animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dipyridamol Sandoz retard 200 mg, modified-release capsules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to provide the batch analysis data of additional batches of drug substance.
- The MAH committed to re-evaluate the drug product specification on KF water content when results from commercial batches are available. It is intended to restrict the limit.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dipyridamol Sandoz retard 200 mg 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 200 mg, 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 three bioequivalence studies in which Dipyridamol Sandoz retard 200 mg (Sandoz B.V., the Netherlands) was compared with the reference product Persantin Retard 200 mg modified- release capsules (Boehringer Ingelheim, UK). One study was a single-dose study under fasting conditions, one study was a single-dose study under fed condition and the last study was a repeat-dose study under fasting conditions. This is in compliance with the requirements for modified-release formulations according to the European guideline (NfG CPMP/EWP/QWP 1401/98).

The choice of the reference product in the bioequivalence studies has been justified by comparison of compositions of reference products in different member states.

The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study I – single-dose, fasting conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasting conditions in 24 healthy, male (12) and female (12) subjects, aged 19-23 years. 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 10 hours. Subjects did not receive any food until at least 4 hours post-dose. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected within 1 hour before dosing (0 hour sample) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, 24, 32, 48 and 72 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is sufficient.

Results
One subject dropped out from the study in the second period due to gastro-intestinal problems. The data set for statistical pharmacokinetic analysis included the 23 subjects who completed the study.

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

Treatment N=23	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	14.4 ± 6.7	14.7 ± 6.7	1.91 ± 0.77	1.5 - 4.0	10.6 ± 3.2
Reference	14.7 ± 8.1	15.0 ± 8.1	1.88 ± 0.82	1.5 - 3.5	10.7 ± 3.4
***Ratio (90% CI)**	0.98 (0.92 - 1.05)	0.98 (0.93 - 1.05)	1.00 (0.91 - 1.10)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Bioequivalence study II – single-dose, fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 32 healthy, male (15) and female (17) subjects, aged 18-47 years. Each subject received a single dose (200 mg) of one of the 2 dipyridamole formulations. The two treatments were administered with 240 ml of water after the subjects consumed a high fat, high caloric breakfast. The breakfast consists of egg, bacon hash browns, butter, toast and milk. Subjects did not receive any food until at least 4 hours post-dose. The capsules were swallowed whole. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected within 1 hour before dosing (0 hour sample) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, 24, 32, 48 and 72 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is sufficient.

Results
The data set for statistical pharmacokinetic analysis included all (32) subjects completing the study.

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

Treatment N=32	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13.1 ± 4.7	13.4 ± 4.7	1.41 ± 0.48	2 - 6	10.7 ± 3.0
Reference	13.2 ± 4.3	13.5 ± 4.3	1.32 ± 0.42	2 - 8	10.5 ± 3.2
***Ratio (90% CI)**	0.99 (0.93 - 1.05)	0.99 (0.93 - 1.05)	1.04 (0.94 - 1.05)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Bioequivalence study III – multiple-dose, fasting conditions
Design
This was a multiple-dose, randomized, two-treatment, two-period, two-sequence, crossover study under fating conditions involving 25 healthy, male (15) and female (10) subjects aged 19-27 years. The products were administered for 5 consecutive days. The two treatments were administered with 240 ml of water. Subjects did not receive any food until at least 4 hours post-dose on days 5 of each treatment period. The capsules were swallowed whole. The doses in the two treatment periods were separated by a washout period of 10 days.

Blood samples were collected within 1 hour before dosing (0 hour sample) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, 24 hours after administration of the products on the last day of each period.

