EMA/439548/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Clopidogrel Teva Pharma B.V.

International non proprietary name: clopidogrel

Procedure No. EMEA/H/C/001226

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

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Table of contents

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 3 September 2009 an application for Marketing Authorisation to the European Medicines Agency for Clopidogrel Teva Pharma B.V., in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1).

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Plavix, 75 mg, Film-coated Tablets instead of non-clinical and clinical unless justified otherwise.

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease
- Patients suffering from acute coronary syndrome:
    - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
    - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy

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: Plavix 75 mg film-coated tablet
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC, France
- Date of authorisation: (dd-mm-yyyy) 15-07-1998
- Marketing authorisation granted by: Community
- Marketing authorisation numbers: EU/1/98/069/001, EU/1/98/069/002, EU/1/98/069/003, EU/1/98/069/004, EU/1/98/069/005, EU/1/98/069/006, EU/1/98/069/007, EU/1/98/069/011

☐ *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: Plavix 75 mg film-coated tablet
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC, France
- Date of authorisation: (dd-mm-yyyy) 15-07-1998
- Marketing authorisation granted by: Community
- Marketing authorisation numbers: EU/1/98/069/001, EU/1/98/069/002, EU/1/98/069/003, EU/1/98/069/004, EU/1/98/069/005, EU/1/98/069/006, EU/1/98/069/007, EU/1/98/069/011

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Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Robert Hemmings

- The application was received by the EMEA on 3 September 2009.
- The procedure started on 23 September 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2009 .
- During the meeting on 20 January 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 January 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 March 2010.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 April 2010.
- During the CHMP meeting on 20 May 2010, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 June 2010.
- During the meeting on 19 - 22 July 2010, 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 Clopidogrel Teva Pharma B.V. on 22 July 2010.

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2. Scientific discussion

2.1. Introduction

Clopidogrel Teva Pharma BV film-coated tablets is a generic medicinal product containing the active substance clopidogrel as clopidogrel hydrobromide. The reference medicinal product is Plavix 75 mg film-coated tablets, containing clopidogrel in the form of hydrogen sulphate. Plavix has been centrally authorised on 15 July 1998. Both medicinal products are administered orally. Bioequivalence has been demonstrated to the reference medicinal product. The Applicant chose to use the hydrobromide salt for patent reasons.

Clopidogrel is a non-competitive inhibitor of adenosine diphosphate (ADP) at the platelet receptors. The effect of ADP on platelets is mediated by two G-protein coupled P2Y receptors (P2Y1 and P2Y12) and the cation channel-coupled P2X1 receptor. The adenylate cyclase-coupled ADP receptor P2Y12 is the main target of clopidogrel and lead to inhibition of platelet activation, aggregation, and Gp IIb/IIIa receptor activation. Clopidogrel is a thienopyridine and only the S-enantiomer is pharmacologically active.

The safety and efficacy profile of clopidogrel has been demonstrated in several clinical trials, details of which can be found in the EPAR for Plavix. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Clopidogrel Teva Pharma B.V. film-coated tablet contains clopidogrel hydrobromide. Since this application is a generic application referring to the reference medicinal product Plavix, summary of the clinical data of clopidogrel hydrogen sulphate is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with clopidogrel hydrobromide.

The indication proposed for Clopidogrel Teva Pharma B.V. is the same as the authorised indication for the reference medicinal product:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease
- Patients suffering from acute coronary syndrome:
    - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
    - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy

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2.2. Quality aspects

2.2.1. Introduction

Clopidogrel Teva Pharma BV is presented in the form of as light pink to pink, capsule-shaped film-coated tablets, debossed with "C75" on one side and plain on the other side.

The film coated tablets contain 94 mg of clopidogrel hydrogenbromide, corresponding to 75 mg clopidogrel as active substance. Other ingredients are defined in the SPC section 6.1.

It is packaged in the following containers:

Blister (alu/alu)

Blister (alu/alu)-peelable

HDPE bottles with polypropylene closures or child resistant closures and silica gel desiccant

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2.2.2. Active Substance

The active substance is clopidogrel (as hydrobromide), chemical name Methyl(+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate, hydrobromide, corresponding to the molecular formula $C_{16}H_{16}ClNO_2S.HBr$. Molecular weight is 402. It is a white to off-white powder, non-hygroscopic and practically insoluble in water. Solubility in aqueous solutions at pH 1.2, 4.5 and 6.8 at 37°C is about 50 mg/ml.

The molecule has one chiral centre and the active substance is synthesised in the form of the (S) enantiomer with a specific optical rotation of about +56° (in methanol).

Clopidogrel hydrobromide exists in several hydrates, solvates and anhydrous forms and in one amorphous form. For this product, it was demonstrated that the active substance form used is pure and stable.

Manufacture

Clopidogrel hydrobromide is manufactured at either of two manufacturing sites by a five-step chemical synthesis. An ASMF has been submitted. Critical process parameters have been defined. Starting materials are described in sufficient detail as well as synthetic intermediates. The required (S) enantiomer is prepared from active substance racemate by crystallization.

