CBG MEB

Public Assessment Report

Scientific discussion

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

(prasugrel hydrobromide)

NL/H/4112/001-002/DC

Date: 24 May 2018

This module reflects the scientific discussion for the approval of Prasugrel Teva 5 mg and 10 mg, film-coated tablets. The procedure was finalised on 9 February 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

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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Prasugrel Teva 5 mg and 10 mg, film-coated tablets, from Teva Nederland 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 state (CMS) involved in this procedure was Hungary.

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

II. QUALITY ASPECTS

II.1 Introduction

- Prasugrel Teva 5 mg is a yellow, oval, film-coated tablet, debossed with “P5” on one side and plain on the other side. Each tablet contains 5 mg prasugrel (as hydrobromide)
- Prasugrel Teva 10 mg is a beige, oval, film-coated tablet, debossed with “P10” on one side and a score line on the other side of the tablet. Each tablet contains 10 mg prasugrel (as hydrobromide) and can be divided into equal doses.

The two strengths are dose weight proportional

The film-coated tablets are packed in:
- OPA/Al/PVC//Al blisters or unit dose blisters
- OPA/Al/PE+desiccant//Al/PE blisters or unit dose blisters.

The excipients are:
Tablet core - microcrystalline cellulose, mannitol, hypromellose, low-substituted hydroxypropyl cellulose, glycerol dibehenate and sucrose stearate
Tablet coating - polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172), iron oxide red (E172) and only for the 5 mg strength black 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 (24 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 24 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. The pharmaceutical development is rather concise, and is strongly based on the composition of the innovator product. It is confirmed that both generic and the innovator product are essentially similar products, although having a drug substance with different salt: hydrochloride (innovator) versus hydrobromide. The qualitative differences in composition refer to the type of disintegrant and different type(s) of lubricant.
Two bioequivalence studies have been performed with the 10 mg film-coated tablets, one under fasting conditions and one under fed conditions. For the 5 mg film-coated tablets the MAH requested a biowaiver based on the bioequivalence study with the 10 mg formulation.

Manufacturing process
The manufacturing process consists of screening, blending, compression and coating and was adequately described. Process validation data on the product have been presented for two batches per strength in accordance with the relevant European guidelines.

Control of excipients
All excipients, except the two film-coat mixtures, comply with the Ph. Eur. The film-coat mixtures comply with in-house specifications. Their components either comply with Ph. Eur. standards or with Commission Regulation (EU) No. 231/2012. 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, uniformity of mass for subdivided parts for the 10 mg strength, identification, dissolution, uniformity of dosage units by content uniformity, assay, impurities/degradation products, water content, identification of colourant, determination of prasugrel base in drug product and microbiological purity. 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 2 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 2 batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable

European guidelines. Slight changes were seen, however remained within the specification limits. A performed photostability study showed that the product is stable. On basis of the data submitted, a shelf life was granted of 24 months without any special storage conditions.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Prasugrel Teva 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 Teva 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Prasugrel Teva 10 mg, film-coated tablets (Teva Nederland B.V., NL) is compared with the pharmacokinetic profile of the reference product Efient 5 mg and 10 mg film-coated tablets (Daiichi Sankyo Europe GmbH, Germany), one under fasting conditions and one under fed conditions.

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

Biowaiver

The applicant requested a biowaiver for the 5 mg strength based on the bioequivalence study performed with the 10 mg tablet. The composition of the core of the 5 and 10 mg tablets is qualitatively the same and quantitatively proportional. The composition of the coating is slightly different but coating components are exempted from this rule for immediate release products according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The biowaiver was, therefore, accepted.

Bioequivalence studies

Bioequivalence study I – fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 58 healthy (26 male/32 female) subjects, aged 21-74 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, 0.42, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 15.00 and 24.00 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 were withdrawn from pharmacokinetic and statistical analysis as they missed one blood sample which could not be collected due to “difficulty with vein”. Therefore, 56 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=56	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	85.1 ± 27.6	90.1 ± 29.3	50.3 ± 18.7	0.5 (0.3 – 2.0)
Reference	83.9 ± 30.0	90.5 ± 33.0	48.4 ± 21.5	0.5 (0.3 – 2.0)
***Ratio (90% CI)**	1.03% (0.99-1.07)	--	1.06 (0.99-1.15)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Bioequivalence study II – fed conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy (19 male/17 female) subjects, aged 21-75 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 30 minutes after the start of a high-fat high-calorie meal. There were 4 dosing periods; each subject received a test and reference product twice. The periods were separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.17, 1.33, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 15.00 and 24.00 hours after administration of the products.

The design of the study is acceptable. A study under fed conditions is considered appropriate as the product can be administered without food. However, the study under fasting conditions is the most relevant. The study under fed conditions is therefore considered supportive.

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 discontinued the study before dosing of period 4, one subject due to personal reasons and one subject due to a positive cotinine test. Since for both test and reference product there was one subject who missed one dose, pharmacokinetic and statistical analyses are based on n=71 for both test and reference product.

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

Treatment N=71	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	99.2 ± 31.9	104.3 ± 33.5	33.0 ± 16.7	1.3 (0.3 – 3.5)
Reference	99.2 ± 34.3	101.8 ± 34.6	33.5 ± 16.6	1.3 (0.5 – 5.0)
***Ratio (90% CI)**	1.00% (0.96 – 1.05)	-	0.98% (0.88 – 1.10)	-
$AUC_{0-\infty}$ 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				

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Prasugrel Teva 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 Teva.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Bleeding o Intracranial haemorrhage o Gastrointestinal haemorrhage o Intraocular haemorrhage o Epistaxis o PCI-related haemorrhage o CABG-related haemorrhage

	o Associated with prasugrel use prior to coronary angiography in NSTEMI patients o Other procedure-related haemorrhage • Hypersensitivity including angioedema • Thrombocytopenia • Thrombotic thrombocytopenic purpura (TTP)
Important potential risks	• Drug-induced hepatic injury • Potential off-label use in patients with prior TIA/stroke • Colorectal cancer
Missing information	• Concomitant use with fibrinolytics, other thienopyridines, warfarin and chronic use of NSAIDs (non-ASA) • Paediatric population • Pregnant/lactating women • Subjects without clinical manifestation of ACS • Subjects with severly compromised cardiac status (cardiogenic shock, class IV CHF, refractory ventricular arrhythmia) • Subjects with severe hepatic impairment

The MAH of the generic product should provide educational material before launch in each member state. in line with the key elements for the aRMM 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 Teva 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 Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 February 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse