Public Assessment Report

Decentralised Procedure

Atransipar 200mg/25mg modified-release capsule, hard

(Dipyridamole and acetylsalicylic acid)

Procedure No: UK/H/6060/001/DC

UK Licence Number: PL 44254/0001

Par Laboratories Europe, Ltd.
LAY SUMMARY

Atransipar 200mg/25mg modified-release capsule, hard
(dipyridamole 200mg and acetylsalicylic acid 25 mg)

This is a summary of the Public Assessment Report (PAR) for Atransipar 200mg/25mg modified-release capsule, hard (PL 44254/0001; UK/H/6060/001/DC). It explains how Atransipar 200mg/25mg modified-release capsule, hard 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 Atransipar 200mg/25mg modified-release capsule, hard.

The product will be referred to as Atransipar throughout the remainder of this public assessment report (PAR).

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

What is Atransipar and what is it used for?
Atransipar is a ‘generic medicine’. This means that Atransipar is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Asasantin Retard (Boehringer Ingelheim Limited, UK).

Atransipar is used for people who have had a:
- Stroke
- Transient Ischaemic Attack (TIA)
which are caused by a clot in the brain. This medicine reduces the risk of them happening again.

How does Atransipar work?
Atransipar contains two active substances, dipyridamole and aspirin (acetylsalicylic acid). Both of these active substances belong to a group of medicines called ‘anti-thrombotic medicines’. Aspirin is also a type of medicine called a ‘Non-Steroidal Anti-inflammatory Drug’ (NSAID). Atransipar works by stopping blood clots from forming.

How is Atransipar used?
The pharmaceutical form of this medicine is a modified release capsule, hard and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose is:
- One capsule twice a day
- Usually one in the morning and one in the evening
- Swallow the capsule whole with a glass of water
- Do not crush or chew it

If the patient gets a severe migraine-like headache at the start of treatment they should tell their doctor as they may need to change the patient’s dose for a short period of time. DO NOT take painkillers containing aspirin to treat a headache.

Use in Children
Do not give to children under 16 years. This is because there is a possible association between aspirin
and Reye’s syndrome when given to children.
- Reye’s syndrome is a very rare disease, which can be fatal
- For this reason aspirin should not be given to children aged under 16 years, unless on the advice of a doctor

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Atransipar is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Atransipar have been shown in studies?**
Because Atransipar is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine, Asasantin Retard (Boehringer Ingelheim Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Atransipar?**
Because Atransipar is a generic medicine and is bioequivalent to the reference medicine Asasantin Retard (Boehringer Ingelheim Limited, UK), its possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Atransipar, see section 4 of the package leaflet available on the MHRA website.

**Why was Atransipar approved?**
It was concluded that, in accordance with EU requirements, Atransipar has been shown to have comparable quality and to be bioequivalent to Asasantin Retard (Boehringer Ingelheim Limited, UK). Therefore, the MHRA decided that, as for Asasantin Retard (Boehringer Ingelheim Limited, UK); the benefits are greater than the risks and recommended that Atransipar can be approved for use.

**What measures are being taken to ensure the safe and effective use of Atransipar?**
A risk management plan (RMP) has been developed to ensure that Atransipar is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Atransipar including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously.

**Other information about Atransipar**
Agreement for granting a Marketing Authorisation was given on 19 April 2017 by the UK and EU member states Denmark, The Netherlands, Norway and Sweden.

A Marketing Authorisation was granted in the UK on 26 April 2017.

The full PAR for Atransipar follows this summary.
For more information about treatment with Atransipar read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2017.
TABLE OF CONTENTS

I  Introduction  Page 6
II  Quality aspects  Page 8
III Non-clinical aspects  Page 11
IV  Clinical aspects  Page 12
V  User consultation  Page 15
VI Overall conclusion, benefit/risk assessment and recommendation  Page 15
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Par Laboratories Europe, Ltd, a marketing authorisation for the medicinal product, Atransipar (PL 44254/0001; UK/H/6060/001/DC). The product is a prescription-only medicine (POM) indicated for secondary prevention of ischaemic stroke and transient ischaemic attacks.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Denmark, The Netherlands, Norway and Sweden as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Asasantine LP 200 mg/25 mg gélule à libération prolongée, which was first authorised to Boehringer Ingelheim in France on 09 July 1997. The corresponding reference product in the UK is Asasantin Retard which was first authorised in the UK to Boehringer Ingelheim Limited on 12 May 1998.