The chemical structure of clopidogrel hydrobromide has been confirmed using analytical data by 1H NMR, 13C NMR, MS, FT-IR, elemental analysis (for the elements: C, H, N, S, Cl, Br), and polymorphic form is confirmed by XRPD, DCS and IR and water by KF analysis. All data are consistent with the proposed structure.

Specification

As there is no monograph of clopidogrel hydrobromide in PhEur, the Applicant developed their own specifications and test methods for the quality control. Control tests include visual appearance, identity by FT-IR and HPLC, polymorphism by XRD, assay and impurities by HPLC, residual solvents by GC, water, heavy metals, bromide content, sulphated ash, particle size distribution, bulk density and tapped density. The limits set for specification parameters are acceptable. Analytical methods used are sufficiently described and fully validated in line with the ICH requirements.

Results of analysis of three commercial batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

The stability of the hydrobromide seems to be less than the hydrogen sulphate (reference product); the active substance in this case needs to be stored under refrigerated conditions.

Stability studies are performed in accordance with the relevant ICH/CHMP guidelines. Stability data of the active substance up to 24 months of storage at 2-8°C (long-term conditions) and 6 months at 25°C/60% RH (accelerated conditions) were provided. Compliance with the specification with slight trend in increase of one of the degradants and total impurities had been confirmed at both conditions.

Re-test periods of 24 months when stored at 2-8°C is approved. The retest period is supported by the available stability data.

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2.2.3. Medicinal Product

Pharmaceutical Development

The aim of the development work was to develop an immediate-release tablet equivalent to the originator's product (Plavix) and exhibiting the same bioavailability.

Experimental batches with different composition were prepared using two alternative manufacturing processes. Both formulations showed similar dissolution results as the reference product. The impact of different hardness of tablets on dissolution rate of clopidogrel hydrobromide was investigated during development and holding times for granulate and bulk tablets during the manufacturing process were determined. Based on these results, a formulation containing hydrogenated castor oil and sodium laurilsulfate as lubricants and crospovidone as disintegrant was selected. It has been confirmed that the polymorphic form of the active substance does not change during manufacture of the finished product.

Critical steps in the manufacturing process were identified, specifications limits were set and validated analytical methods were developed and used for testing of the pilot batches.

The excipients are commonly used in tablet manufacture and comply with PhEur requirements, except for some of the components used in the Opadry pink film coating mixture. These are tested against in-house specification.

No excipients susceptible to the risk of TSE are used in the manufacture of the finished product. The only excipient of human/animal origin is lactose, which is derived from milk sourced from healthy

animals in the same conditions as milk collected for the human consumption and for which the required statements on minimizing the risk of BSE/TSE were submitted.

Manufacture of the Product

The manufacturing process of Clopidogrel 75 mg film-coated tablets is a standard process commonly used for film-coated tablets. Critical steps in the manufacture of Clopidogrel Teva 75 mg film-coated tablets are granulation and tabletting. The production steps are accompanied by suitable in-process controls. As demonstrated by validation studies, the process is reproducible and capable to consistently yield product within quality specification.

Product Specification

The specification for the finished product includes standard testing parameters typical for this kind of dosage form. The finished product is tested for identification, appearance, assay, impurities and degradation products, uniformity of dosage units by mass variation, dissolution, water content, methyl bromide and ethyl bromide content, identification of colorants and microbiological purity. Impurities/degradation products have been evaluated. An impurity was identified, its formation being a result of exposure to light and moisture during manufacture. This impurity is well controlled by the specification and the limit is in line with the relevant guideline.

Generally the same specification and limits are applied for both release and shelf-life, with identification of the active substance and colorants and uniformity of dosage units tested only at release. The choice of tests and the limits are acceptable and justified.

Analytical methods used for the finished product control were sufficiently described and appropriately validated.

Batch analysis results of four pilot batches confirming compliance with the specification and consistency of manufacture have been submitted.

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Stability of the Product

Stability of the finished product is monitored for pilot batches in bulk and in all types of containers to be used for marketing. Three commercial batches were also placed on stability. Stability conditions correspond to ICH requirements. For HDPE bottles 24-month results at long-term conditions (25 °C/60 % RH), 12-month results at intermediate conditions (30 °C/65 % RH) and 6-month results at accelerated conditions (40 °C/75 % RH) were provided. For the finished product packaged in aluminium - aluminium peelable blisters 12-month stability data and for the aluminium - aluminium blisters 6-month stability data were submitted. As supportive data, 24-month stability results for the product packaged in Aluminium/PET/paper (peel push) – aluminium blisters were provided. These peel-push blisters are not intended for authorization.

At accelerated conditions after 6 months, all batches in all blister and HDPE containers failed (at variable levels) to comply with the specification. At intermediate and long term conditions, the initial pilot batches in blister and HDPE containers complied with the specification up to 12 and 18 months, respectively, without any negative trend.

