22 March 2018
EMA/243820/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prasugrel Mylan

International non-proprietary name: prasugrel

Procedure No. EMEA/H/C/004644/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ACS	Acute Coronary Syndrome
AR	Assessment report
API	Active Product Ingredient
ASMF	Active Substance Master File
API	Active Pharmaceutical Ingredient
GC	Gas Chromatography
GMP	Good Manufacturing Practice
INN	International Non-proprietary Name
IR	Infrared
HPLC	High Performance Liquid Chromatograph
LOD	Limit of Detection
LOQ	Limit of Quantitation
LT	lower than
NF	National Formulary
NfG	Note for Guidance
NMT	Not more than
Ph. Eur.	European Pharmacopoeia
PVC	polyvinylchloride
PVDC	polyvinylidene chloride
USP	United States Pharmacopeia
UV	Ultraviolet
ADP	adenosine 5'-diphosphate
CYP	cytochrome
EC50	mean effective concentration
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
IC50	mean inhibitory concentration
kg	kilogram
LD	low dose
LD50	mean lethal dose
mg	milligram
mL	milliliters
NOAEL	no observable adverse effect limit
NSTEMI	non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PPI	proton pump inhibitor
RBC	red blood cells
SBOA	summary basis of approval
SEM	standard error of mean
AS	Active substance
AR	Assessment Report
ASMF	Active Substance Master File = Drug Master File
CHMP	Committee for Medicinal Products for Human Use
CFU	Colony Forming Units
DLS	Dynamic Light Scattering

EC	European Commission
EU	European Union
HPLC	High performance liquid chromatography
GC	Gas Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
KF	Karl Fisher
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
N/A	Not applicable
NMR	Nuclear Magnetic Resonance
ppm	part per million
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PSD	Particle size distribution
PVC	Poly vinyl chloride
QWP	Quality Working Party
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 27 April 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Prasugrel Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2016

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication

"Prasugrel Mylan, 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).

For further information please refer to section 5.1.".

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Efient instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Efient 5 mg, 10mg film-coated tablets
- Marketing authorisation holder: Daiichi Sankyo Europe GmbH
- Date of authorisation: 25-02-2009
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/08/503/001-016

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Efient 5 mg, 10 mg film-coated tablets
- Marketing authorisation holder: Daiichi Sankyo Europe GmbH
- Date of authorisation: 25-02-2009

- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/08/503/001-016

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Efient 10 mg film-coated tablets
- Marketing authorisation holder: Daiichi Sankyo Europe GmbH
- Date of authorisation: 25-02-2009
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/08/503/008-014, 016
- Bioavailability study number(s): C15229 and PRAS-17037

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Alar Irs

- The application was received by the EMA on 27 April 2017.
- The procedure started on 18 May 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 18 August 2017.
- During the meeting on 14 September 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on 21 November 2017.
- During the meeting on 30 November 2017, the PRAC agreed on the PRAC Assessment Overview

and Advice to CHMP.

- During the CHMP meeting on 14 December 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 January 2018.
- The Rapporteur circulated the joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on 19 February 2018.
- During the CHMP meeting on 22 February 2018, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated second List of Outstanding Issues on 27 February 2018.
- The Rapporteur circulated the joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on 07 March 2018.
- During the meeting on 22 March 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Prasugrel Mylan.

2. Scientific discussion

2.1. Introduction

This is a MA Application of a generic prasugrel containing product where prasugrel is conjugated to a different salt compared to the originator.

The application for marketing authorisation of Prasugrel Mylan 5mg and 10 mg film-coated tablets is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. The reference product Efient 5mg film-coated tablets and 10mg film-coated tablets (Daiichi Sankyo Europe GmbH, Germany), authorised in EU since 25/02/2009 through centralised procedure (EU/1/08/503/001-016).

Prasugrel besilate is an antiplatelet agent, chemically described as 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-2-yl acetate benzenesulfonate.

Prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits the platelet P2Y12 receptor, inhibiting platelet activation and aggregation. The active metabolite of Prasugrel is R-138727, a sulfhydryl compound that binds covalently to the P2Y12 receptor via a disulfide bond similar to clopidogrel active metabolite. It has been suggested that R-138727 binds to the cysteine residues at positions 97 and 175 of the P2Y12 receptor. Irreversible binding of the active metabolite leads to permanent blockade of ADP-mediated P2Y12 receptor signaling and the inhibition of glycoprotein (GP) IIb/IIIa receptor activation and platelet aggregation. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke.

Prasugrel co-administered with acetylsalicylic acid (ASA) and 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). The product is a subject to the medical prescription.

Prasugrel Mylan film-coated tablets are administered orally with or without food. The tablets are not to be crushed or broken. The proposed drug product package is the high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closures with desiccant, containing 28 film-coated tablets per bottle.

The recommended starting dose of Prasugrel is 60mg and then treatment is continued with 10mg once a day. Patients taking Prasugrel should also take ASA daily (75 mg to 325mg).

The main identified safety concerns are bleeding, thrombocytopenia, hypersensitivity including angioedema and thrombotic thrombocytopenic purpura (TTP).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 5 or 10 mg of prasugrel as the active substance.

Other ingredients of the tablet core are microcrystalline cellulose, mannitol, crospovidone, colloidal anhydrous silica and magnesium stearate. The film coating is composed of polyvinyl alcohol, talc, titanium dioxide (E171), glyceryl monocaprylocaprate , sodium lauryl sulfate, iron oxide yellow (E172) for both strengths. Sunset yellow FCF aluminium lake (E110) and iron oxide red (E172) are added to the film coating of Prasugrel Mylan 10 mg.

The product is available in white opaque HDPE bottle closed with white opaque polypropylene screw cap and aluminium induction sealing liner wad as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of prasugrel is [5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]- 4,5,6,7-tetrahydrothieno [3,2-c]pyridine-2-yl acetate benzenesulfonate corresponding to the molecular formula C20H20FNO3S · C6H6O3S. It has a relative molecular mass 531.62 g/mol and has the following structure:

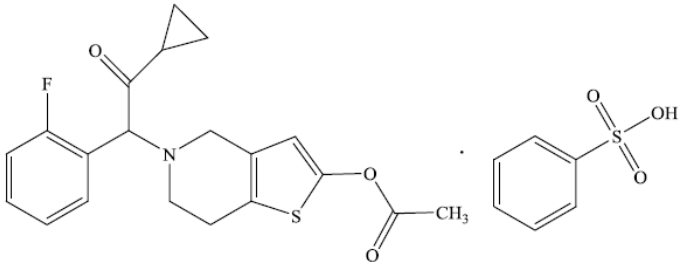

Figure 1. *Structure of prasugrel*

The structure of the active substance was elucidated by a combination of elementary analysis, infrared spectroscopy (IR), ultraviolet (UV), NMR (1H and 13C), mass spectrometry (MS) and X-Ray Powder Diffraction (XRPD). Prasugrel is sufficiently characterised and its structure is adequately elucidated.