The antithrombotic action of the acetylsalicylic acid (aspirin) /dipyridamole combination is based on the different biochemical mechanisms involved. Acetylsalicylic acid (aspirin) inactivates irreversibly the enzyme cyclo-oxygenase in platelets thus preventing the production of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction.

Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells in vitro and in vivo; the inhibition amounts to approximately 80% at maximum and occurs dose-dependently at therapeutic concentrations (0.5 – 2 mcg/ml). Consequently, there is an increased concentration of adenosine locally to act on the platelet A2-receptor, stimulating platelet adenylate cyclase, thereby increasing platelet cAMP levels.

Thus, platelet aggregation in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (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 has also been shown in stroke patients to reduce the density of prothrombotic surface proteins (PAR-1: Thrombin receptor) on platelets as well as to reduce levels of c-reactive protein (CRP) and von Willebrand Factor (vWF). In-vitro investigations have shown that dipyridamole selectively inhibits inflammatory cytokines (MCP-1 and MMP-9) arising from platelet-monocyte interaction. Dipyridamole inhibits phosphodiesterase (PDE) in various tissues.

Whilst the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cGMP-PDE, thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as nitric oxide (NO)).

Dipyridamole increases the release of t-PA from microvascular endothelial cells and was shown to amplify the antithrombotic properties of endothelial cells on thrombus formation on adjacent subendothelial matrix in a dose dependent manner. Dipyridamole is a potent radical scavenger for oxy- and peroxyradicals.

Dipyridamole also stimulates the biosynthesis and release of prostacyclin by the endothelium and reduces the thrombogenicity of subendothelial structures by increasing the concentration of the protective mediator 13-HODE (13-hydroxyoctadecadienic acid).

Whereas acetylsalicylic acid (aspirin) inhibits only platelet aggregation, dipyridamole in addition inhibits platelet activation and adhesion. Therefore an additional benefit from combining both drugs can be expected.
Three bioequivalence studies (two single dose studies conducted under fasting and fed conditions and one multiple dose study conducted under fasting conditions) were submitted to support this application. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 19 April 2017. After a subsequent national phase, licences were granted in the UK on 26 April 2017.
II QUALITY ASPECTS

II.1 Introduction
Each capsule contains dipyridamole 200 mg and acetylsalicylic acid (aspirin) 25 mg as the active ingredients. Other ingredients consist of the pharmaceutical excipients:

*Dipyridamole prolonged-release pellets:*
Prolonged-release coating:
Tartaric acid, hypromellose, talc, acacia, stearic acid, povidone, ethylcellulose, hypromellose phthalate, triacetin and colloidal anhydrous silica.

*Acetylsalicylic acid (aspirin) tablet:*
Core tablet:
Lactose, alginic acid, pregelatinised starch and stearic acid.

Film-coating:
Polyvinyl alcohol-part hydrolysed [E1203], titanium dioxide [E171], talc [E553b], lecithin [E322] and xanthan gum [E415].

Capsule shells:
Capsule cap:
Gelatin, allura red AC [E129], titanium dioxide [E171], sunset yellow FCF [E110] and sodium lauril sulfate.

Capsule body:
Gelatin, iron oxide red [E172], iron oxide yellow [E172], titanium dioxide [E171] and sodium lauril sulfate.

Printing Ink:
Shellac, propylene glycol, black iron oxide [E172] and potassium hydroxide.