In general, the results support the shelf life and storage conditions as defined in the SPC.

The Applicant also conducted an in-use study for the finished product packaged in HDPE bottles. The results of this study support in-use shelf-life to be 30 days for 30-tablet bottles and 100 days for 100-tablet bottles.

The finished product is sensitive to light, therefore it is recommended to keep it in the original container.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

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2.3. Non-Clinical aspects

Clopidogrel is widely used well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised and new non clinical studies were not provided. This generic application contains a different salt of the active substance. On the basis of the CHMP Guidance for users of the centralised procedure for generic application (EMEA/CHMP/225411/2006), when different salts of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from that of the reference medicinal product is needed. A summary of the literature with regard to non-clinical data of clopidogrel hydrogensulphate and justifications that the different clopidogrel salt does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

The excipients used in the product formulation are conventional, well known and broadly used in other medicinal products.

Introduction of the product onto the market is unlikely to result in any significant increase in the combined sales volumes for all clopidogrel hydrogensulphate products, and would thus not be expected to have an adverse effect upon the environment. With this regard and on the basis of CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00), a formal environmental risk assessment is not considered necessary.

2.4. Clinical Aspects

2.4.1. Introduction

The parent drug clopidogrel is a pro-drug and its active metabolite, a thiol derivative, is formed by oxidation to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by the Cytochrome P450 isoenzymes 2B6 and 3A4 and to a lesser extent by the 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

After repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites. Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative, which represents about 85 % of the circulating compound in plasma.

The CHMP assessment addressed pharmacokinetic data in respect of three bioequivalence studies and one pharmacokinetic study.

2.4.2. GCP

The clinical studies were performed by contract research organisations.

All of the studies included in the application were conducted in accordance with the guidelines set forth by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the US Code of Federal Regulations Guidelines for Good Clinical Practice (21 CRF Parts 50 and 56) and the Declaration of Helsinki regarding the treatment of human subjects in a study.

Medicinal product no longer authorised

2.4.3. Clinical studies

A four way replicate study was submited by the Company to compare test and reference formulations (analyte = parent).

This pivotal bioequivalence study was an open-label, single-dose, randomised, four-period, two-sequence, two-treatment, replicate crossover study, designed to evaluate the comparative bioavailability of two formulations of Clopidogrel hydrobromide 75mg tablets administered to healthy male and female subjects under fasting conditions.

One dose of 75 mg clopidogrel tablet was administered with 240 ml of room temperature potable water after an overnight fast of at least 10 hours. For each subject there were 4 dosing periods, separated by a wash-out period of 7 days.

The study protocol version 1 and the Informed Consent Form (ICF), were submitted to the Ethics Review Board and approved.

A Quality Assurance Statement was provided to confirm compliance with GCP.

Comparisons of the mean values for the Primary and Additional pharmacokinetic parameters are summarized in Tables 1 and 2.

Table 1
Summary of Pharmacokinetic Parameters for Clopidogrel 75mg (n=96)

	Test 1		Test 2	
Test Variable	**Mean ± SD (n)**	**CV (%)**	**Mean ± SD (n)**	**CV (%)**
AUC_{0-t} (ng/ml.h)	3.6380 ± 8.9720 (96)	246.6160	3.7124 ± 9.0932 (86)	244.9388
AUC_{∞} (ng/ml.h)*	4.1575 ± 10.4344 (81)	250.9771	4.1098 ± 10.6698 (70)	259.6184
C_{max} (ng/ml)	2.2311 ±5.0588 (96)	226.7380	2.1691 ±4.6873 (86)	216.0971

Kel (l/h)	0.1481 ± 0.0728 (81)	49.1446	0.1450 ± 0.0799 (70)	55.0798
t_{max} (h)	0.85 ±0.33 (96)	38.18	0.96 ± 1.05 (86)	110.09
$t_{1/2}$ (h)	5.52 ± 2.25 (81)	40.76	5.69 ± 2.27 (70)	39.89

	Reference 1		**Reference 2**	
Reference Variable	**Mean ± SD (n)**	**CV (%)**	**Mean ± SD (n)**	**CV (%)**
AUC_{0-t}(ng/ml.h)	3.7451 ± 11.4092 (96)	304.6476	3.8262 ± 10.0877 (89)	263.6466
AUC_{∞} (ng/ml.h)*	4.7308 ± 14.2089 (75)	300.3473	5.1958 ± 12.7256 (64)	244.9222
C_{max} (ng/ml)	2.2642 ± 5.3858 (96)	237.8697	2.2840 ± 5.3545 (89)	234.4382
Kel (l/h)	0.1506 ± 0.0910 (75)	60.4048	0.1683 ± 0.1620 (64)	96.2636
t_{max} (h)	0.92 ±0.65 (96)	69.85	1.02 ±1.44 (89)	141.14
$t_{1/2}$ (h)	5.89 ± 3.11 (75)	52.80	6.13 ±3.43 (64)	56.00

Table 2
ANOVA 90% CI (Log transformed) and CV% for primary parameters of Clopidogrel (test vs. reference) (n=96).