Prasugrel besilate appears as a white to light brown colour, hygroscopic crystalline powder. Prasugrel is soluble in methanol, slightly soluble in acetone and practically insoluble in water. The active substance is a racemic mixture.

Prasugrel besilate is a crystalline form. The active substance is known to exhibit polymorphism. The polymorphic form is adequately controlled by PXRD identification test as part of the active substance specification for release and stability.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The synthesis of prasugrel besilate comprises numerous steps of chemical synthesis following purification and salt formation stages. The choice of the starting material has been justified; they are well defined and sufficiently controlled by acceptable specifications. A satisfactory discussion of the synthesis of the proposed starting materials, including the used reagents, catalysts and solvents has been provided together with a discussion about possible impurities and their carry-over into the final active substance.

Final active substance batches are micronised using clean compressed nitrogen in order to achieve the desired particle size.

Critical and non-critical process steps and parameters have been identified and adequate in-process controls are applied during the synthesis of the active substance. The control strategy ensures consistent quality of the active substance. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The potential impurities are controlled in the active substance and intermediate specifications as well as in the in-process control during the manufacturing of the active substance by validated test methods. It has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. The proposed tests and acceptance criteria for prasugrel active substance, intermediate and in process controls are considered acceptable and justified.

Prasugrel is packed in HMLDPE bag and sealed under nitrogen. It is then inserted in triple laminated aluminium bag with silica gel sachets and molecular sieve and sealed under nitrogen. Both these bags are then put into outer bag of triple laminated aluminium bag, with silica gel sachets and more molecular sieve and sealed under nitrogen. These bags are further packed in HDPE drums, closed with plastic lids having rubber gasket followed by locking ring and a metal seal. The polyethylene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual),

solubility, identification (IR, HPLC, PXRD), water content (KF), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), mesityl oxide (by GC), benzene sulfonic acid content (potentiometry), methyl benzenesulfonate content (GC-MS) and particle size distribution (DLS).

The potential impurities are controlled in the final active substance by validated test methods. As the results are either below detection limit or not detected, it has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. Based on the data provided, the fate and carry-over and fate of above impurities have been sufficiently demonstrated.

The specifications, which include relevant physical and chemical parameters to assure the quality of the active substance and are in accordance to the corresponding guidelines, are acceptable and adequately justified.

The analytical procedures used in the control of the active substance have generally been satisfactorily described and validated in accordance with the relevant ICH guidelines. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data for six batches were provided. The results are within the specifications and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data on three production scale batches of prasugrel besilate active substance stored in the intended commercial packaging for up to 18 months under long term conditions (25 °C / 60 % RH) and for up to 6 months under accelerated conditions (40 °C / 75 % RH) was provided according to the ICH guidelines.

Additional stability data on three production scale batches of prasugrel besilate active substance stored in the intended commercial packaging for up to 18 months under long term conditions (5° ± 3°C) and for up to 6 months under accelerated conditions (25 °C, 60 % RH) was provided according to the ICH guidelines.

Samples were tested for identification, assay, related substances and water content. The test methods are stability indicating. No significant changes to any of the measured parameters were observed under long term and accelerated conditions and all remained within specification.

Stress testing (heat, acid and base exposure and oxidation) was also performed. Rapid degradation was observed when prasugrel besilate sample were exposed to basic conditions at room temperature. Significant degradation was observed when prasugrel besilate sample were exposed to acidic conditions and peroxide at room temperature, heat and light. The substance is proven to be light sensitive and slightly hygroscopic. No significant degradation was observed when prasugrel besilate samples exposed to humidity at 90% RH.

The stability results justify the proposed retest period of 24 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a yellow film-coated, capsule shaped, biconvex tablet, debossed with 'PH3' on one side and 'M' on the other side containing 5 of prasugrel, or beige, film-coated, capsule shaped, biconvex tablet debossed with 'PH4' on one side of the tablet and 'M' on the other side containing 10 mg of Prasugrel.

The aim of the pharmaceutical development work was to develop a generic medicinal product of the reference product, Efient; i.e. an immediate release oral dosage form, which contains 5 mg and 10 mg of prasugrel besilate as active substance presented in the form of film coated tablets and bioequivalent to the reference medicinal product.

Prasugrel besilate is a white to light brown colour, hygroscopic, very fine and crystalline powder. It has good flow property. The active substance belongs to BCS Class II, it is practically insoluble. It is a racemic mixture known to exhibit polymorphism. The polymorphic form is adequately remains unchanged in the finished product at release and during shelf life.

The besilate salt of prasugrel is used in the composition as an active substance, whereas the reference product uses the hydrochloride salt. In terms of physicochemical properties, the besilate salt does not differ significantly from the hydrochloride salt.

The in-vitro dissolution data demonstrated the equivalent dissolution profiles for the approved hydrochloride salt and the proposed besilate salt formulations. Prasugrel base was formulated as the hydrochloride salt in reference product in order to enhance exposure to the active metabolite. In the current application, an alternate salt form (prasugrel besilate) has been utilized for the same purposes. Hence, the active moiety (prasugrel) is unchanged and unaffected by the choice of salt.

Taking into account the low solubility of prasugrel besilate, particle size is considered as critical parameter on performance of the finished product. The effect of particle size distribution (PSD) of active substance on tablet characteristics and dissolution was evaluated. Physical parameters were found to be satisfactory and drug release comparable to reference product in the formulations with difference in particle size of active substance. The test product and the reference product exhibit similar physical characteristics, assay and impurity profile.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except film coating material (Opadry). The individual components used in the manufacturing of Opadry coating materials comply with the monograph in Ph. Eur.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The choice and function of the excipients in the formulation has been justified.

The compatibility of prasugrel besilate with the excipients is demonstrated by stability studies. The samples were evaluated for any change in the physical characteristics and related substances at initial time and after one-month exposure. As no significant changes in the physical appearance and in level of total impurities were observed, prasugrel besilate is regarded compatible with all the selected excipients.

An in vivo bioequivalence study between the 10 mg film coated tablets reference product and the generic product has been performed. A comparative *in vitro* dissolution study of the generic

medicinal product formulation and the reference product at four representative physiological pH buffers (0.1 N HCl, QC test medium, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer) has been performed. The dissolution profiles can be considered similar in all four dissolution media.

Additionally, to support the request for a biowaiver for the 5 mg dosage strength a justification and results of comparative dissolution tests have been provided. As all criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence were fulfilled, the biowaiver was granted for 5 mg strength.

Based on the results of dissolution method development studies, the proposed QC dissolution method is considered sufficiently justified. Sink conditions were met and operating conditions are suitable. The discriminatory power of the dissolution method has been adequately demonstrated by comparing batches manufactured with slight changes to the formulation and different manufacturing process parameters.