The finished product is packed into white high density polyethylene (HDPE) bottles with a child resistant polyethylene screw cap containing a desiccant made from silica gel and is available in a pack size of 60 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances
(1) Dipyridamole
INN: Dipyridamole
Chemical name: \(2,2',2'',2''''-[\{4,8-\text{Di(piperidin-1-yl)}\text{pyrimido}[5,4-\text{d}]\text{pyrimidine-2,6-diyl}d\text{nitrilo}\}\text{tetraethanol}.\)

Structural formula:
Molecular formula: $C_{24}H_{40}N_8O_4$
Molecular mass: 504.6 g/mol
Appearance: Bright yellow, crystalline powder.

Dipyridamole is the subject of a European Pharmacopoeia monograph.

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

(2) Acetylsalicylic acid (aspirin)
INN: Acetylsalicylic acid
Chemical name: 2-(Acetyloxy)benzoic acid.
Structural formula:

![Structural formula of acetylsalicylic acid](image)

Molecular formula: $C_9H_8O_4$
Molecular mass: 180.2 g/mol
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Slightly soluble in water, freely soluble in ethanol (96 per cent).

Acetylsalicylic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, acetylsalicylic acid, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious modified-release capsules, hard containing 200 mg of dipyridamole and 25 mg of acetylsalicylic acid (aspirin) per capsule, that are generic versions of the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film coating and gelatin hard capsule shells which comply with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.
With the exception of lactose and gelatin none of the excipients used contain material of animal or human origin. The supplier of lactose has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are 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 this product.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing processes have been validated at commercial scale batch sizes and have shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation studies on future commercial-scale batches and a satisfactory validation protocol has been provided.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the product**
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened container with the storage condition ‘Store in the original container in order to protect from moisture. Keep the bottle tightly closed. This medicinal product does not require any special temperature storage conditions’. The in-use shelf life of the product is 30 days after first opening the bottle.

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

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of this application from a pharmaceutical viewpoint.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of dipyridamole and acetylsalicylic acid are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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

**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 (ERA)
The applicant has not conducted an in depth environmental risk assessment in accordance with regulatory guidelines (EMEA/CHMP/SWP/4447/00). The applicant calculated the predicted environmental concentration surface water of acetylsalicylic acid to be 0.25 μ/l and 2 μ/l for dipyridamole which exceeds the 0.01 μ/l trigger value for further environment risk assessment. However, it is agreed that the proposed product will be used in place of the reference product and/or other marketed products containing dipyridamole and acetylsalicylic acid. Therefore the risks to the environment are not expected to increase and further environmental assessments are not considered necessary. Appropriate wording has been included in the proposed SmPC and package leaflet regarding the disposal of the proposed product.

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 clinical pharmacology of dipyridamole and acetylsalicylic acid is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of dipyridamole and acetylsalicylic acid.

Based on the data provided, Atransipar (Par Laboratories Europe, Ltd, UK) can be considered bioequivalent to Asasantin Retard (Boehringer Ingelheim Limited, UK).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence studies:

STUDY 1
An open-label, balanced, randomised, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of the applicant’s test product Atransipar (Par Laboratories Europe, Ltd, UK) versus the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least eight hours, subjects were administered a single dose (1 x 200 mg dipyridamole /25 mg acetylsalicylic acid capsule) of the test or reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 4 hours for the analyte acetylsalicylic acid; 12 hours for the analyte salicylic acid and 48 hours for the analyte dipyridamole after each administration. The washout period between the treatment phases was 3 days. The pharmacokinetic results are presented below:

Table: Summary statistics for the pharmacokinetic parameters for analytes acetylsalicylic acid, salicylic acid and dipyridamole are presented below (single dose fasted study):
**Acetylsalicylic acid**

![Table](image)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Least Square Means</th>
<th>T/R Ratio (%)</th>
<th>90% Confidence Interval (%)</th>
<th>ISCV (%)</th>
<th>Power (%)</th>
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<td>103.82</td>
<td>99.66</td>
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*<C><sub>max</sub>* maximum plasma concentration

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

**Salicylic acid**

![Table](image)

<table>
<thead>
<tr>
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<th>Geometric Least Square Means</th>
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**Dipyridamole**

![Table](image)

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**Study Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for acetylsalicylic acid, salicylic acid and dipyridamole (administered under fasting conditions) 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 applicant’s test product is bioequivalent to the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK).

**STUDY 2**

An open-label, balanced, randomised, single-dose, two-treatment, four-period, two-sequence, four-way crossover, oral bioequivalence study of the applicant’s test product Atransipar (Par Laboratories Europe, Ltd, UK) versus the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK) in healthy, adult, subjects under fed conditions.

Following an overnight fast of at least eight hours, subjects were served a high-fat, high-calorie breakfast (971Kcal; 63.6% fat, 14% protein, 21.7% carbohydrate) which was consumed exactly 30
minutes prior to subjects being administered a single dose (1 x 200 mg dipyridamole /25 mg acetylsalicylic acid capsule) of the test or reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 5 hours for the analyte acetylsalicylic acid; 12 hours for the analyte salicylic acid and 48 hours for the analyte dipyridamole after each administration. The washout period between the four treatment phases was 3 days. The pharmacokinetic results are presented below:

Table: Summary statistics for the pharmacokinetic parameters for analytes acetylsalicylic acid, salicylic acid and dipyridamole are presented below (single dose fed study):

**Acetylsalicylic acid**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Least Square Means</th>
<th>T/R Ratio (%)</th>
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**Salicylic acid**

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**Dipyridamole**

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<td>17.39</td>
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**Study Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for acetylsalicylic acid, salicylic acid and dipyridamole (administered under fed conditions) 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 applicant’s test product is bioequivalent to the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK).
STUDY 3
An open-label, balanced, randomised, multiple-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of the applicant’s test product Atransipar (Par Laboratories Europe, Ltd, UK) versus the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK) in healthy, adult, subjects under fasting conditions.

After maintaining at least 8 hours of overnight fasting prior to morning dosing, subjects were dosed orally for 05 consecutive days [twice a day on days 01 to day 04, morning & evening (12 hrs since morning dose) and once a day on day 05, morning] with the test or reference product as per the randomisation schedule with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 4 hours on Day 5 for the analyte acetylsalicylic acid; 12 hours on day 5 for the analyte salicylic acid and 12 hours on day 5 for the analyte dipyridamole after each administration. The washout period between the treatment phases was 6 days. The pharmacokinetic results are presented below:

Table: Summary statistics for the pharmacokinetic parameters for analytes acetylsalicylic acid, salicylic acid and dipyridamole are presented below (multiple dose fasting study):

### Acetylsalicylic acid

<table>
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<tr>
<th>PK Parameter#</th>
<th>Geometric Mean (ng/mL)</th>
<th>Least Square Means</th>
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<tbody>
<tr>
<td>C_{max,05}</td>
<td>Test (T)</td>
<td>Reference (R)</td>
<td>98.68</td>
<td>91.27 - 106.68</td>
<td>26.21</td>
<td>99.64</td>
</tr>
<tr>
<td>AUC_{0-7}</td>
<td>361.4456</td>
<td>344.6888</td>
<td>104.86</td>
<td>100.68 - 109.22</td>
<td>13.50</td>
<td>100.00</td>
</tr>
</tbody>
</table>

#C_{min} data are not available for Acetylsalicylic acid.

### Salicylic acid

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean (ng/mL)</th>
<th>Least Square Means</th>
<th>T/R Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max,55}</td>
<td>Test (T)</td>
<td>Reference (R)</td>
<td>100.28</td>
</tr>
<tr>
<td>AUC_{0-7}</td>
<td>5665.4789</td>
<td>5474.9351</td>
<td>103.48</td>
</tr>
</tbody>
</table>