Variable	**Geometric mean**	**90% Confidence limits**	**CV (%) Test**	**CV (%) Ref**
AUC_t (ratio test/reference)	107.69	99.33 – 116.76	42.02	53.26
AUC_{∞} (ratio test/reference)	104.42	94.48 – 115.40	40.10	57.82
C_{max} (ratio test/reference)	104.50	95.69 – 114.12	43.86	61.45

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters, AUC_t, AUC_{∞} and C_{max} were within 80-125% acceptance range for Clopidogrel.

Three other pharmacokinetic studies were provided as supportive studies:

- Two way replicate study under fasting conditions to evaluate intra-subject variability for clopidogrel (analyte = parent drug).
- Proposed product vs Plavix under fasting conditions (analyte = parent drug).
- Proposed product vs Plavix under fasting conditions (analyte = clopidogrel carboxylic acid).

A Single-Dose, Pharmacokinetic Study of Plavix® 75 mg Film-Coated Tablets Under Fasting Conditions to evaluate intra-subject variability for clopidogrel (analyte = parent drug).

The objective of this study is to estimate the intra-subject variability of the pharmacokinetic parameters AUC_t, AUC_{inf} and C_{max} of Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) after a single-dose in healthy subjects under fasting conditions. This was an open-label, single-dose, two-period, single-treatment study, performed on 18 healthy males and females volunteers using a 75 mg single dose under fasting conditions. Concentrations of clopidogrel were measured from the samples collected over a 16-hour interval after dosing in each period. The study protocol version 1and ICF were submitted to the Ethics Review Board and approved. The clinical study was initiated completed.

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A Single-Dose, Comparative Bioavailability Study of Two Formulations of Clopidogrel 75 mg Tablets Under Fasting Conditions (analyte = parent drug).

The objective of this study is to evaluate the comparative bioavailability between Clopidogrel hydrobromide tablets (75 mg Clopidogrel) (Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg FC Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) after a single-dose in healthy subjects under fasting conditions. This was an open-label, randomised, single-dose, two-period, two-sequence, two-treatment, cross-over study performed on 120 healthy males and females volunteers using a 75 mg single dose. Concentrations of clopidogrel were measured from the samples collected over a 16-hour interval after dosing in each period. The study protocol versions 1 and 2 and Informed Consent Form (ICF) were submitted to the Ethics Review Board and approved. The clinical study was initiated and completed.

A Single-Dose, Comparative Bioavailability Study of Two Formulations of Clopidogrel 75 mg Tablets Under Fasting Conditions (analyte = clopidogrel carboxylic acid).

The objective of this study is to evaluate the comparative bioavailability between Clopidogrel hydrobromide tablets (equivalent to 75mg of clopidogrel from Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg tablets (Sanofi-Synthelabo Ltd., UK) after a single-dose in healthy subjects under fasting conditions. This was an open-label, randomised, single-dose, two-period, two-sequence, two-treatment, cross-over study performed on 24 healthy males and females volunteers using a 75 mg single dose. Concentrations of clopidogrel carboxylic acid were measured from samples collected over a 36-hour interval after dosing in each period. The study protocol version 1 and ICF were submitted to the Ethics Review Board and approved. The clinical study was initiated and completed.

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Test and reference products

Pivotal study

Clopidogrel hydrobromide tablets (75 mg Clopidogrel); Batch No.: K-40832; Teva Pharmaceutical Industries Ltd.

Plavix® 75 mg film coated tablets; Batch No.: BN394; Sanofi Pharma Bristol-Myers Squibb SNC, France.

Supportive studies

- *Pharmacokinetic Study of Plavix® 75 mg (analyte = parent drug).*

Plavix® 75 mg Tablets; Lot No.: CE315; Sanofi Pharma Bristol-Myers Squibb SNC, France

- *Comparative Bioavailability Study (analyte = parent drug).*

Clopidogrel hydrobromide tablets (75 mg clopidogrel); Batch No.: K-38711; Teva Pharmaceutical Industries Ltd.

Plavix® 75 mg film coated tablets; Batch No.: CE315; Sanofi Pharma Bristol-Myers Squibb SNC, France.

- *Comparative Bioavailability Study (analyte = clopidogrel carboxylic acid).*

Clopidogrel hydrobromide tablets (equivalent to 75 mg clopidogrel); Batch No.: K-38711; Teva Pharmaceutical Industries Ltd.

Plavix® 75 mg Tablets; Batch No.: CC314; Sanofi-Synthelabo Ltd., UK

Population(s) studied

In all studies, the study population included non-smoking, male and female volunteers between 18-55 years of age (inclusive) with a BMI between 19 and 30 (inclusive), who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination.

