IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Prasugrel Krka 10 mg Film-coated tablets
Prasugrel
PA1347/080/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number HU/H/0508/001-002/DC with HU as RMS. The responsibility of RMS was transferred to Ireland on 09/03/2021 under procedure number IE/H/1149/001-002/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1347/080/001-002
Marketing Authorisation Holder: KRKA, d.d., Novo mesto

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The HU public assessment report published at the time of the initial marketing authorisation is provided herein.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Prasugrel Krka 5 mg, 10 mg film-coated tablet, from KRKA d.d.

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 0507: BG, CZ, EE, HR, LT, LV, RO, SI.

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

II. QUALITY ASPECTS

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II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Prasugrel Krka 5 mg, 10 mg film-coated tablet via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e a generic application). The products have been developed by KRKA dd., Novo mesto.

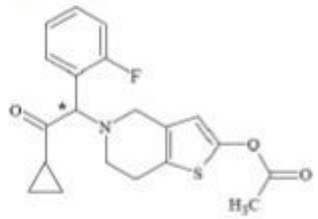
Reference products are Efient 5 mg and 10 mg film-coated tablets (containing 5 mg and 10 mg prasugrel (in hydrochlorid form) as active ingredient) which have been registered in the EEA by Daiichi Sankyo Europe GmbH since 23 February 2009 through centralised procedure EU/1/08/503.

II.2 Drug substances

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

I.N.N.: Prasugrel
Chemical name: 5-[(1RS)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c] pyridin-2-yl acetate

Structure:



The active substance is a white to slightly brown powder. It is practically insoluble in water, slightly soluble in methanol, sparingly soluble in dichloromethane, soluble in ethyl acetate and acetonitrile and freely soluble in acetone. Prasugrel is a chiral molecule containing one asymmetric carbon atom; the manufacturing process produces racemic mixture. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

The structural elucidation of prasugrel has been carried out by elemental analysis and the following spectroscopic methods: IR, NMR, MS, UV, DSC, and XRD. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Prasugrel is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: solubility, identification by IR, loss on drying (Karl-Fisher), sulphated ash, related substances, assay, residual solvent, particle size and microbiological quality. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.
Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period and storage condition is acceptable.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the development was to develop a product with Prasugrel as active ingredient in a formulation bioequivalent to the reference product Efient® film-coated tablets. A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.

5 mg film-coated tablets: Pale brownish yellow, oval, biconvex, film-coated tablets, dimensions 8.5 mm x 4.5 mm.
10 mg film-coated tablets: Pink, oval, slightly biconvex, film-coated tablets, dimensions 10.5 mm x 5.5 mm.
The excipients used in the finished product are cellulose, microcrystalline, macrogol 4000, poloxamer 188, fumaric acid, croscarmellose sodium, hydrophobic colloidal silica, mannitol, magnesium stearate and film-coating (hypromellose, lactose monohydrate, titanium dioxide, triacetin and yellow or red iron oxide).

All excipients used comply with their respective European Pharmacopoeia or USP/NF monograph. Compliance of the product with the general monograph of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence studies are presented.

The container closure system of the product is OPA/Alu/PE+DES//Alu/PE blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 18 months is approved with the following storage restriction: "Store below 30°C. Store in the original package in order to protect from moisture."

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: the product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicology/environmental risk assessment

Since Prasugrel Krka 5 mg, 10 mg film-coated tablet 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.

From non-clinical points of view the product is approvable.

IV. CLINICAL ASPECTS

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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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence, for immediate release products claiming essential similarity to the reference product, a bioequivalence study is required to support the application. The applicant has submitted one pilot and one pivotal bioequivalence study. The pivotal study is a single dose 2-way crossover comparative bioequivalence study of prasugrel 10 mg film-coated tablet formulations in healthy male and female volunteers under fasting conditions.

On 3 August 2017 a new daft version of the prasugrel product specific bioequivalence guideline (EMA/CHMP/158772/2016/Rev.1) was published, stating: "An additional study under fed conditions is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel."

Since, concerning the current application the test product contains prasugrel base while the originator Efient contains prasugrel hydrochloride and elevated gastric pH seems to have an adverse effect on the rate and/or extent of absorption of the free base to a bigger extent than seen with prasugrel hydrochloride, the Applicant presented additional information for establishing the proof of concept of bioequivalence.
As part of this documentation two additional bioequivalence studies performed against the originator's reference product Efient™ (prasugrel hydrochloride) were submitted:

- Bioequivalence study under fed conditions that demonstrates bioequivalence between the proposed formulation Prasugrel 10 mg film-coated tablets (Test administered as Treatment A) and Efient® 10 mg film-coated tablets (Reference administered as Treatment B) after single-dose administration under fed conditions.

- Supportive in vitro testing and in vivo study with a proton pump inhibitor.

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 studies

Pivotal bioequivalence study

Design

Main objective of this study was to compare the rate and extent of absorption of the Test- and Reference products administered to healthy adult volunteers in a single dose under fasting conditions.
Design of this investigation was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-sequence bioequivalence study of prasugrel with a 7-day washout period between the two periods, in healthy adult male and female subjects **under fasting condition.**
Mean terminal half-life of R-95913 inactive metabolite of prasugrel is approximately 8 hour on the basis of relevant special literature after a single 10 mg oral dose of prasugrel.
The Reference drug can be taken with- or without food according to its SmPC.

Subjects were administered the Test- and Reference medications (as per the randomisation scheme) as a single oral dose of 1 tablet of Test (10 mg prasugrel) and 1 tablet of Reference products (10 mg prasugrel) with approximately 240 mL of room temperature water after at least 10 hours fasting, in each study period, under fasting conditions.

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
R-95913:

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS*		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=38)	REFERENCE (n=38)		LOWER	UPPER
C_{max}	20.9	36.144	38.006	95.10	87.77	103.05
AUC_{0-T}	10.9	65.426	64.018	102.20	98.00	106.59

* units are ng/mL for C_{max} and ng h/mL for AUC_{0-T}

Bioequivalence was met for the primary parameters in this study.
The intra-subject coefficient of variations, calculated on the basis of ANOVA MSE (mean squares error), were 10.9% and 20.9% for AUC_{0-T} and C_{max}, respectively (see in the above table).

Conclusion
On the basis of results of this pivotal bioequivalence study, a single dose of Applicant's Prasugrel 10 mg film-coated tablets is bioequivalent to a single dose of Efient® 10 mg film coated tablets (prasugrel) in healthy adult subjects under fasting conditions.

On 3 August 2017 a new daft version (currently under public consultation) of the pasugrel product specific bioequivalence guideline (EMA/CHMP/158772/2016/Rev.1) was published, stating:
"An additional study under fed conditions is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel."
Since, concerning the current application the test product contains prasugrel base while the originator Efient contains prasugrel hydrochloride, and elevated gastric pH seems to have an adverse effect on the rate and/or extent of absorption of the free base to a bigger extent than seen with prasugrel hydrochloride, two additional bioequivalence studies performed against the originator's reference product Efient™ (prasugrel hydrochloride) were submitted:

- **Bioequivalence study** under **fed conditions** that demonstrates bioequivalence between the proposed formulation Prasugrel 10 mg film-coated tablets (Krka d. d., Novo mesto) (Test administered as Treatment A) and Efient® 10 mg film-coated tablets (Daiichi Sankyo Europe GmbH, Germany, EU) (Reference administered as Treatment B) after single-dose administration under fed conditions.

Results of the study (for R-95913 prasugrel inactive metabolite):

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	Reference Product
$AUC_{(0-T)}$ (ng·h/mL)	100.027 (±36.429)	96.686 (±29.188)
$AUC_{(0-\infty)}$ (ng·h/mL)	110.050 (±40.410)	106.119 (±31.859)
C_{max} (ng/mL)	50.812 (±25.535)	51.968 (±25.438)
T_{max} [1] (hours)	0.75 (0.33- 3.00)	0.75 (0.33-2.50)

[1] Median (Min, Max)

No pre-dose concentration was detected in the beginning of second period of the study.

Summary of bioequivalence results:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals (%)	CV%[1]
$AUC_{(0-T)}$	101.83	96.84 - 107.08	14.7
C_{max}	97.45	87.30 - 108.77	32.9

[1] Estimated from the Residual Mean Squares

The study was conducted in compliance with the requirements of guideline on Good Clinical Practice, ICH Topic E6 (CPMP/ICH/135/95), and Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) and ethical principles stated of the latest version of Declaration of Helsinki.
Methodology used in statistical evaluation of pharmacokinetic parameters and bioequivalence criteria were in accordance with the bioequivalence guideline regarding type of the ANOVA and 90% confidence interval used for decision on bioequivalence between the Test- and Reference products (CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010).
On the basis of results obtained in the study, the Prasugrel 10 mg film-coated tablets (Krka d.d, Novo mesto, Slovenia, EU) (Test) and the Efient® 10 mg film-coated tablets (Daiichi Sankyo, Europe GmbH, EU, obtained from EU market) (Reference) can be considered bioequivalent under fed conditions.

Conclusion on bioequivalence studies:

On the basis of all the above results the Prasugrel 10 mg film-coated tablets (Krka d.d, Novo mesto, Slovenia, EU) (Test) and the Efient® 10 mg film-coated tablets (Daiichi Sankyo, Europe GmbH, EU, obtained from EU market) (Reference) can be considered bioequivalent under fasting and fed conditions.
The results of the bioequivalence studies with the 10 mg formulation can be extrapolated to other strengths 5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacovigilance

IV.3.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

IV.3.2 Risk Management Plan

IV.3.2.1 Summary of safety concerns

Important identified risks:	Bleeding risk, including: intracranial haemorrhage, gastrointestinal haemorrhage, intraocular haemorrhage, epistaxis, percutaneous coronary intervention (PCI) - related haemorrhage, CAGB-related haemorrhage, risk associated with prasugrel use prior to coronary angiography in NSTEMI patients, other procedure-related haemorrhage
	Hypersensitivity including angioedema
	Thrombocytopenia
	Thrombotic thrombocytopenic purpura
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)
	Use in paediatric population
	Use in pregnancy and lactation
	Use in subjects without clinical manifestation of ACS
	Use in subjects with severely compromised cardiac status (cardiogenic shock, class IV CHF, refractory ventricular arrhythmia)
	Use in subjects with severe hepatic impairment

IV.3.2.2 Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to KRKA's product containing prasugrel.
No additional activities are proposed.

IV.3.2.3 Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are not considered sufficient to manage all of the safety concerns connected to connected to KRKA's product containing prasugrel.
The originator's product (Efient), KRKA's products containing prasugrel **has educational material** as additional risk minimasition measure for the risk of "bleeding".
The KRKA should provide educational material to all physicians who may be involved in treating patients with prasugrel.
The educational material should include:

- A copy of the SPC
- Emphasis that:
    - o Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg

o Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.

o 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.

o Patients weighing < 60 kg should have a reduced maintenance dose of 5 mg

The format and means of dissemination, of this material should be discussed with the appropriate learned societies. The results of the discussion, and where appropriate the material, should be agreed with the national competent authority and be available prior to launch in each member state.

Since in Hungary physicians, who prescribe prasugrel, have already known this risk well so National Institute of Pharmacy and Nutrition does not request the distribution of this educational material to them.

IV.6.3 PSUR

The MAH shall submit the first periodic safety update report for this product with a period of 5 years following authorisation. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.

IV.7 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. Package Leaflet and user consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Clopidogrel Krka 75 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

V. OVERALL CONCLUSIONS

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

Based on the review of the data on quality, safety and efficacy, the National Institute of Pharmacy and Nutrition (OGYÉI) considers that the application for Prasugrel Krka 5 mg, 10 mg film-coated tablet indicated co-administered with acetylsalicylic acid (ASA) 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).

V.2 Classification

Prescription-only medicine.

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From HU/H/0508/001-002/DC to IE/H/1149/001-002/DC			