### Dipyridamole

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean (ng/mL)</th>
<th>Least Square Means</th>
<th>T/R Ratio (%)</th>
<th>90% Confidence Interval (%)</th>
<th>ISCV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{min,55}</td>
<td>Test (T)</td>
<td>Reference (R)</td>
<td>92.97</td>
<td>86.49 - 99.94</td>
<td>24.22</td>
<td>99.88</td>
</tr>
<tr>
<td>C_{max}</td>
<td>2502.9952</td>
<td>2413.4981</td>
<td>103.71</td>
<td>98.77 - 108.89</td>
<td>16.22</td>
<td>100.00</td>
</tr>
<tr>
<td>AUC_{0-7}</td>
<td>16116.2480</td>
<td>16632.6200</td>
<td>96.90</td>
<td>92.16 - 101.88</td>
<td>16.69</td>
<td>100.00</td>
</tr>
</tbody>
</table>
During this study it was observed that 25 subjects who completed the study had vomited at least once during the dosing days in either of the periods and treatments. Considering the extended release pattern of dipyridamole, an additional statistical analysis was performed after removing these 25 subjects and results are given below:

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean</th>
<th>Least Square Means</th>
<th>T/R Ratio (%)</th>
<th>90% Confidence Interval (%)</th>
<th>ISCV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{min,ss} (ng/mL)</td>
<td>623.7890</td>
<td>683.6770</td>
<td>91.24</td>
<td>83.04</td>
<td>100.25</td>
<td>23.97</td>
</tr>
<tr>
<td>C_{max,ss} (ng/mL)</td>
<td>2345.0941</td>
<td>2296.6063</td>
<td>102.11</td>
<td>95.64</td>
<td>109.03</td>
<td>16.55</td>
</tr>
<tr>
<td>AUC_{0-+} (hr*ng/mL)</td>
<td>14900.1010</td>
<td>15536.7670</td>
<td>95.90</td>
<td>89.55</td>
<td>102.71</td>
<td>17.33</td>
</tr>
</tbody>
</table>

**Study Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for acetylsalicylic acid, salicylic acid and dipyridamole (administered at steady state) 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 applicant’s test product is bioequivalent to the reference product Asasantin Retard (Boehringer Ingelheim Limited, UK).

**Overall conclusion for all three studies**

In general, the results of all studies demonstrated bioequivalence of the test formulation with the reference product i.e. under fasting, fed conditions and at steady state, as for all key pharmacokinetic parameters the 90% CI of all ratios were within the 80%-125% range, in line with CHMP guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). In terms of safety, the studies did not raise any major concerns.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for an application of this type.

**IV.5 Clinical safety**

No new safety data were submitted and none were required for this application.

**IV.6 Risk Management Plan (RMP) and Pharmacovigilance System**

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Atransipar. A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding events</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Use in children under 16 years due to risk of Reye’s syndrome</td>
</tr>
<tr>
<td>Use in patients with severe coronary artery disease</td>
</tr>
<tr>
<td>Use in patients with severe hepatic &amp; renal impairment</td>
</tr>
<tr>
<td>Use in pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug interactions with anticoagulants, antiplatelet agents, SSRI’s, anticonvulsants, NSAIDs, cortical steroids, alcohol, hypoglycaemic agents, methotrexate, spironolactone, uricosuric agents, adenosine, and cholinesterase inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

There are no differences from the reference product in terms of proposed uses, strength, maximum pack size or pharmaceutical form that would have any implications for safety. In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is agreed.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet 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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet 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
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dipyridamole and acetylsalicylic acid is considered to have demonstrated the therapeutic value of the compounds. The product is bioequivalent to the marketed reference product and their risk-benefit balance is considered similar and positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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

The approved labelling for this medicine is presented below:

1. Par logo is attributed by pantone 294 colour.
2. Product name and the count band is signified by pantone 3272 colour.
3. Textual matters are illustrated in black colour.
4. Varnished area for Batch Number and Expiry Date is tinted in lightest grey colour.
5. Die-lines are marked with pink colour.
6. Space for internal material code/JDE code.
Description of Colours:
1. Par logo is printed in Pantone 294 colour.
2. Product name and the count band is printed in Pantone 3272 colour.
3. Textual matters are illustrated in black colour.
4. Varnished area for Batch Number and Expiry Date is printed in light grey colour.
5. Die lines are marked with pink colour.
6. Braille font colour is denoted in pink but will only be impressed not printed.
7. Space for internal material code/UDI code.
8. 2D Barcode & Human Readable data will be implemented before Feb 2019.
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>