Pivotal study

Ninety-six (96) subjects were included in the pharmacokinetic and statistical analysis. Eighty-two (82) subjects completed all four periods of the study and fourteen (14) subjects completed two periods of the study receiving both test and reference product. The subjects who dropped out before the end of the second period were not included in the analysis.

Supportive studies

- *Pharmacokinetic Study of Plavix® 75 mg (analyte = parent drug).*

Sixteen (16) subjects were dosed, completed the study and are included in the pharmacokinetic and statistical analysis. Drop-outs handling was performed according to the protocol requirements.

- *Comparative Bioavailability Study (analyte = parent drug).*

One hundred and seventeen (117) subjects completed the study and are included in the pharmacokinetic and statistical analysis. Drop-outs handling was performed according to the protocol requirements.

- *Comparative Bioavailability Study (analyte = clopidogrel carboxylic acid).*

Twenty-three (23) subjects were dosed, completed the study and are included in the pharmacokinetic and statistical analysis. Drop-outs handling was performed according to the protocol requirements.

The selected population in all four clinical trials is in accordance with the NfG on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 and the protocol deviations were not considered to have impact on the efficacy and safety evaluation.

Analytical methods

The plasma samples were assayed for clopidogrel and its metabolite using a LC/MS/MS method.

Pharmacokinetic Variables

The primary investigated pharmacokinetics parameters were AUC_t, AUC_{inf} and C_{max}.

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Statistical methods

Pivotal study

Analysis of variance (ANOVA) was performed on the ln-transformed Cmax, AUC0-t, AUC∞ and to untransformed Kel and T1/2 parameters. The significance of the sequence, period, treatment and subject-within-sequence were tested.

The least square means, the differences between the treatments least square means and the corresponding standard errors were estimated for log-transformed AUCt, AUC∞ and Cmax parameters. Based on these statistics, the ratios of the geometric means for the treatments and the corresponding 90% confidence intervals were calculated. Values for the Tmax parameter were analyzed by a non-parametric approach.

The acceptance range for the 90% confidence intervals for the ratios of test (T) and reference (R) product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC0-t and AUC0-∞ were 80-125%, and Cmax were 75-133%. This proposed widening of the acceptance range for Cmax is acceptable for this highly variable drug as the widening has been prospectively defined in the study protocol.

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Supportive studies

- *Pharmacokinetic Study of Plavix® 75 mg (analyte = parent drug).*

The statistical calculations were performed using PROC GLM procedure from SASR .

Analysis of variance (ANOVA) was performed on the ln-transformed Cmax, AUC0-t, AUC∞ and to untransformed Kel and T1/2 parameters. The significance of the sequence, subjects-within-sequence, period and treatment effects was tested. Values for the Tmax parameter were analyzed by a non-parametric approach. The statistical methods have been adequate described and are considered acceptable.

- *Comparative Bioavailability Study (analyte = parent drug).*

Analysis of variance (ANOVA) was performed on the ln-transformed Cmax, AUC0-t, AUC∞ and to untransformed Kel and Thalf parameters. The significance of the group, sequence-within-group, period-within-group and treatment, treatment-by-group interaction, and subject-within-sequence-by group were tested. The least square means, the differences between the period least square means and the corresponding standard errors were estimated for log-transformed AUCt, AUC∞ and Cmax parameters. Based on these statistics, the ratios of the geometric means for the periods and the corresponding 90% confidence intervals were calculated. The intra-subject variability of each of the pharmacokinetic parameters was also calculated. Values for the Tmax parameter were analyzed by a non-parametric approach.

The following acceptance criteria for the conclusion of bioequivalence were predefined in the protocol:

- The 90% confidence interval for the exponential of the difference between the Test and the Reference product for the ln-transformed parameters AUC_{0-t} and AUC_{∞} should be within 80-125%.
- The 90% confidence interval for the exponential of the difference between the Test and the Reference product for the ln-transformed parameter C_{max} should be within 75-133%.

This is not considered acceptable as the study was not of a replicate design as per the 'NfG on the investigation of Bioavailability and bioequivalence CPMP/EWP/QWP/1401/98.

- *Comparative Bioavailability Study (analyte = clopidogrel carboxylic acid).*

The statistical calculations were performed using PROC GLM procedure from SAS.

Analysis of variance (ANOVA) was performed on the ln-transformed C_{max}, AUC_{0-t}, AUC_{∞} and to untransformed K_{el} and $t_{1/2}$ parameters. The significance of the group, sequence-within-group, period-within-group, treatment, treatment-by-group interaction, and subject-within-sequence-by group were tested. Values for the T_{max} parameter were analyzed by a non-parametric approach.

The following acceptance criteria for the conclusion of bioequivalence were predefined in the protocol:

- The 90% confidence interval for the exponential of the relative mean plasma clopidogrel carboxylic acid AUC_{0-t}, AUC_{∞} and C_{max} of the Test to the Reference product should be within 80-125%.

This is in line with the bioequivalence guideline.

Results

Pivotal study

Comparisons of the mean values for the Primary and Additional pharmacokinetic parameters are summarized in Tables 1 and 2.

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Table 1
Summary of Pharmacokinetic Parameters for Clopidogrel 75mg (n=96)

	Test 1		Test 2	
Test Variable	**Mean ± SD (n)**	**CV (%)**	**Mean ± SD (n)**	**CV (%)**
AUC_{0-t} (ng/ml.h)	3.6380 ± 8.9720 (96)	246.6160	3.7124 ± 9.0932 (86)	244.9388
AUC_{∞} (ng/ml.h)*	4.1575 ± 10.4344 (81)	250.9771	4.1098 ± 10.6698 (70)	259.6184
C_{max} (ng/ml)	2.2311 ±5.0588 (96)	226.7380	2.1691 ±4.6873 (86)	216.0971
Kel (l/h)	0.1481 ± 0.0728 (81)	49.1446	0.1450 ± 0.0799 (70)	55.0798
t_{max} (h)	0.85 ±0.33 (96)	38.18	0.96 ± 1.05 (86)	110.09
$t_{1/2}$ (h)	5.52 ± 2.25 (81)	40.76	5.69 ± 2.27 (70)	39.89

	Reference 1		Reference 2	
Reference Variable	**Mean ± SD (n)**	**CV (%)**	**Mean ± SD (n)**	**CV (%)**
AUC_{0-t}(ng/ml.h)	3.7451 ± 11.4092 (96)	304.6476	3.8262 ± 10.0877 (89)	263.6466
AUC_{∞} (ng/ml.h)*	4.7308 ± 14.2089 (75)	300.3473	5.1958 ± 12.7256 (64)	244.9222
C_{max} (ng/ml)	2.2642 ± 5.3858 (96)	237.8697	2.2840 ± 5.3545 (89)	234.4382
Kel (l/h)	0.1506 ± 0.0910 (75)	60.4048	0.1683 ± 0.1620 (64)	96.2636
t_{max} (h)	0.92 ±0.65 (96)	69.85	1.02 ±1.44 (89)	141.14
$t_{1/2}$ (h)	5.89 ± 3.11 (75)	52.80	6.13 ±3.43 (64)	56.00

Table 2. ANOVA 90% CI (Log transformed) and CV% for primary parameters of Clopidogrel (test vs. reference) (n=96).

Variable	**Geometric mean**	**90% Confidence limits**	**CV (%) Test**	**CV (%) Ref**
AUC_t (ratio test/reference)	107.69	99.33 – 116.76	42.02	53.26
AUC_{∞} (ratio test/reference)	104.42	94.48 – 115.40	40.10	57.82
C_{max} (ratio test/reference)	104.50	95.69 – 114.12	43.86	61.45

Medicinal product no longer authorised

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters, AUC_t, AUC_{∞} and C_{max} were within 80-125% acceptance range for Clopidogrel.

Adverse events

No serious adverse events occurred during the study. There were 95 adverse events involving 50 subjects in the study.

The summary of AEs is presented below.

Treatment Group	Severity			Relation to the Drug		Intervention	
	Mild	Mod	Severe	Reasonable possibility	No Reasonable possibility	Required Drug Therapy	Required Non-Drug Therapy
A	41	1	0	14	28	7	5
B	53	0	0	18	35	2	3
Total	94	1	0	32	63	9	8

No serious or unexpected adverse events were reported during the conduct of this study. No significant difference between formulations was observed.

The 90% confidence intervals calculated for the primary parameters Cmax, AUC∞ and AUC0-t for clopidogrel fall within the 80 – 125% acceptance range after single dose administration under fasting conditions. It is considered by the CHMP that bioequivalence has been shown.

Supportive studies

- *Pharmacokinetic Study of Plavix® 75 mg (analyte = parent drug).*

Pharmacokinetic parameters of clopidogrel (non-transformed values; geometric means, arithmetic means (CV%), tmax median), N=16

Parameters	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**T_{max}** h	**$T_{1/2}$** h
Period 1	0.9429 1.9818 (168)	1.0809 2.4966 (154)	0.5527 1.4782 (188)	0.71 (22)	4.76 (61)
Period 2	0.9397 1.8782 (138)	1.2825 2.5981 (117)	0.6710 1.4349 (150)	0.79 (60)	4.77 (61)
***Ratio of Geometric Means (%) 90% CI**	100.33 78.99-127.45	84.28 63.80-111.33	82.36 67.32-100.77		
Intra-subject CV (%)	40	33	33		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life
K_{el} elimination rate constant
**ln-transformed values*

Medicinal product no longer authorised

Adverse events

No serious adverse events occurred during the study.
There were 28 adverse events involving 9 subjects in the study.
The summary of AEs is presented below.

	Severity			Relation to the Drug				Intervention	
	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Probable	Required Drug Therapy	Required Non- Drug Therapy
Total	28	0	0	17	1	10	0	4	3

None of these events had a significant impact on the safety of the subjects or on the integrity of the study results. However, some AEs such as had headache, nausea and emesis, sore throat, cough, dizziness and feeling hot led to drop-out.

