European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT
FOR

Clopidogrel Teva

International Nonproprietary Name:
clopidogrel

Procedure No. EMEA/H/C/001053

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant TEVA Pharma B.V. submitted on 15 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Clopidogrel Teva, 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) of Directive 2001/83/EC.

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 tablets**
- Marketing authorisation holder: **Sanofi Pharma Bristol-Myers Squibb SNC, France**
- Date of authorisation: (dd-mm-yyyy) **15-07-1998**
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number: **EU/1/98/069/001-007**

■ 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 tablets**
- Marketing authorisation holder: **Sanofi Pharma Bristol-Myers Squibb SNC, France**
- Date of authorisation: (dd-mm-yyyy) **15-07-1998**
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number(s): **EU/1/98/069/001-007**

The Rapporteurs appointed by the CHMP were:

Rapporteur:	Dr. Lipnik-Štangelj
Pharmacovigilance Rapporteur :	Prof. Sampaio

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

Clopidogrel Teva has been given a Marketing Authorisation in Canada on 14 March 2007.
Clopidogrel Teva has been given a Marketing Authorisation in Israel on 31 January 2008.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 15 July 2008.
- The procedure started on 20 August 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 November 2008.
- During the meeting on 15-18 December 2008, 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 18 December 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 February 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 April 2009.
- During the CHMP meeting on 20-23 April 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 07 May 2009.
- During the meeting on 26 to 29 May 2009, 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 75 mg Film-coated tablets on 29 May 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Clopidogrel Teva 75 mg film-coated tablets is a generic medicinal product containing the active substance clopidogrel as clopidogrel hydrogen sulphate. The reference medicinal product is Plavix 75 mg film-coated tablets, also 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.

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 leads 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 75 mg film-coated tablet contains clopidogrel hydrogen sulphate. 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 hydrogen sulphate.

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

2.2 Quality aspects

Introduction

The medicinal product Clopidogrel Teva contains as active substance 97.875 mg clopidogrel hydrogen sulphate corresponding to 75 mg clopidogrel base. Other ingredients include; (tablet core): lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose (E463), crospovidone, hydrogenated vegetable oil, sodium laurilsulphate, (tablet coating): lactose monohydrate, hypromellose (E464), titanium dioxide (E171), macrogol 4000, iron oxide red (E172), iron oxide yellow (E172) and indigo carmine aluminium lake (E132).
Clopidogrel Teva is presented as light pink to pink, film-coated capsule shaped tablets. One side of the tablet is debossed with the number “93”, the other side of the tablet is debossed with the number “7314”. The tablets are packed in aluminium–aluminium perforated unit-dose blisters or in HDPE bottles with polypropylene closures or child resistant polypropylene closures and silica gel desiccant.

Active Substance

The chemical name for clopidogrel hydrogen sulphate is Methyl(+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulphate (1:1). The active substance is optically active and is presented as the S-enantiomer in the finished product.
There is no monograph for clopidogrel hydrogen sulphate in the Ph. Eur., but there is one in the USP.
Clopidogrel hydrogen sulphate (syn. clopidogrel bisulfate) is a white to off-white crystalline non-hygroscopic powder. Clopidogrel hydrogen sulphate exists in several crystalline forms and in an amorphous form. However, this medicinal product contains one pure polymorph form and does not contain any detectable amounts of other forms.
Clopidogrel hydrogen sulphate is practically insoluble in water at neutral pH, but freely soluble at pH 1.0. It is freely is soluble in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether.
The active ingredient has been fully characterised and the chemical structure of clopidogrel hydrogen sulphate has been confirmed using analytical data by ^{1}H NMR, ^{13}C NMR, MS, FT-IR, elemental analysis (for the elements: C, H, N, S, Cl), and the chosen polymorphic form is confirmed by XRPD.
All data are consistent with the proposed structure.

- Manufacture

Clopidogrel hydrogen sulphate is obtained by a synthetic manufacturing process of five steps. Detailed information about the manufacturing, validation and analytical controls of the active substance has been supplied in the form of an active substance master file (ASMF). The starting materials have been adequately characterized and the manufacturing process has adequately been validated. No component of animal or human origin is used in the manufacturing process and therefore, there is no TSE risk.

- Specification

Appropriate active substance specifications have been proposed. As there is no Ph. Eur. monograph for the active substance, in-house specifications are proposed partly based on the USP monograph of clopidogrel hydrogen sulphate.
The specifications include tests for appearance, identity (FTIR, HPLC), assay and organic impurities (HPLC), polymorph form, heavy metals, sulphated ash, water content, residual solvents, particle size distribution, bulk density and tapped density. The analytical methods are described in the Ph.Eur. or are developed in-house. The in-house methods have been satisfactorily described and validated in accordance with the ICH guidelines.
The limits set for impurities and residual solvents are acceptable and there is no concern in relation with safety or efficacy. The batch analysis data provided support the proposed acceptance limits and show that the manufacturing process is under control.

