Public Assessment Report

Scientific discussion

Prasugrel CF 5 mg and 10 mg, film-coated tablets

(prasugrel hydrobromide)

NL/H/4009/001-002/DC

Date: 23 July 2018

This module reflects the scientific discussion for the approval of Prasugrel CF 5 mg and 10 mg, film-coated tablets. The procedure was finalised on 12 April 2018. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
### List of abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Prasugrel CF 5 mg and 10 mg, film-coated tablets, from Centrafarm B.V.

The product, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

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 products Efient 5 mg and 10 mg film-coated tablets which have been registered in the EEA by Daiichi Sankyo Europe GmbH since 23 February 2009 through centralised procedure EU/1/08/503.

The concerned member states (CMS) involved in this procedure were Germany, Spain, France 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

- Prasugrel CF 5 mg is a oval, biconvex, yellow film-coated tablet and contains 5 mg prasugrel (as hydrobromide)
- Prasugrel CF 10 mg is a oval, biconvex, beige film-coated tablet and contains 10 mg prasugrel (as hydrobromide)

The two strengths are dose weight proportional

The film-coated tablets are packed in oPA/Al/PVC/Al blisters.

The excipients are:

**Tablet core** - mannitol (E421), maltodextrin DE 14, lactose monohydrate, microcrystalline cellulose, hypromellose (E 464), crospovidone (type B) and magnesium stearate

**Tablet coating** - Hypromellose (E464), lactose monohydrate, triacetin, titanium dioxide (E171), yellow iron oxide (E172) and only for the 10 mg strength red iron oxide (E172).

II.2 Drug Substance

The active substance is prasugrel hydrobromide, an established active substance, not described in the European Pharmacopoeia (Ph.Eur.). Prasugrel hydrobromide is a off-white to brownish powder. It is sparingly soluble at low pH and solubility further decreases with increasing pH. The active substance is present as a racemate. The active substance shows polymorphism and the anhydrous (form I) is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.
Manufacturing process
The manufacturing process is a four step synthesis. The starting materials and solvents are adequately described and approved. No metal catalysts are used. The active substance has been adequately characterised. The specifications for the proposed starting materials are also approved. Acceptable specifications have been adopted for solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is established in-house. It contains tests for appearance, identification, water, bromides, sulfated ash, assay, chromatographic purity, and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 commercial batches stored at 5°C (36 months) and 25°C/60% RH (6 months). A significant change in the level of any unspecified impurity was seen after six months storage at accelerated conditions. No significant changes or trends were seen at long term conditions. Based on the provided stability data, the claimed re-test period of 36 months is acceptable. Keep in a well closed container, keep in the original package. Store in a refrigerator at 2°C to 8°C. Protect from light and moisture with desiccant.

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. A bioequivalence study has been performed with the 10 mg film-coated tablets. For the 5 mg film-coated tablets the MAH requested a biowaiver. The provided dissolution studies support bioequivalence. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of fluid bed granulation, mixing, dry granulation, final blending, compression and film-coating and is adequately described. Process validation data on the product have been presented for 3 pilot scale batches per strength in accordance with the relevant European guidelines.

Control of excipients
All excipients, except for the iron oxides, comply with the Ph. Eur. The iron oxides comply with Commission Regulation 231/2012 as amended. All 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 appearance, identification, average mass, uniformity of dosage units by content uniformity, dissolution, assay, related substances, and microbiological 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 3 pilot scale batches per strength from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 pilot scale batches per strength stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. Significant changes have been observed at accelerated conditions and none at long term and intermediate conditions. A performed photostability study showed that the product is stable. On basis of the data submitted, a shelf life was granted of 24 months with the storage condition: “Store below 30°C. Store in the original packaging in order to protect from moisture” is justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
The excipients lactose monohydrate is sourced from healthy animals in the same conditions as for human consumption. No calf rennet or other ruminant materials are used. Lactose monohydrate complies with the CPMP “Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products”. A certificate regarding the TSE/BSE-safety of lactose monohydrate is provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Prasugrel CF 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 Prasugrel CF 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 Efient 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

Prasugrel 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Prasugrel CF 10 mg, film-coated tablets (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product Efient 10 mg film-coated tablets (Daiichi Sankyo Europe GmbH, Germany), under fasting conditions.