No serious or unexpected adverse events were reported during the conduct of this study A pharmacokinetic study has been presented to demonstrate the high intra-individual variability of the originator Plavix 75mg FC tablets. Based on data from this study, it can be concluded that the clopidogrel meets the definition of a highly variable medicinal product as defined in the EU guideline EMEA/CHMP/EWP (Note for guidance on the investigation of bioavailability and bioequivalence).

- *Comparative Bioavailability Study (analyte = parent drug).*

Pharmacokinetic parameters of clopidogrel (for non-transformed value, geometric means, arithmetic means, CV%; *for ln-transformed, geometric mean, is reported; ** arithmetic mean only reported); N = 117

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	Tmax h	$**T_{1/2}$ h	$**K_{el}$ (1/h)
Test	1.4595 2.3462 (117)	1.8156 2.7292 (102)	0.8996 1.6555 (133)	0.68 (39)	6.36 (56)	0.1711 (115)
Reference	1.5192 2.4558 (124)	1.7894 2.9045 (114)	1.0338 2.0224 (204)	0.78 (42)	6.66 (57)	0.1757 (119)
***Ratio (90% CI)**	96.07 87.75-105.18	101.46 90.29-114.02	87.03 78.00-97.09	-	-	-
Intra-subject CV (%)	44	44	54	-	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

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Adverse events

No serious adverse events occurred during the study. There were 121 adverse events involving 49 subjects in the study.

The summary of ARs is presented below.

	Severity			Relation to the Drug			Intervention	
	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Required Drug Therapy	Required Non-Drug Therapy
Test	54	0	0	32	6	16	0	0
Ref	67	0	0	32	12	23	0	3
Total	121	0	0	64	18	39	0	3

None of these events had a significant impact on the safety of the subjects or on the integrity of the study results. No serious or unexpected adverse events were reported during the conduct of this study. No significant difference between formulations was observed.

Medicinal product no longer authorised

The 90% confidence intervals calculated for the primary parameters AUC0-∞ and AUC0-t for clopidogrel fall within the 80 – 125% acceptance range after single dose administration under fasting conditions. However, the 90% confidence intervals for the primary parameter Cmax, fell outside of this limit but within the pre-specified 75 – 133% range.

Although bioequivalence has not been shown, this study is considered adequate as a supportive study.

- *Comparative Bioavailability Study (analyte = clopidogrel carboxylic acid).*

Pharmacokinetic parameters of clopidogrel carboxylic acid (non-transformed values; geometric means, arithmetic means, CV%), N = 23

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**Tmax** h	****$T_{1/2}$** h
Test	10866.5 11125.9 (23)	11327.8 11605.2 (23)	3858.4 3964.8 (23)	0.65 (29)	10.04 (24)
Reference	10750.4 11169.0 (29)	11221.6 11641.8 (28)	4242.7 4360.4 (24)	0.74 (16)	9.86 (29)
***Ratio (90% CI)**	101.08 96.31-106.09	100.95 96.58-105.51	90.94 83.65-98.86	-	-
Intra-subject CV (%)	10	9	17	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life
**ln-transformed values*

Adverse events

No serious adverse events occurred during the study. There were 29 adverse events involving 12 subjects in the study.

The summary of AEs is presented below.

	Severity			**Relation to the Drug**				**Intervention**	
	Mild	Mod	Severe	Unrelated	Unlikely	Possible 16	Probable	Required Drug Therapy	Required Non- Drug Therapy
Test	13	0	0	7	0	2	4	0	1
Ref	16	0	0	5	1	0	10	0	0
Total	29	0	0	12	1	2	14	0	1

None of these events had a significant impact on the safety of the subjects or on the integrity of the study results.

No serious or unexpected adverse events were reported during the conduct of this study. No significant difference between formulations was observed.

The 90% confidence intervals calculated for the primary parameters AUC∞, AUC0-t and Cmax for clopidogrel carboxylic acid fall within the 80 – 125% acceptance range after single dose administration under fasting conditions. The extrapolated AUC of clopidogrel carboxylic acid is below 20% in each

Medicinal product no longer authorised

individual subject. No pre-dose levels of clopidogrel carboxylic acid are observed before period 2 drug administration and no subject reached Cmax at the first sample time, indicating that the sampling period is adequate.

According to the requirements of the revised draft guideline (CHMP/EWP/QWP/1401/98 Rev.1) on the investigation of bioequivalence, the measurement of the parent compound is acceptable if the pharmacokinetics of the pro-drug and active metabolite is linear. Neither the linearity of the parent clopidogrel pharmacokinetics nor the linearity of the active metabolite pharmacokinetics is established. Therefore, there is no evidence that the pharmacokinetics of parent clopidogrel may reflect that of the active metabolite. However, this study is considered adequate as a supportive study.

