Attia 200 mg Modified-Release Capsules, Hard
(dipyridamole)
PL 08553/0458

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dr Reddy’s Laboratories (UK) Limited a Marketing Authorisation for the medicinal product Attia 200 mg Modified-Release Capsules, Hard (PL 08553/0458) on 31 August 2012. This medicine is only available on prescription from your doctor and is used to:

- help prevent blood clots, which sometimes occur with the use of artificial heart valves
- reduce the risk of having another stroke (a blood clot in the brain) in people who have already suffered a stroke.

Attia 200 mg Modified-Release Capsules, Hard contain the active ingredient, dipiridamole. Dipiridamole belongs to a group of medicines called anti-thrombotic agents, which are used to prevent the formation of blood clots. Each capsule contains 200 mg dipiridamole, which is slowly released in the body over a number of hours.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Attia 200 mg Modified-Release Capsules, Hard outweigh the risks and a Marketing Authorisation was granted.
Attia 200 mg Modified-Release Capsules, Hard
(dipyridamole)
PL 08553/0458

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Dr Reddy’s Laboratories (UK) Limited a Marketing Authorisation for the medicinal product Attia 200 mg Modified-Release Capsules, Hard (PL 08553/0458) on 31 August 2012. The product is a prescription-only medicine indicated as:

- 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.

This application was submitted under Article 10(1) of Directive 2001/83/EC (as amended), claiming to be a generic medicinal product of Persantin Retard 200 mg Capsules (Boehringer Ingelheim Limited, UK), which was first authorised in the UK on 03 February 1997.

The active ingredient, dipyridamole, is a platelet adhesion inhibitor that may function by increasing platelet cyclic adenosine monophosphate (cAMP) concentrations by inhibiting adenosine uptake. The increased levels of cAMP inhibit adhesion of the platelets. It also inhibits platelet cyclic guanosine monophosphate (cGMP) phosphodiesterase with in turn inhibits platelet aggregation and activations. Dipyridamole also stimulates prostacyclin synthesis and potentiates the antiplatelet effects of prostacyclin. All of these effects are reversible.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

Three bioequivalence studies were submitted to support this application, comparing the applicant’s test product Dipyridamole Retard 200 mg Modified Release Capsules (manufactured by Dr. Reddy’s Laboratories Ltd, India) with the reference product Persantin Retard 200 mg Modified Release Capsules (Boehringer Ingelheim Limited, UK) under fasting, fed and steady state conditions. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Attia 200 mg Modified-Release Capsules, Hard outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Dipyridamole
Chemical Name: 2,2’,2”,2””-[4,8-di(piperidin-1-yl)pyrimidol[5,4-d]pyrimidine-2,6-diyl]dinitrilo]tetraethanol;
Ethanol,2,2’,2”,2””-[4,8-di(piperidin-1-yl)pyrimidol[5,4-d]pyrimidine-2,6-diyl]dinitrilo]tetrakis
Molecular Formula: C_{24}H_{40}N_{8}O_{4}
Structure

Molecular weight: 504.6
Appearance: A bright yellow crystalline powder.
Solubility Practically insoluble in water and in ether, freely soluble in acetone, soluble in ethanol. It dissolves in dilute mineral acid solutions.

Dipyridamole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance dipyridamole are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the capsule, capsule shells and printing ink namely tartaric acid, hypromellose, povidone, acacia, talc, methacrylic acid-methyl methacrylate copolymer (1:2), hypromellose phthalate, dimethicone, triacetin, stearic acid, gelatin, brilliant blue (E133), ponceau 4R (E124), quinoline yellow (E104), titanium dioxide (E171), sodium lauryl sulphate, shellac, and potassium hydroxide. Appropriate justification for the inclusion of each excipient has been provided.

With the exception of brilliant blue (E133), ponceau 4R (E124) and quinoline yellow (E104), all excipients comply with their respective European Pharmacopoeia monographs. Brilliant blue (E133), ponceau 4R (E124) and quinoline yellow (E104) are controlled to suitable in-house specifications and the specifications are also in compliance with current EU Directives (Directive 2009/35/EC of 23 April 2009, Annex I to Directive 94/36/EC and Annex to Commission Directive 95/45/EC of 26 July 1995) concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.
With the exception of gelatin, none of the excipients contains materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product Persantin Retard 200mg Capsules (Boehringer Ingelheim Limited, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution and impurity profiles have been provided for this product and the reference product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future production-scale batches.