The choice of the reference product in the bioequivalence study is accepted, as Efient has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH requested a biowaiver for the 5 mg strength based on the bioequivalence study performed with the 10 mg tablet. As the following criteria have been met, the biowaiver for the 5 mg film-coated tablets has been granted:
- both strengths of Prasugrel (5 mg and 10 mg) film-coated tablets are manufactured by the same manufacturer using the same manufacturing process,
- the qualitative composition of both strengths is the same,
- the composition of the strengths are quantitatively proportional,
- both strengths have appropriate in-vitro dissolution data,
- pharmacokinetics of prasugrel is linear over the dosage range of 5 mg – 10 mg.

Bioequivalence study

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 18-52 years. Each subject received a single dose (10 mg) of one of the 2 prasugrel formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.17, 1.33, 1.50, 1.67, 1.83, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00 hours after administration of the products.

The design of the study is acceptable. A study under fasting conditions is considered appropriate as the product can be administered without food.

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
Two subjects dropped out due to personal reason. Therefore, 70 subjects completed the study were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng.h/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (ng.h/ml)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$t_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>139.5 ± 52</td>
<td>152.8 ± 56</td>
<td>97.5 ± 41</td>
<td>0.5 (0.333 – 2.500)</td>
</tr>
<tr>
<td>Reference</td>
<td>138.1 ± 51</td>
<td>150.0 ± 56</td>
<td>90.6 ± 37</td>
<td>0.5 (0.333 – 2.000)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.00 (0.97-1.04)</td>
<td>--</td>
<td>1.07 (1.00-1.14)</td>
<td>--</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to infinity
$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
$C_{\text{max}}$ maximum plasma concentration
$t_{\text{max}}$ time for maximum concentration

*In-transformed values

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for $\text{AUC}_{0-t}$ and $C_{\text{max}}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Prasugrel CF is considered bioequivalent with Efient.

The MEB has been assured that the bioequivalence study has 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 Prasugrel CF.

- Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Drug-induced hepatic injury</td>
<td>Concomitant use with fibrinolytics, other thienopyridines, warfarin and chronic use of NSAIDs (non-ASA)</td>
</tr>
<tr>
<td>o Intracranial haemorrhage</td>
<td></td>
<td>Paediatric population</td>
</tr>
<tr>
<td>o Gastrointestinal haemorrhage</td>
<td></td>
<td>Pregnant/lactating women</td>
</tr>
<tr>
<td>o Intraocular haemorrhage</td>
<td></td>
<td>Subjects without clinical manifestation of ACS</td>
</tr>
<tr>
<td>o Epistaxis</td>
<td></td>
<td>Subjects with severely compromised cardiac status (cardiogenic shock, class IV CHF, refractory ventricular arrhythmia)</td>
</tr>
<tr>
<td>o PCI-related haemorrhage</td>
<td></td>
<td>Subjects with severe hepatic impairment</td>
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<tr>
<td>o CABG-related haemorrhage</td>
<td></td>
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<tr>
<td>o Associated with prasugrel use prior to coronary angiography in NSTEMI patients</td>
<td></td>
<td></td>
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<tr>
<td>o Other procedure-related haemorrhage</td>
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<tr>
<td>Hypersensitivity including angioedema</td>
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<td>Thrombocytopenia</td>
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<td>Thrombotic thrombocytopenic purpura (TTP)</td>
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The MAH of the generic product should provide educational material before launch in each member state in line with the key elements for the additional risk minimisation measures of the innovator product Efient. This educational material should contain the following key elements:

- A copy of the SmPC
- Emphasis that:
  - Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg.
  - Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.
  - If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5mg should be prescribed.
  - Patients weighing < 60 kg should have a reduced maintenance dose of 5mg.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Efient. 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 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 3 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 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

Prasugrel CF 5 mg and 10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Efient 5 mg and 10 mg film-coated tablets. Efient 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 Prasugrel CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 April 2018.
<table>
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<tr>
<th>Procedure number</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
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