2.4.4. Clinical Safety

The Applicant provided additional data on the potential risk of bromism in patients with normal and severely impaired renal function.

Overall, the use of the hydrobromide salt of clopidogrel is considered justified in terms of safety for patients with normal renal function, since the maximum dose of bromide ion is well below that likely to cause adverse effects such as bromism and is also less than the Tolerable Daily Intake of 60mg/day set by the International Program on Chemical Safety (IPCS).

However, insufficient supportive evidence to claim safety in patients with severely impaired renal function was provided and at the request of the CHMP, the Applicant provided an assessment of the risk of acute and chronic bromide toxicity, drug interactions, and the potential risk of bromism in patients with renal impairment. The provided data were considered adequate to claim safety in this population.

A further issue has been raised during discussion of this procedure regarding the concentration of bromide ion, following acute and chronic use, in respect of the potential transplacental transfer and its consequential teratogenic, congenital and developmental effects.

From bibliographic sources, bromide passes through the placenta and enters breast milk. Foetal abnormalities have been observed including polydactyly, GI anomalies, clubfoot, and congenital dislocation of the hip.

At the request of the CHMP, the applicant provided a review of the relative safety factors from available animal studies. It was demonstrated that in terms of reproductive toxicity, as a result of exposure of bromide ion, clopidogrel hydrobromide was at least as safe as clopidogrel hydrogen sulphate.

The CHMP considered that the Applicant had provided sufficient additional data and discussion on the potential transplacental transfer and its consequential teratogenic, congenital and developmental effects.

Post marketing experience

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

Medicinal product no longer authorised

2.4.5. Discussion on Clinical aspects

Clopidogrel has been marketed for many years throughout the EU. The efficacy, safety and clinical pharmacology of the active ingredient clopidogrel hydrogen sulphate are already well-established and documented for original medicinal product Plavix.

For this generic product application, the applicant used a different salt of clopidogrel (clopidogrel hydrobromide). The bioequivalence studies and statistical evaluation or both the pivotal and supportive package were in accordance with accepted standards for bioequivalence testing, as stated in the Notes for Guidance. The parameters used to establish bioavailability included AUC and Cmax of the parent compound of Clopidogrel (pivotal study) and its metabolite (supportive studies). Bioequivalence has been established as the calculated 90% confidence interval (CI) for ln-transformed AUCt, AUC_{∞} and Cmax fell within the acceptance range of 80-125% for both the parent drug Clopidogrel and inactive metabolite Clopidogrel carboxylic acid after single dose administration under fasting conditions.

No bioequivalence study was conducted under fed conditions despite the acknowledged food effect when administered with a high fat meal. However, the requirements for a fed study have been reviewed by CHMP's EWP-PK subgroup (Questions and Answers: Positions on specific questions addresses to the EWP therapeutic subgroup on Pharmacokinetics [EMEA/618604/2008 Rev.1]) who concluded that "bioequivalence [for clopidogrel] should be demonstrated under fasting conditions irrespective of salt form." The absence of a fed study was therefore considered acceptable by the CHMP.

The applicant provided sufficient supportive evidence to claim safety in patients with normal and severely impaired renal function. In addition, the applicant has provided sufficient supportive evidence to claim safety regarding the concentration of bromide ion, following acute and chronic use, in respect of the potential transplacental transfer and its consequential teratogenic, congenital and developmental effects.

Medicinal product no longer authorised

2.4.6. Conclusions on clinical aspects

Based on the submitted pivotal bioequivalence study and supportive bioequivalence study package, Clopidogrel Teva 75mg Film-coated tablets (containing Clopidogrel hydrobromide) of Teva Pharma B.V., The Netherlands is considered bioequivalent with Plavix 75mg film-coated tablets (containing clopidogrel hydrogen sulphate), marketed by Sanofi Pharma Bristol-Myers Squibb SNC, France under fasting conditions.

The Applicant had provided adequate additional data and discussion on the potential transplacental transfer and its consequential teratogenic, congenital and developmental effects.

2.5. Pharmacovigilance

PSUR

The PSUR submission schedule for Clopidogrel Teva Pharma B.V. 75mg Film-coated tablets (hydrobromide) should follow PSUR submission schedule for the reference medicinal product Plavix 75 mg film-coated tablets.

Description of the Pharmacovigilance system

The CHMP considered that the pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The company must ensure that this system is in place and functioning before the product is placed on the market.

Risk Management Plan

The applicant considers that no description of Risk Management System has to be provided since the application concerns a medicinal product containing a known active substance for which no safety concern requiring additional risk minimisation activities has been identified. This is considered acceptable by the CHMP.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

Medicinal product no longer authorised

2.6. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. 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.

2.7. Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Clopidogrel Teva Pharma B.V. for the prevention of atherothrombotic events in adults in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- Patients suffering from acute coronary syndrome:
    - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA)
    - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy

was favourable and therefore recommended the granting of the marketing authorisation.

Medicinal product no longer authorised