Results
Five subjects were withdrew for adverse effects or personal reasons. The data set for statistical pharmacokinetic analysis included all (20) subjects who completed the study

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (range)) of dipyrimadole in steady state

Treatment N=20	**AUC_{0-t}** µg.h/ml	**C_{max}** µg.h/ml	**C_{min}** µg/ml	**t_{max}** h	**Fluct.** %
Test	13.7 ± 4.2	1.93 ± 0.50	0.20 ± 0.09	1.5 - 5.0	316 ± 73
Reference	13.5 ± 5.4	1.95 ± 0.72	0.20 ± 0.11	1.5 - 3.0	319 ± 73
***Ratio (90% CI)**	1.03 (0.98 - 1.11)	1.02 (0.93 - 1.14)	0.99 (0.92 - 1.09)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
Fluct%	fluctuation index

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and C_{min} are within the bioequivalence acceptance range of 0.80–1.25. Food did not influence the exposure of dipyridamole after administration of the test product. Based on the submitted bioequivalence studies Dipyridamol Sandoz retard 200 mg is considered bioequivalent with Persantin Retard 200 mg, modified-release capsules, hard under fasting and fed conditions, and in steady state.

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 Sandoz retard 200 mg.

Summary table of safety concerns as approved in RMP

Important identified risks	Angina pectoris
	Hepatobiliary disorders including cholangitis and gallstones
	Hypersensitivity reactions, including rash, urticaria, angioedema and anaphylactic reactions
	Increased bleeding during or after surgery
	Hypotension
	Thrombocytopenia
	Aggravation of myasthenia gravis
Important potential risks	None
Important missing information	Pregnancy and Lactation
	Use in children < 18 years

The member states agreed that routine pharmacovigilance activities and risk minimisation activities are sufficient for this product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Persantin Retard 200 mg, modified-release capsules, hard. No new clinical studies were conducted. The MAH demonstrated through a 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

No user consultation with target patient groups was performed on the package leaflet (PL). Instead, a bridging report was submitted, making reference to the originator product Persantin Retard 200 mg. The bridging to the innovator and the approved design and layout style of the MAH meet the requirements of the bridging guideline. Therefore, the member states agree that there is no need for a full consultation test.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Persantin Retard 200 mg. Persantin Retard 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 for modified-release formulations under fasted and fed conditions, and at steady state.

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 Sandoz retard 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 15 February 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Summary Public Assessment Report

Generics

Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard

dipyridamole

NL/H/2913/001/DC

Date: 9 July 2014

Summary Public Assessment Report

Generics

Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard

Active substance: dipyridamole

This is a summary of the public assessment report (PAR) for Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Dipyridamol Sandoz retard.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard and what is it used for?
Dipyridamol Sandoz retard 200 mg is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Persantin Retard 200 mg, modified-release capsules.

This medicine is used to help stop blood clots (thrombosis) forming. It is prescribed in the following cases:

- to prevent the recurrence of stroke (cerebral infarction) or a short-term obstruction of blood flow in the brains (called TIA) after a stroke or TIA. This medicine should be used in combination with acetylsalicylic acid, unless patients are allergic to acetylsalicylic acid.
- in combination with other blood coagulation inhibitory agents as an adjunct to surgery in which a heart valve is replaced by a mechanical valve, in order to prevent the formation of clots in the blood stream.

How is this medicine used?
The medicine can only be obtained with a prescription. The recommended dose is one capsule twice a day, usually one capsule in the morning and one in the evening. It is best to take it with food and to swallow the capsule whole with water, without crushing or chewing it.

How does this medicine work?
Dipyridamole is an anti-thrombotic agent. It helps to stop blood clots forming and thus reduces the risk of a blood clot blocking a blood vessel.

How has this medicine been studied?
Because Dipyridamol Sandoz retard 200 mg is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Persantin retard 200 mg, modified-release capsules. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of this medicine?
Because Dipyridamol Sandoz retard is a generic medicine and is bioequivalent to the reference medicine Persantin Retard 200 mg, its benefits and risks are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, this medicine has been shown to have comparable quality and to be bioequivalent to Persantin Retard 200 mg. Therefore, the view was that, as for Persantin Retard 200 mg, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product

characteristics and the package leaflet for Dipyridamol Sandoz retard 200 mg, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about this medicine
In the Netherlands, the marketing authorisation for Dipyridamol Sandoz retard 200 mg, modified-release capsules, hard was granted on 18 March 2014.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human. For more information about treatment with Dipyridamol Sandoz retard 200 mg, read the package leaflet (http://mri.medagencies.org/download/NL_H_2913_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in July 2014.