**Control of Finished Product**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The tablets are packaged in white high-density polyethylene (HDPE) bottles, with child resistant plastic caps containing molecular sieve pillow pouches as desiccant, in pack sizes of 30 and 60 (2x30) hard capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the product stored in the unopened HPDE bottle, with the storage conditions ‘Store in the original package in order to protect from moisture. Keep the bottle tightly closed’. After first
opening the HDPE bottle, the product should be used within 15 days. This medicinal product does not require any special temperature storage precautions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

User testing of the package leaflet has been accepted, based on the results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended, and a bridging report provided by the applicant that makes reference to the user tested 2-column format house style of the PILs for Repaglinide 0.5 mg, 1 mg and 2 mg Tablets, Mycophenolate mofetil 250 mg hard Capsules and Quetiapine 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated Tablets.

**MAA (Marketing Authorisation Application) Form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
NON-Clinical Assessment

Pharmacodynamics, pharmacokinetics and toxicology
As the pharmacodynamic, pharmacokinetic and toxicological properties of dipyridamole are well-known, no further non-clinical studies are required and none have been provided.

Non-clinical expert report (non-clinical overview)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Conclusion
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of dipyridamole is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence studies:

Study 1
A randomised, open label, single-dose, two-treatment, two-sequence, two-period, crossover study to compare the pharmacokinetics of the test product Dipyridamole Retard 200 mg Modified Release Capsules (manufactured by Dr Reddy’s Laboratories Ltd, India) versus the reference product Persantin Retard 200 mg Modified Release Capsules (Boehringer Ingelheim Limited, UK) in healthy adult male subjects under fasting conditions.

The subjects were administered one capsule of either the test or the reference product with 240±2 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

| Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI]) of dipyridamole | | |
|---|---|---|---|
| | Geometric Least Square Means | Test/Ref Ratio (% | 90% CI |
| | Dipyridamole Retard 200mg (Test) | Persantin Retard 200mg (Reference) | | |
| Cmax (ng/mL) | 2321.4884 | 2426.2032 | 95.68 | 89.25-102.59 |
| AUC0-t (ng hr/mL) | 14767.2118 | 16764.3010 | 88.09 | 81.20-95.56 |
| AUC0-inf (ng.hr/mL) | 15360.2599 | 17146.9260 | 89.58 | 82.74-96.99 |

* Cmax: maximum plasma concentration
* AUC0-t: area under the plasma concentration-time curve from time zero to t hours
* AUC0-inf: area under the plasma concentration-time curve from time zero to infinity

Ratios and 90% CI calculated from ln-transformed data

Study 2
A randomised, open label, single-dose, two-treatment, two-sequence, two-period, crossover study to compare the pharmacokinetics of the test product Dipyridamole Retard 200 mg Modified Release Capsules (manufactured by Dr Reddy’s Laboratories Ltd, India) versus the reference product Persantin Retard 200 mg Modified Release Capsules (Boehringer Ingelheim Limited, UK) in healthy adult male subjects under fed conditions.

The subjects were administered one capsule of either the test or the reference product with 240±2 ml of water, 30 minutes after the start of a high fat, high calorie breakfast. The subjects fasted for at least 10 hours prior to the scheduled time for breakfast.
Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was 11 days. The pharmacokinetic results are presented below:

**Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI]) of dipyridamole**

<table>
<thead>
<tr>
<th></th>
<th>Geometric Least Square means</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dipyridamole Retard 200mg</td>
<td>Persantin Retard 200mg</td>
<td></td>
</tr>
<tr>
<td>(Test)</td>
<td>(Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1925.0345</td>
<td>1801.0726</td>
<td>106.88</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt; (ng hr/mL)</td>
<td>15315.5307</td>
<td>15715.7955</td>
<td>97.45</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.hr/mL)</td>
<td>15605.5815</td>
<td>16015.0991</td>
<td>97.44</td>
</tr>
</tbody>
</table>