- Stability

Results of two stability studies have been provided. Both encompass long term and accelerated study conditions. The stability study conditions, numbers of batches tested and testing frequency are in accordance with the relevant ICH guidelines. The test parameters investigated in these stability studies are: appearance, identification by HPLC and XPRD (for polymorphic form), chromatographic purity (i.e. unspecified individual impurity, total impurities), enantiomeric purity and assay of clopidogrel hydrogen sulphate. The stability data justify the proposed retest period without special storage conditions.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to obtain a stable immediate-release tablet, bioequivalent with the reference medicinal product, Plavix film-coated tablets.
Experimental batches have been prepared in order to select the most suitable excipients and manufacturing method. The obtained formulations have been compared with Plavix with regards to in-vitro dissolution test results and the impurities in the stability studies.
Based on the results, a formulation containing hydrogenated vegetable oil type I and sodium laurilsulphate as lubricants and crospovidone as disintegrant was selected.

- Adventitious agents

Clopidogrel Teva contains only one excipient from animal origin. Lactose monohydrate is derived from milk sourced from healthy animals in the same conditions as milk collected for human consumption. The supplier has provided the required statements on the risk of BSE/TSE.

- Manufacture of the Product

The manufacturing process is a well known and standard process and is satisfactorily described and validated. The critical steps in the manufacture of Clopidogrel Teva are controlled by appropriate in-process controls.
The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the in-process and finished product specifications.
The excipients used in the formulation comply with the monographs of the current Ph.Eur, except hydrogenated vegetable oil type I and coating mixture Opadry. Hydrogenated vegetable oil type I complies with BP. Opadry II OY-L-34836 pink is specified according to in-house specifications. Ingredients of Opadry, except colorants, also comply with Ph. Eur. Colorants meets the relevant requirements for colours for use in foodstuffs. Certificates of analysis are provided for all excipients.

- Product Specification

The medicinal product specifications for Clopidogrel Teva include tests for appearance, identification and assay (HPLC) of the active substance, dissolution (HPLC), uniformity of dosage units (mass variation), impurities (HPLC), microbial contamination (plate count method) and water content (Karl Fischer).
The analytical methods are described in the Ph. Eur. or are developed in-house. The in-house methods have been satisfactorily described and validated in accordance with the ICH guidelines.
Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis results comply with the proposed specification and confirm consistency & uniformity of manufacture and indicate that the process is under control.

- Stability of the Product

Stability studies have been performed. All intended market containers are included in the study. The stability study conditions, numbers of batches tested and testing frequency are in accordance with the relevant ICH/CHMP guidelines. The stability studies include a study at 25 °C/60 % RH, at study at 40 °C/75 % RH and a photostability study. The analytical methods used are the same as for release testing and are all stability indicating. In the stability protocol all stability indicating quality aspects are included: appearance, dissolution, assay, impurities, water and microbiological purity. In all cases

the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Clopidogrel Teva 75 mg film-coated tablets is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for the marketing authorisation. There are no major deviations from EU and ICH requirements.

The active substance is well known and is described in a USP monograph. The quality of the active substance is regarded to be suitable for the intended use and appropriately controlled by the applicant. The excipients comply with Ph. Eur., BP or adequate in-house specifications.
The packaging material is commonly used and well documented. The manufacturing process of the finished product has been adequately described and controlled with appropriate in process controls. Stability tests indicate that the medicinal product is chemically stable during the proposed shelf life.

In comparison with the EU reference product, Clopidogrel Teva contains the same qualitative and quantitative composition in terms of the active substance, however some excipients are different. Both the EU reference product and Clopidogrel Teva exhibit similar dissolution profiles.

In conclusion, information on development, manufacture and control of the active substance and medicinal product have 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.

At the time of the Opinion no quality issues remained unresolved.

2.3 Non-Clinical aspects

Clopidogrel is a 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 the same salt of the active substance as the reference medicinal product. A summary of the literature with regard to non-clinical data of clopidogrel hydrogen sulphate was provided. Further studies are not required, because the active substance used in the reference product and the generic product are the same, and the excipients used in the formulation are conventional, well known and broadly used in other medicinal products. An overview based on the literature is thus appropriate.

Introduction of the medicinal product onto the market is unlikely to result in any significant increase in the combined sales volumes for all clopidogrel hydrogen sulphate 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

Introduction

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

GCP

The clinical studies were performed by a CRO in Canada. It was stated that the clinical studies were carried out in accordance with the ICH Good Clinical Practice (GCP) requirements. No GCP inspection has been requested.

Clinical studies

Two bioequivalence studies comparing Clopidogrel Teva 75 mg film-coated tablets with the originator Plavix 75 mg film-coated tablets, were conducted. Both studies were performed in fasting subjects, one involved measuring the parent drug and another involved measuring the major (inactive) metabolite, clopidogrel carboxylic acid. In addition, one pharmacokinetic study of Plavix 75 mg film-coated tablets was conducted in order to estimate the intra-subject variability of selected pharmacokinetic parameters under fasting conditions.

Pharmacokinetics

- Methods

STUDY DESIGN

Study code: X-1362
A single-dose, comparative bioavailability study of two formulations of clopidogrel bisulfate 75 mg tablets under fasting conditions
The objective of this study is to evaluate the comparative bioavailability between Clopidogrel Bisulfate 75 mg Tablets (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, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study performed on around 100 healthy males and females volunteers using a 75 mg single dose. Concentrations of clopidogrel were measured from the plasma samples collected over a 36-hour interval after dosing in each period. The study protocol and Informed Consent Form (ICF) were approved by the Ethics Review Board and approved on in March 2007. The clinical study was initiated on 14 March 2007 and completed on 22 March 2007.

Study code: X-1676
A single-dose, comparative biovailability study of two formulations of clopidogrel 75 mg tablets under fasting conditions
The objective of this study is to evaluate the comparative bioavailability between clopidogrel bisulfate tablets (75 mg clopidogrel) (Teva Pharmaceutical Industries Ltd.) and Plavix 75 mg film coated tablets (Sanofi-Synthelabo Ltd., UK) after a single-dose in healthy subjects under fasting conditions. This was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to evaluate the comparative bioavailability of two formulations of clopidogrel administered to 24 healthy male and female subjects under fasting conditions. Concentrations of clopidogrel carboxylic acid were measured from samples collected over a 36-hour interval after dosing in each period. The study protocol and ICF was submitted to the Ethics Review Board and approved on 24 January 2008. The clinical study was initiated on 29 January 2008 and completed on 6 February 2008.

Study code: X-1706
A single-dose, pharmacokinetic study of Plavix 75 mg film-coated tablets under fasting conditions
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 cross-over 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 and ICF were submitted to the Ethics Review Board and approved on 13 March 2008. The clinical study was initiated on 20 March 2008 and completed on 28 March 2008.

TEST AND REFERENCE PRODUCTS

Study code: X-1362
Clopidogrel Bisulfate 75 mg Tablets; Batch No.: K-37665; Teva Pharmaceutical Industries Ltd.

Plavix 75 mg Tablets; Lot No.: BF221; Sanofi-Synthelabo Ltd., UK

Study code: X-1676
Clopidogrel Bisulfate Tablets (75 mg Clopidogrel); Batch No.: K-37665; Teva Pharmaceutical Industries Ltd.

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

Study code: X-1706
Plavix 75 mg Tablets; Lot No.: CE315; Sanofi Pharma Bristol-Myers Squibb SNC, France

POPULATION(S) STUDIED

Study code: X-1362
The study population included non-smoking, male and female volunteers between 18-55 years of age with a BMI between 19 and 30 kg/m^2, who were judged to be healthy based on a medical examination. Ninty-seven (97) subjects completed the study and are included in the analysis. Drop-outs handling was performed according to the protocol requirements. The protocol deviations were not considered to have impact on the efficacy and safety evaluation.

Study code: X-1676
The study population included non-smoking, male and female volunteers between 18-55 years of age with a BMI between 19 and 30 kg/m^2, who were judged to be healthy based on a medical examination. Twenty-three (23) subjects completed the study and are included in the pharmacokinetic and statistical analysis. Drop-outs handling was performed according to the protocol requirements. The protocol deviations were not considered to have an impact on the efficacy and safety evaluation.

Study code: X-1706
The study population includes 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. 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. The protocol deviations were not considered to have an impact on the efficacy and safety evaluation.

The selected population in all three clinical trials is in accordance with the N*f*G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. Subjects participating in the studies were of different races and met the inclusion criteria and did not fulfil the exclusion criteria described in the study protocol.

ANALYTICAL METHODS

The plasma samples were assayed for clopidogrel and its metabolite using LC/MS/MS method. The analytical method was validated by a CRO in Canada.

PHARMACOKINETIC VARIABLES

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

STATISTICAL METHODS

Analysis of variance (ANOVA) was performed on the ln-transformed C_{max}, AUC_{0-t}, AUC_{inf} and to untransformed K_{el} and T_{half} parameters. The significance of the sequence, period and treatment effects and the subject within sequence random effects were tested. Values for the T_{max} parameter were analyzed by a non-parametric approach.