Regarding the manufacturing process development, direct compression technology has been chosen using free flowing directly compressible excipients in formulation. This approach has been considered because of prasugrel besilate active substance sensitivity towards moisture, the low doses and its good flow property. The manufacturing process follows a conventional approach for solid dosages forms, employing widely used manufacturing equipment.

The container closure system of the finished product is a High Density Polyethylene (HDPE) bottle pack with white opaque polypropylene screw cap with aluminium induction sealing liner wad and a desiccant (2 g canister) is included in the container (as loose) along with the tablets. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process for the finished product comprises the following main steps:

- sifting
- blending
- lubrication
- compression
- film coating
- packaging

The manufacturing process is considered a standard process and it has been described satisfactorily.

The critical steps of the manufacturing process were defined as blending, compression, film-coating and packaging. The in-process controls (IPCs) during the manufacturing process have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

Holding time studies were successfully finalized for lubricated blend, tablet cores and film coated tablets and based on the review of the results a cumulative holding time was established.

The manufacturing process has been validated on three commercial batches. Process validation data complies with set acceptance criteria.

In conclusion, it has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this type of dosage form: description (visual), identification of prasugrel (HPLC, PDA), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), water (KF) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and validated in accordance with the relevant ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data from 3 pilot scale batches have been presented for both strengths. All data is within specification. The results show that the finished product can be manufactured with consistent quality and meeting its specifications.

Stability of the product

Stability data of three pilot scale batches for both strengths of finished product stored under long term conditions for up to 12 months (25 °C / 60% RH), for up to 12 months under intermediate conditions (30 °C / 65% RH) and for up to 6 months under accelerated conditions (40 °C/ 75% RH) according to the ICH guidelines were provided. The stability batches were packed in the primary packaging proposed for marketing.

The following stability-indicating parameters have been investigated: description, dissolution, assay, related substances, water and microbiological quality. The methods used were the same as for release testing and are stability indicating.

The stability study results indicate that the 5 mg strength product complies with the proposed finished product shelf life specifications at long term and intermediate storage conditions and that the 10 mg strength product complies with the proposed finished product shelf life specifications at long term storage conditions.

Non-compliant results were observed at accelerated storage conditions for the 5 mg strength and at accelerated and intermediate storage condition for the 10 mg strength product. The results of assay test failed to meet the specification limits for both strengths stored under accelerated conditions and there was a discrepancy in the mass balance of the assay and impurities results for the 10 mg product at accelerated conditions and at intermediate conditions. The validated HPLC methods for determination of the assay and detecting the impurities have been demonstrated to be reliable and stability indicating.

A photostability study has been performed on one commercial scale batch of Prasugrel film-coated tablets according to ICH Q1B Guideline. The following parameters were tested: description, assay, dissolution, water (KF) and degradation products. The obtained stability results indicated that there are no out of specification results and thus, it can be concluded that Prasugrel film-coated tablets are not photosensitive.

Forced degradation study under acid, alkali, peroxide, thermal, photolytic and humidity conditions

was carried out on the finished product in order to demonstrate the stability indicating nature of the assay and related substances methods. The results of degradation studies demonstrate that the validated HPLC method is suitable for the determination of all degradants in prasugrel preparation.

Based on the provided stability data, the proposed shelf life of 15 months stored not above 30ºC for prasugrel 5 mg tablets and shelf life of 12 months stored not above 25ºC for prasugrel 10 mg tablets, both in the original package in order to protect from moisture, as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. A summary of the literature with regard to non-clinical data and justifications that the different salt (prasugrel besilate) of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product (prasugrel hydrochloride) were provided and were considered accepted by assessor. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of prasugrel besilate manufactured by Mylan Laboratories is considered unlikely to result in any significant increase in the combined sales volumes for all prasugrel containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Prasugrel Mylan and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film coated tablets containing prasugrel besylate. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fasting and fed conditions. This study was the pivotal study for the assessment.

Relevant guidance documents for this assessment are the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)* as well as the *Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09)*.

The applicant did not seek CHMP Scientific Advice pertinent to the clinical investigation.

Reference product is Efient 5 mg & 10 mg (Prasugrel) film-coated tablets registered by Daiichi Sankyo Europe GmbH (*formely of Eli Lilly Nederland BV, The Netherlands*). The community granted marketing authorisation of the reference product Efient 5 mg and 10 mg film-coated tablets on 23/02/2009 under number EMEA/H/C/000984. The applicant has developed Prasugrel film-coated tablets generic to the medicinal product Efient 5 mg and 10 mg film-coated tablets. The composition of the proposed and reference product can be considered essentially similar except for the salt form of the drug substance: Prasugrel hydrochloride (Efient) vs Prasugrel besilate (Prasugrel Mylan).

Prasugrel is co-administered with salicylic acid (ASA) and 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).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Two bioequivalence studies have been conducted on the 10 mg strength under fed and fasting conditions. To fulfil the requirements of a biowaiver for lower strength, 5 mg film-coated tablets, dissolution testing was performed and extended the *in-vivo* performance of 10 mg strength to 5 mg strength.

As described by clinical expert, the waiver was considered justified, since the following general biowaiver requirements were met:

a) Both the strengths of Prasugrel film-coated tablets (5 mg and 10 mg) are manufactured by the same manufacturer at the same manufacturing site using same manufacturing process.

b) The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.

c) The qualitative composition of both the strengths is the same. Both strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same for both the strengths (see Table 1).

d) Both the strengths exhibit similar *in-vitro* performance. The dissolution profiles are similar.

e) The absorption kinetics of Prasugrel is linear within the therapeutic dose range.

Comparative dissolution profile study results for Prasugrel film-coated 10 mg tablet (Bio-batch No. 2012095) versus Prasugrel film-coated 5 mg tablet at pH 1.0, 4.5, 6.8 and QC test medium were presented and shown to be similar by means of f2 comparison.

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies.

Study No. C15229 (fasting conditions)

Clinical study site (Aizant Drug Research Solutions Pvt. Ltd.) has been inspected by DCG-India (Apr 2008, Mar 2010, Jun 2014), FDA-US (Apr 2010, Jun 2013, Aug 2016), ANVISA-Brazil (Jul 2010, Feb 2015), WHO (Oct 2011, Mar 2015), MoH-Turkey (Dec 2011), ANSM-France (Oct 2013) and MHRA (Oct 2015). No relevant findings concerning this application have been reported.

Bioanalytical study site (Mylan Laboratories Limited, India) has been successfully inspected by FDA-US (Aug 2014), AGES-Austria (Jan 2015), WHO (Mar 2015, Jul 2016), MHRA (Jul 2015) and EMA (Nov 2016).