*C<sub>max</sub>* maximum plasma concentration

*AUC<sub>0-t</sub>* area under the plasma concentration-time curve from time zero to t hours

*AUC<sub>0-inf</sub>* area under the plasma concentration-time curve from time zero to infinity

Ratios and 90% CI calculated from ln-transformed data

**Study 3**

A randomised, open label, multiple-dose, two-sequence, two-period, crossover study to compare the pharmacokinetics of the test product Dipyridamole Retard 200 mg Modified Release Capsules (manufactured by Dr. Reddy’s Laboratories Ltd, India) versus the reference product Persantin Retard 200 mg Modified Release Capsules (Boehringer Ingelheim Limited, UK) in healthy adult male and female subjects under fasting conditions.

The subjects were administered two capsules (one in the morning and one in the evening) of either the test or the reference product for four consecutive days (Days 1 to 4) and one capsule of either the test or the reference product in the morning of Day 5. The capsules were administered with 240±2 ml of water after an overnight fast. Blood samples were collected before each administration on Days 1-5 and before and up to 12 hours after administration on Day 5. The washout period between the treatment phases was 10 days. The pharmacokinetic results are presented below:

**Pharmacokinetic parameters (means±SD, ratios and confidence intervals [CI]) of dipyridamole**

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dipyridamole Retard 200mg</td>
<td>Persantin Retard 200mg</td>
<td></td>
</tr>
<tr>
<td>(Test)</td>
<td>(Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub:ss&lt;/sub&gt; (ng/ml*h)</td>
<td>15951.737±9613.867</td>
<td>15678.065±7096.475</td>
<td>98.746</td>
</tr>
<tr>
<td>C&lt;sub&gt;maxss&lt;/sub&gt; (ng/mL)</td>
<td>2405.969±1195.498</td>
<td>2250.008±848.511</td>
<td>105.026</td>
</tr>
<tr>
<td>C&lt;sub&gt;minss&lt;/sub&gt; (ng/mL)</td>
<td>666.537±472.244</td>
<td>670.483±402.543</td>
<td>96.740</td>
</tr>
</tbody>
</table>

*AUC<sub:ss</sub>* area under the plasma concentration-time curve during the dosage interval at steady state

*C<sub>maxss</sub>* peak drug concentration in the dosing interval at steady state obtained directly from the data without interpolation

*C<sub>minss</sub>* minimum drug concentration in the dosing interval at steady state obtained directly from the data without interpolation

SD Standard deviation

Ratios and 90% CI calculated from ln-transformed data
The *Note for Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80.00 to 125.00 % for AUC and $C_{\text{max}}$ values. The 90 % confidence intervals of the test/reference ratios for AUC$_{0-t}$, AUC$_{ss}$, AUC$_{0-\text{inf}}$, $C_{\text{max}}$ and $C_{\text{maxss}}$ lie within the acceptable limits. Thus, the data support the claim that the applicant’s test product Dipyridamole Retard 200 mg Modified Release Capsules (manufactured by Dr. Reddy’s Laboratories Ltd, India) is bioequivalent to the reference product Persantin Retard 200 mg Modified Release Capsules (Boehringer Ingelheim Limited, UK) under fasting, fed and steady-state conditions.

**EFFICACY**
The efficacy of dipyridamole is well-known. No new efficacy data have been submitted and none are required for this type of application.

**SAFETY**
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence studies.

**PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

**SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**
The SmPC, PIL and labelling are satisfactory from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

**CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**CONCLUSION**
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Attia 200 mg Modified-Release Capsules, Hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of dipyridamole are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s 200 mg modified release capsule (manufactured by Dr. Reddy’s Laboratories Ltd, India) and the reference product Persantin Retard 200 mg Modified Release Capsules (Boehringer Ingelheim Limited, UK) under fasting, fed and steady state conditions.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of dipyridamole is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dipyridamole is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
Attia 200 mg Modified-Release Capsules, Hard
(dipyridamole)
PL 08553/0458

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 11 April 2011.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 18 May 2011.
3. Following assessment of the application the MHRA requested further information relating to the clinical dossier on 14 November 2011 and 22 May 2012.
4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 20 March 2012 and 13 July 2012.
5. The application was granted on 31 August 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.