Study No PRAS-17037 (fed conditions)

Clinical site: West Virginia University Research Corporation, d.b.a WVU Clinical and Pharmacologic Research Center, USA

Analytical study site: Mylan Pharmaceuticals Inc., Bioanalytical Department, 3711 Collins Ferry Road Morgantown, WV 26505, USA

2.4.2. Pharmacokinetics

To support the application, the applicant has submitted one bioequivalence study under the fasting conditions (study No. C15229) and one additional bioequivalence study under the fed conditions (study No. PRAS-17037).

Study No. C15229: A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Prasugrel Tablets 10 mg of Mylan Laboratories Limited, India, with EFIENT (Prasugrel hydrochloride) Tablets 10 mg of Lilly SA Avda de la Industria 30 E-28108 Alcobendas (Madrid) Spain., in normal healthy adult human subjects under fasting conditions.

Study design

Study No. C15229 was an open-label, laboratory-blinded, randomized, single dose, two-period, two-treatment cross-over bioequivalence study in healthy male subjects under fasting conditions with a wash out period of 7 days between two administrations. In each period single oral dose of either test or reference product of Prasugrel Tablets 10 mg was orally administered.

CRO and principal investigator: Aizant Drug Research Solutions Pvt. Ltd. The principal investigator was Dr. Chakravarthy K.

Sponsor: Mylan Laboratories Limited, India.

Site and dates of clinical part of the study: Aizant Drug Research Solutions Pvt. Ltd., India; Feb 15, 2017 to Feb 24, 2017. First dose was administered on Feb 16, 2017 in Period 1 and on Feb 23, 2017 in Period 2.

Site and dates of analytical part of the study: Mylan Laboratories Limited, India; between Mar 02, 2017 and Mar 22, 2017

Protocol no. C15229 version 01 dated Jan 09, 2017 and the informed consent forms were approved by Independent Ethics Committee on Jan 20, 2017.
The final report is dated Apr 06, 2017.

Biostatisticians and bio-statistical institute: Mr. S. Siva Durga Prasad, Aizant Drug Research Solutions Pvt. Ltd., India.

Food and fluid intake

Subjects were confined to the clinical facility at least 10.5 hours prior to drug administration and remained at the study centre until their 24 hrs post-dose blood sample was collected. Study drug was taken orally after a 10-hour overnight fast with 240 ml water. Standard meals were provided at scheduled times, i.e. at 4, 6 and 12 hrs after the dose. Water was not permitted 1 hour before dosing until 1 hours post-dosing except 240 mL of water during drug administration.

Sampling schedule

20 blood samples were collected for the assessment of Prasugrel metabolites R-95913 in plasma. Blood collections were performed prior to the administration of study medication (0 pre-dose within 1.5 hour prior to drug administration) and at 0.083, 0.167, 0.33, 0.50, 0.667, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours after study drug administration. The washout period of 7 days was kept between two consecutive dosing periods.

Test and reference products

Test Product: Prasugrel Tablets 10 mg (14.236 mg of Prasugrel besilate) by Mylan Laboratories Limited, India; batch No.: 2012095; batch size: 160.000 tablets; manufacturing date: Aug 2016, expiry date: Jul 2018.

Reference Product: Efient film-coated tablets 10 mg by Eli Lilly Nederland BV, The Netherlands (MAH: Daiichi Sankyo Europe GmbH, Germany); Lot No.: C540261 from UK market; expiry date: Jun 2017.

Population(s) studied

A total of 48 healthy male subjects (Asian race, aged 21 – 43 years, BMI 19.01 – 29.90) were included in the study. Only non-smokers were allowed in this study.

47 subjects completed both study phases and were included in the pharmacokinetic and statistical analysis. No major protocol deviations were reported. Inclusion and exclusion criteria were presented and were acceptable for a BE study and for the product under investigation.

Drop outs: Subject No. 18 dropped out due to adverse events (Headache) in period one.

Analytical methods

Plasma concentrations of Prasugrel inactive metabolite R-95913 were determined using a validated reversed phase LC-MS/MS method over a concentration range of 0.998 to 151.749 ng/ml. Study drugs were extracted from 200 µl of plasma using solid phase extraction. 2-oxo Prasugrel D4 (R-95913-D4) was used as internal standards.

Blood samples were collected into K_3EDTA tubes and centrifuged. The plasma samples were frozen and retained at -70°C until assay. The bioanalyses were carried out between Mar 02, 2017 and Mar 22, 2017.

9 non-zero calibrates and 4 levels of QC samples were used. The calibration curve range covered 0.998 to 151.749 ng/mL for Prasugrel metabolite R-95913. LOQ was 0.998 ng/ml. The quality control (QC) concentrations were 3.009 (low), 20.195 (medium 1), 76.740 (medium 2) and 113.090 (high) ng/mL for study sample analysis.

The linear calibration curve calculated by weighted linear regression (weight = $1/x^2$) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report are presented. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. Composition of analytical runs has been described.

Incurred sample reanalysis was conducted on 160 samples (8.3 % of 1898 samples). 98.75% (158/160) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

The maximum study sample storage period from first blood draw (Feb 16, 2017) to last sample analysis (Mar 22, 2017) was 35 days for Prasugrel metabolite. The long-term stability of Prasugrel inactive metabolite (R-95913) in human plasma in presence of Prasugrel active metabolite (R-138727 Prasugrel metabolite R-95913 covers 54 days at -70°C.

All concentration values below limit of quantification were set as zero for PK analysis.

Reanalysis of study samples: A total of 1898 study samples were received and analysed in 27 analytical runs. Twenty-one (21 i.e. 1.11%) samples were re-assayed for analytical reasons (bad chromatography, sample concentration above ULOQ, unacceptable IS response).

Pharmacokinetic variables

Primary variables were C_{max} and AUC_{0-t}.

The following pharmacokinetic parameters for Prasugrel metabolites R-95913 were determined: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$ %, K_{el} and $t_{1/2}$.

Statistical methods

Pharmacokinetic and statistical analyses were performed using Phoenix WinNonlin version 6.3 and SAS version 9.2 software.

PK parameters for each individual were tabulated and graphically presented. Individual AUC parameters were calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Non-parametric analysis of t_{max} was performed on untransformed data. ANOVA model included Sequence, Formulation, Period and Subject (Sequence) as fixed effects.

Criteria for conclusion of bioequivalence:

The 90% confidence intervals for the difference of means of ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Prasugrel inactive metabolite R-95913 were within 80.00 to 125.00% to conclude the test product was bioequivalent to the reference product under fasting conditions.

Results

Table 7: Pharmacokinetic parameters for Prasugrel metabolites R-95913 (non-transformed values)

Pharmacokinetic parameter	Test N=47		Reference N=47	
	arithmetic mean geometric mean	SD CV%	arithmetic mean geometric mean	SD CV%
$AUC_{(0-t)}$ (ng*h/mL)	**137.385** 129.100	± 49.0571 35.7 %	**145.149** 136.088	± 58.1393 40.1 %
$AUC_{(0-\infty)}$ (ng*h/mL)	**148.164** 139.147	± 53.0046 35.8 %	**157.819** 148.067	± 61.6537 39.1 %
C_{max} (ng/mL)	**101.722** 95.159	± 38.3232 37.7 %	**92.467** 85.084	± 39.020 42.2%
T_{max}* (h)	0.500	0.330-2.000	0.500	0.330-2.500

$<AUC_{0-t}$	area under the plasma concentration-time curve from time zero to t hours>
$<AUC_{0-72h}$	area under the plasma concentration-time curve from time zero to 72 hours>
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 8: Statistical analysis for Prasugrel metabolites R-95913 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV% *
$AUC_{(0-t)}$	94.66	90.15-99.39	14.2
$AUC_{(0-\infty)}$	93.76	89.24-98.50	14.3
C_{max}	111.81	102.45-122.03	25.6
* eestimated from the Residual Mean Squares			

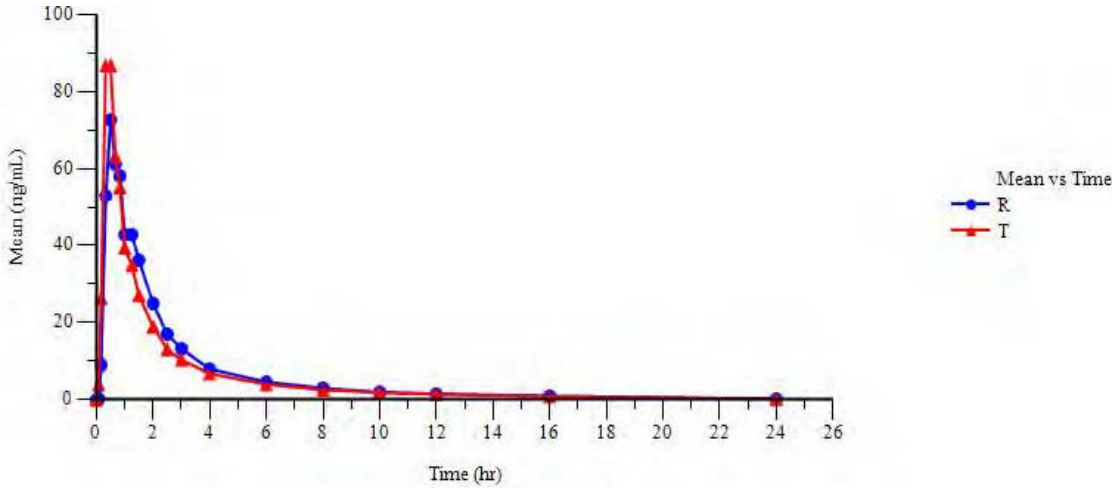

Figure 1: Linear plot of mean plasma concentrations of Prasugrel inactive metabolite R-95913 after administration of Test and Reference formulations (10 mg) to healthy subjects (N=47).

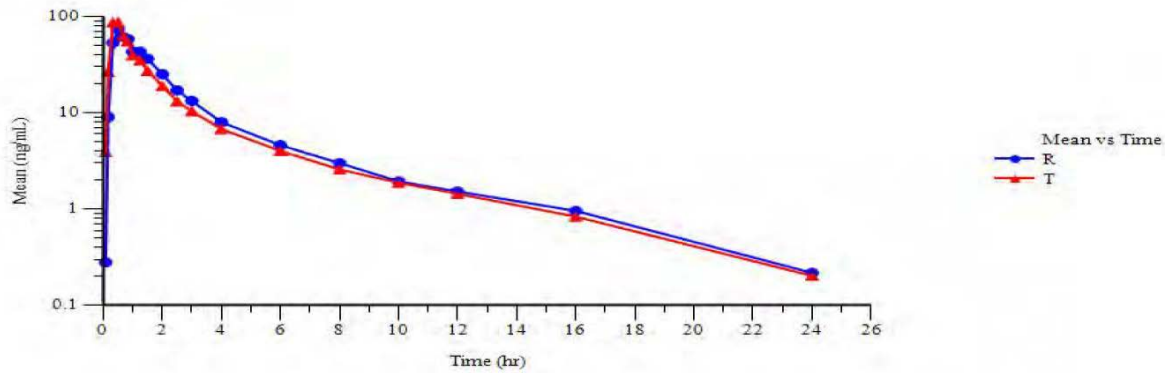

Figure 2: Semi-logarithmic plot of mean plasma concentrations of Prasugrel inactive metabolite R-95913 after administration of Test and Reference formulations (10 mg) to healthy subjects (N=47).

Safety data

No serious adverse events (AEs) were reported during the study.

One adverse event was reported for one subject (Headache) during entire duration of the study.

During post-study safety assessment, total eleven AEs were reported for six subjects. In which elevated eosinophils and elevated ABS (Eosinophils) were reported for 4 subjects, decreased haemoglobin for one subject, and elevated RBC count and elevated total bilirubin for one subject.

All the eleven adverse events were graded as mild and considered possible related to the study drug administration.

<u>Study No. PRAS-17037</u>: Single-Dose Fed Bioequivalence Study of Prasugrel Tablets (10 mg; Mylan) versus Efient Tablets (10 mg; Lilly) in Healthy Adult Volunteers.

Study design

Study No. PRAS-17037 was a single-dose, randomized, four-period, two-treatment, replicate design, crossover study investigating the bioequivalence of Mylan's prasugrel tablets, Lilly's Efient Tablets, following administration of a single, oral dose of 10 mg to healthy adult subjects under fed conditions.

CRO and principal investigator: West Virginia University Research Corporation, d.b.a WVU Clinical and Pharmacologic Research Center, 763 Chestnut Ridge Road, P.O. Box 9103, Morgantown, WV 26506-9103, USA. The principal investigator was Dr. Todd Crocco.

Sponsor: Mylan Laboratories Ltd.

Clinical facility: West Virginia University Research Corporation, d.b.a WVU Clinical and Pharmacologic Research Center, USA

Dates of clinical part of the study: Period 1: Oct 27, 2017 – Oct 30, 2017;
Period 2: Nov 03, 2017 – Nov 06, 2017;
Period 3: Nov 10, 2017 – Nov 13, 2017;
Period 4: Nov 17, 2017 – Nov 20, 2017

Protocol No. **PRAS-17037** version 1.0 dated Sep 29, 2017 and the informed consent form (ICF) dated Oct 06, 2017 were approved by the Western Institutional Review Board (WIRB) on Oct 12, 2017. The protocol (Version 1.1) dated Oct 18, 2017 was approved by WIRB on Oct 23, 2017.
The final report is dated Dec 13, 2017.

Statistical Site: Pharmacokinetics/Drug Metabolism Department, Mylan Pharmaceuticals Inc., USA

Analytical facility: Mylan Pharmaceuticals Inc., Bioanalytical Department, 3711 Collins Ferry Road Morgantown, WV 26505, USA

Dates of analytical part of the study: Nov 28, 2017 – Dec 07, 2017

Food and fluid intake

Subjects were confined to the clinical facility at least 15 hours prior to drug administration and remained at the study centre until their 24 hrs post-dose blood sample was collected. They returned to the clinical facility for the scheduled blood sample collections at 36 and 48 hours' post-dose. Dosing occurred following an overnight fast of at least 10 hours and 30 minutes after consumption of a standard high-fat breakfast. Study drug was taken orally with 240 ml water.

The standard breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. A fast was maintained for at least 5 hours after dosing. Standard meals were provided at scheduled times after the dose. Water was not permitted 1 hour before dosing until 1 hours post-dosing.

Sampling schedule

19 blood samples were collected for the assessment of Prasugrel metabolites R-95913 in plasma. Blood samples were collected within 120 minutes prior to dose administration (0; pre-dose) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after study drug administration. The washout period of 7 days was kept between consecutive dosing periods.

C_{max} is the first point: Subject 2, Period 3, T; Subject 3, Period 2, T; Subject 6, Period 4, T; Subject 9, Period 3, T; Subject 14, Period 4, T; Subject 16, Period 3, T; Subject 20, Period 1, T; Subject 20, Period 3, T; Subject 28, Period 1, T; Subject 28, Period 3, T; Subject 30, Period 2, T; Subject 32, Period 1, T; Subject 32, Period 3, T; Subject 47, Period 1, T; Subject 47, Period 2, T.

Test and reference products

Test Product: Prasugrel Tablets 10 mg (14.236 mg of Prasugrel besilate) by Mylan Laboratories Limited, India; batch No.: 2012095; batch size: 160.000 tablets; manufacturing date: Aug 2016, expiry date: Jul 2018

Reference Product: Efient film-coated tablets 10 mg by Lilly S.A., Spain (MAH: Daiichi Sankyo Europe GmbH, Germany); Lot No.: C776905 from UK market; expiry date: Aug 2019

Population(s) studied

A total of 48 healthy non-smoking male and female subjects (an Asian, white or black race; aged 19 – 61 years; BMI 19.1 – 30.4) were included in the study.

42 subjects completed all study phases. All subjects who completed at least two periods of the study were analysed. 44 subjects were included in the pharmacokinetic and statistical analysis. Inclusion and exclusion criteria has been presented and is adequate for a BE study and for the product under investigation. As assessed by the PI, none of the protocol deviations had an impact on data integrity or conclusions of this study.

Drop outs: Subject No. 38 did not report to clinic for Period 2 dosing. Subject No. 33 (Period 3), No.39 (Period 1), No.42 (Period 2) and No.48 (Period 1) were discontinued due to out of range hemoglobin/hematocrit value as specified by protocol. Subject No.40 was discontinued due to an adverse event (rash) prior to Period 2 dosing.

Analytical methods

Plasma concentrations of Prasugrel inactive metabolite R-95913 were determined using a validated reversed phase LC-MS/MS method over a concentration range of 1.00 to 300 ng/mL. Study drugs were extracted from 200 µl of plasma fortified with ascorbic acid using solid phase extraction. 2-oxo Prasugrel D_4 (R-95913-D_4) was used as internal standards.

Blood samples were collected into K_2EDTA tubes and centrifuged. The plasma samples were frozen and retained at -70°C until assay. The bioanalyses were carried out between Nov 28, 2017 to Dec 07, 2017.

8 non-zero calibrates and 4 levels of QC samples were used. LOQ was 1.00 ng/mL. The quality control (QC) concentrations were 3.00 (low), 18.00 (medium 1), 50.00 (medium 2) and 230.00 (high) ng/mL for study sample analysis.

The linear calibration curve calculated by weighted linear regression (weight = $1/x^2$) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report are presented. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. Composition of analytical runs has been described.

Incurred sample reanalysis was conducted on 289 samples (8.7 % of 3305 samples). 98.60% (285/289) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

The maximum study sample storage period from first blood draw (Oct 28, 2017) to last sample analysis (Dec 07, 2017) was 40 days for Prasugrel metabolite. The long-term stability of Prasugrel inactive metabolite (R-95913) in human plasma covers 40 days at -70°C.

All concentration values below limit of quantification were set as zero for PK analysis.

Reanalysis of study samples: A total of 3305 study samples were received and analysed in 66 analytical runs. Eight (8 i.e. 0.24%) samples were re-assayed for analytical reasons (sample processing error, abnormal IS response). Eight runs, subjects 1 through 8, were re-assayed due to being outside the batch acceptance criteria.

Statistical methods

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC).

PK parameters for R-95913, the inactive metabolite of Prasugrel, were calculated using non-compartmental techniques. PK parameters for each individual were tabulated and graphically presented. Individual AUC parameters were calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Non-parametric analysis of t_{max} was performed on untransformed data. ANOVA model included Sequence, Formulation, Period and Subject (Sequence) as fixed effects.

Criteria for conclusion of bioequivalence:

The 90% geometric confidence intervals of the ratio (T/R or A/B) of least-squares means from the ANOVA of the natural log transformed AUC_{0-t} and C_{max} should be within 80.00% to 125.00%. If the intra-subject variability for C_{max} was greater than or equal to 30% for the reference product, bioequivalence criteria for C_{max} using the scaled bioequivalence method will be utilized.

Pharmacokinetic variables

Primary variables were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Prasugrel metabolite, R-95913.

The following pharmacokinetic parameters for Prasugrel metabolites R-95913 were determined: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$ %, K_{el} and $t_{1/2}$.

Results

Table 9: Pharmacokinetic parameters for Prasugrel metabolites R-95913 (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic means **geometric mean**	**SD** **CV**	**arithmetic means** **geometric> mean**	**SD** **CV**
$AUC_{(0-t)}$ ng*hr/mL	**76.65** 71.91	±27.98 36.51%	**77.54** 73.13	±26.44 34.10%
$AUC_{(0-\infty)}$ ng*hr/mL	**83.04** 77.92	±30.10 36.25%	**84.48** 79.64	±28.81 34.10%
C_{max} ng/mL	**30.18** 27.90	±12.81 42.45%	**32.06** 29.45	±14.73 45.94%
T_{max}*	1.33 (0.33 – 4.00)		1.33 (0.67 – 3.00)	

<AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>
<AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours>
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 10: Statistical analysis for Prasugrel metabolites R-95913 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	0.99	95.43% – 102.50%	15.84%
C_{max}	0.95	88.62% – 101.99%	25.50%

* eestimated from the Residual Mean Squares

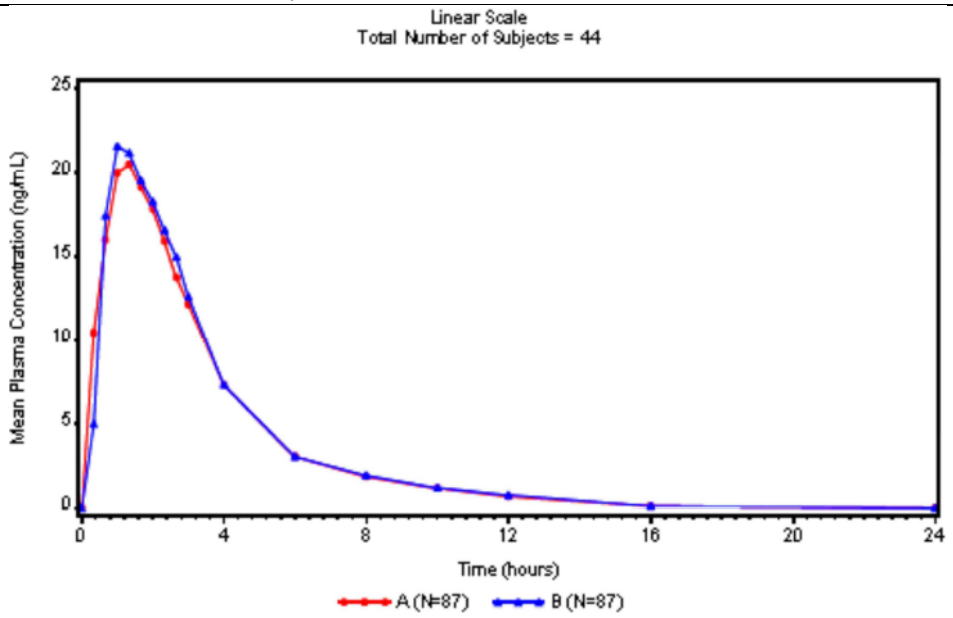

Figure 3. Linear plot of mean plasma concentrations of Prasugrel inactive metabolite R-95913 after administration of Test and Reference formulations (10 mg) to healthy subjects.

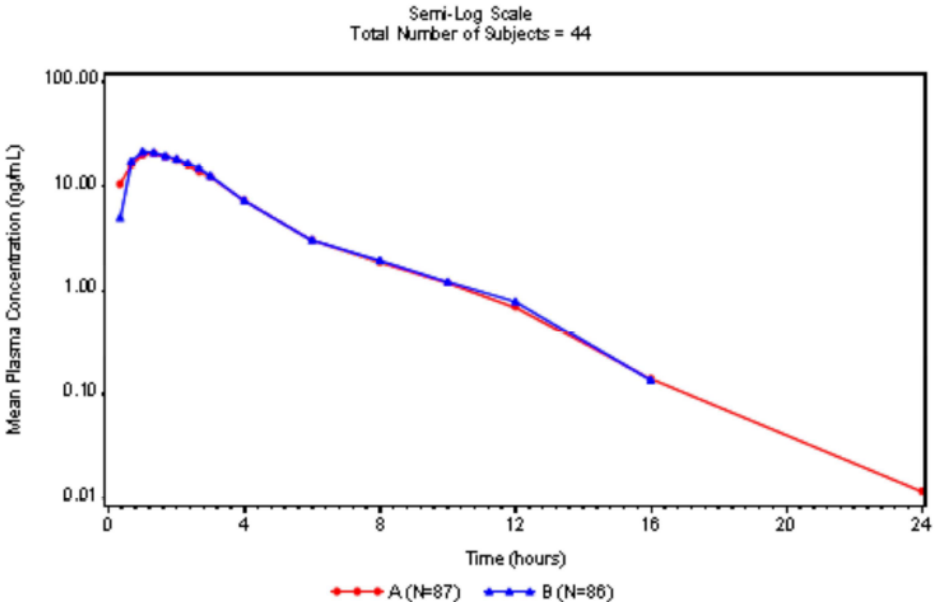

Figure 4. Semi-logarithmic plot of mean plasma concentrations of Prasugrel inactive metabolite R-95913 after administration of Test and Reference formulations (10 mg) to healthy subjects.

Safety data

Two (2) pre-dose (dizziness and headache) and seven (7) post-dose adverse events (AEs) were experienced by eight (8) subjects over the course of this study. The AEs were mild in severity. No serious adverse events (SAEs) were reported.

The most frequently reported AEs following administration of Treatment A (test) was headache reported by 2/45 (4.44%) subjects. Additionally, the dry skin was reported. No AE was reported more than once (nausea, sensitivity of teeth, headache, rash) following administration of Treatment B (reference).

Conclusions

Based on the presented bioequivalence studies Prasugrel Mylan was considered bioequivalent with Efient.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support the application, the applicant has submitted a open-label, laboratory-blinded, randomized, single dose, two-period, two-treatment cross-over bioequivalence study in healthy male subjects under fasting conditions to demonstrate essential similarity with the reference product Efient (by Eli Lilly Nederland BV, The Netherlands). According to the SmPC of reference product, the pharmacokinetics of Prasugrel metabolites appears linear over the therapeutic dosage range and prasugrel can be taken without regard to food. Therefore, the selection of the highest dose, 10 mg, used in the bioequivalence study is justified and in accordance to guidelines.

Prasugrel Mylan contains besilate as the salt form of the drug substance which differs from the originator Efient (prasugrel hydrochloride). As per increasing scientific knowledge, different salts of prasugrel may have different and pH dependent solubility. Therefore, additional data were asked from the applicant to demonstrate that the *in vivo* bioavailability of Prasugrel Mylan is not affected by the change in gastric pH induced by the concomitant food intake or concomitant medications, which may increase gastric pH.

Together with the Day 180 responses applicant submitted the results of an additional bioequivalence study under the fed conditions to demonstrate that the possible increase of the gastric pH due to the concomitant food intake does not affect the *in vivo* bioavailability of Prasugrel tablets.

Prasugrel is a prodrug that requires enzymatic transformation in the liver to its active metabolite, R-138727. Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to thiolactone (R-95913) by human carboxylesterase. This intermediate is further metabolized to its active metabolite (R-138727) in a single step by cytochrome P450 enzymes in the liver. Thus, Prasugrel metabolite R-95913 is considered as parent compound and is used as main surrogate for demonstrating the BE for Prasugrel, which is considered acceptable.

Additionally, the applicant has requested biowaiver for the 5 mg dosage strength. To support the request, a justification and results of comparative dissolution tests have been provided. The *in vitro* dissolution tests complimentary to the bioequivalence study comparing the test and the reference bio-batches over physiological pH range were conducted on 12 units at rotation speed 50 rpm.

Comparative dissolution profiles demonstrated that the bio-batch and additional strength were essentially similar over the physiological pH range. The Applicant has also performed the comparative dissolution study between test products and reference product for both strengths including bio-batches. The dissolution profiles from these experiments demonstrate similarity between test product and reference formulation in 0.1 N HCl, as more than 85% of drug is released within 15 minutes. The calculated f2 values between formulations and strengths tested at the QC test medium and at pH 4.5 and 6.8, were found to be greater than 50. As all criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence were fulfilled, the biowaiver can be granted for 5 mg strength.

Fasting conditions (Study No. C15229)

The BE study was conducted under standardised conditions. The sampling period was sufficient, the sampling time schedule and wash-out period were adequate taking into account the T_{max} and elimination half-life of the Prasugrel active metabolite (R-138727). The extrapolated AUC was less than 20% for all, except one, subject indicating that the duration of sampling was sufficient.

Data regarding the test and reference product were sufficient.

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were appropriate for a single dose study. The 90% confidence intervals for ln-transformed

pharmacokinetic variables C_{max} and AUC_{0-t} were within the conventional bioequivalence range of 80.00% to 125.00%.

The pharmacokinetic variables for Prasugrel metabolites R-95913 were comparable between test and reference product. Both formulations were well tolerated in the study.

Fed conditions (Study No. PRAS-17037)

GCP and GLP statements are provided however further information is needed regarding the outcome of the inspections performed by the competent authorities at the clinical and analytical study sites.

The Applicant has expected higher intra-subject variability for C_{max} therefore a study was designed accordingly and four-period replicate cross-over study was carried out. Overall study design was acceptable and in line with pharmacokinetic properties of Prasugrel. Prasugrel intermediate metabolite R-95913 was used as main surrogate for demonstrating the BE for Prasugrel, which is acceptable.

The BE study was conducted under standardised conditions. The composition of the meals has been described as indicated in the EMA BE guideline. The sampling period was sufficient and wash-out period was adequate taking into account the elimination half-life of Prasugrel active metabolite (R-138727). The extrapolated AUC was less than 20% for all subjects indicating that the duration of sampling was sufficient. First-point C_{max} occurred in 11 subjects (overall in 15 profiles), as some occurrences were on both periods of dosing for the test product. Only 8 profiles (~9%) for 4 subjects consistently demonstrated first-point C_{max}. The recalculation of BE parameters excluding all subjects with first time point C_{max} or only profiles with first time point C_{max} did not change the initial BE conclusion as the 90% CIs of ratios for C_{max} and AUCs remained within 80-125% acceptance limits. Thus, the sampling frequency could be considered sufficient.

Overall, the data provided on the test and reference product can be considered sufficient.

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were appropriate for a single dose study. The 90% confidence intervals for ln-transformed pharmacokinetic variables C_{max} and AUC_{0-t} were within the conventional bioequivalence range of 80.00% to 125.00%.

The pharmacokinetic variables for Prasugrel metabolites R-95913 were comparable between test and reference product. Both formulations were well tolerated in the study under fed conditions.

2.4.6. Conclusions on clinical aspects

In conclusion, based on submitted bioequivalence studies, the Prasugrel Mylan 5 mg and 10 mg film-coated tablets by Mylan Laboratories Limited, India could be considered bioequivalent with Efient 5 mg and 10 mg film-coated tablets by Eli Lilly Nederland BV, The Netherlands (MAH: Daiichi Sankyo Europe GmbH, Germany).

2.5. Risk management plan

Safety concerns

The applicant identified the following safety concerns in the RMP version 3.0 of 22.01.2018:

Table 9: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Bleeding risks, including: - Intracranial haemorrhage - Gastrointestinal haemorrhage - Intraocular haemorrhage - Epistaxis - PCI-related haemorrhage - CABG-related haemorrhage - Associated with Prasugrel use prior to coronary angiography in NSTEMI patients - Other procedure-related haemorrhage • Hypersensitivity including angioedema • Thrombocytopenia and Thrombotic thrombocytopenic purpura
Important potential risks	• Drug-induced hepatic injury • Potential off-label use in patients with prior Transient Ischaemic Attack (TIA)/ stroke • Colorectal cancer
Missing information	• Concomitant use with fibrinolytics, other tienopyridines, warfarin and chronic use of NSAIDs • Use in paediatric population • Use in pregnant/lactating women • Use in patients with compromised CV status (cardiogenic shock, class IV CHF, refractory ventricular arrhythmia) • Use in subjects with severe hepatic impairment • Use in subjects without clinical manifestations of ACS

The safety concerns are in alignment with the reference product Efient.

Pharmacovigilance plan

The Applicant has proposed routine pharmacovigilance for all safety concerns. This is in alignment with the reference product Efient.

Risk minimisation measures

Table from RMP section V.3.0 is copied in below.

Table 10: Summary table of additional Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Bleeding risk(s) • Including: Intracranial haemorrhage, Gastrointestinal haemorrhage, Intraocular haemorrhage, Epistaxis, PCI-related haemorrhage, CABG-related haemorrhage, Other procedure-related haemorrhage. • Associated with prasugrel use prior to coronary angiography in NSTEMI patients and other procedure-related haemorrhage.	Section 4.4, 4.5 and 4.8 of SPC for prasugrel contain adequate warnings on this risk. Section 2 and 4 of PL for prasugrel contains adequate information regarding the risk. Product is POM.	Educational material.

The PRAC Rapporteur having considered the data submitted was of the opinion that:

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Conclusion

The RMP version 3.0 is acceptable. No new risks have been identified for the generic product that is not recognised for the reference product and there are no outstanding issues.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on

the basis of a bridging report making reference to Efient. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of prasugrel film-coated tablets. The reference product Efient, 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). No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does contain new data on the pharmacokinetics.

Two bioequivalence studies were provided and form the pivotal basis for approval: (1) A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Prasugrel Mylan film-coated tablets 10 mg, with Efient (prasugrel hydrochloride) film-coated tablets 10 mg in normal healthy adult human subjects **under fasting conditions** and (2) A single-dose, randomized, four-period, two-treatment, replicate design, crossover study investigating the bioequivalence of Prasugrel Mylan film-coated tablets and Efient film-coated tablets, following administration of a single, oral dose of 10 mg to healthy adult subjects **under fed conditions**.

The studies design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Prasugrel Mylan met the protocol-defined criteria for bioequivalence when compared with the Efient under fed and fasting conditions. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Hence, the bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Prasugrel Mylan is favourable in the following indication:

Prasugrel Mylan, 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).

For further information please refer to section 5.1.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH should provide educational material to all physicians who may be involved in treating patients with prasugrel. 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.

The educational material should include:

- A copy of the SPC
- Emphasis that:
    - Severe haemorrhagic events are more frequent in patients $\geqslant$ 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.