- Results

Study code: X-1362
Pharmacokinetic parameters of clopidogrel (non-transformed values; arithmetic mean ± SD, t_{max} median), N = 97, are presented in the table below.

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**Tmax** h	**$T_{1/2}$** h
Test	13835 2.1649 (122)	1.5869 2.4083 (117)	0.9091 1.5739 (143)	0.74 (45)	5.90 (73)
Reference	1.4199 2.3520 (127)	1.6390 2.7134 (120)	0.9351 1.6516 (136)	0.85 (116)	6.30 (72)
***Ratio (90% CI)**	97.44 88.72-107.02	96.82 87.18-107.52	97.22 87.43-108.10		
Intra-subject CV (%)	41	40	47		
$AUC_{0-\infty}$ 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*

The following acceptance criteria were set as per clinical study report:

- 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_{inf} 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%.**

The AUC0-t, AUC0-∞, Cmax were considered as primary parameters for bioequivalence conclusion with the proposed acceptance range of 80-125% for the AUC and 75-133% for the Cmax defined in the study protocol. The 90% confidence intervals for AUCt and AUCinf proposed for study X-1695 are in line with the recommendation of the CHMP guideline CPMP/EWP/QWP/1401/98 Rev.1 and the observed results of the clinical study fulfil this requirement. However, widening of the limits for bioequivalence conclusions for Cmax values was not acceptable according to the current CHMP recommendations. Nevertheless, since the Cmax results of the study are within the standard 80-125% limits required by the N*f*G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, the proposal for widening the confidence intervals for Cmax is not of

importance. Differences in tmax between test and reference products were not considered to be clinical relevant.

No serious adverse events (SAEs) occurred in study X-1362. There were 130 adverse events (AEs) involving 46 subjects in the study. The most commonly reported AEs associated with clopidogrel were blood GGT, AST, ALT increased, loose stool, light-headedness, abdominal pain, elevated urea in blood, increased creatinine, headache and other. The AEs were believed not to have a significant impact on the safety of the subjects or on the integrity of the study results. Tolerability of the test product was found to be acceptable.

Three subjects withdrew; two subjects withdrew due to personal reasons and one subject was dismissed from the study after period 2 dosing due to missed blood draws. There were post-dose blood sampling deviations and one subject refused to provide blood samples for post-study haematology and serum chemistry tests. The protocol deviations were not considered to have an impact on the efficacy and safety.

Study code: X-1676
Pharmacokinetic parameters of clopidogrel carboxylic acid (non-transformed values; arithmetic mean ± SD, t_{max} median), N=23, are presented in the table below.

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**T_{max}** h	**$T_{1/2}$** h
Test	9492.2 9786.1 (24)	9850.0 10142.8 (24)	3453.0 3597.8 (28)	0.68 (30)	9.02 (38)
Reference	9745.2 10034.4 (25)	10081.9 10381.5 (25)	3589.3 3780.0 (28)	0.73 (15)	9.09 (23)
***Ratio (90% CI)**	97.40 95.30 - 99.55	97.70 95.14 - 100.33	96.20 88.11 – 105.04		
Intra-subject CV (%)	4	5	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
K_{el} elimination rate constant

**ln-transformed values*

The 90% confidence interval values for the ln-transformed pharmacokinetic parameters of $C_{max,}$ AUC_t and AUC_{inf} are within the acceptance range of 80-125% as defined in the study protocol. Low intra-subject variability for all pharmacokinetics parameters has been shown. No pre-dose levels of clopidogrel carboxylic acid are observed before period 2 drug administration and no subject reached C_{max} at the first sample time, indicating that the sampling period is adequate. T_{max} is not significantly different between test and reference products. Calculated intra-subject variability was reasonably low for clopidogrel carboxylic acid.

No serious adverse events (SAEs) occurred during the study. There were 24 adverse events (AEs) involving 12 subjects in the study. Amongst the adverse events reported in relation to the drug was dizziness, somnolence or increased levels of creatinine. The AEs were believed not to have a significant impact on the safety of the subjects or on the integrity of the study results.

One subject was dismissed from the trial prior to check-in for period 2 due to an adverse event rectal bleeding. There were some post-dose blood sampling deviations greater than or equal to 1 minute deviations from the scheduled sampling time. These were accounted for during the pharmacokinetic analysis. No other protocol deviations were noted in this study and those that occurred were not considered to have impact on the efficacy and safety evaluation.

Study code: X-1706
Pharmacokinetic parameters of clopidogrel (non-transformed values; geometric means, arithmetic means (CV%), t_{max} median), N=16

Parameters	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**Tmax** 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*

Pharmacokinetic study X-1706 was conducted to establish whether Plavix 75 mg film-coated tablets is a medicinal product with a high pharmacokinetic intra-individual variability. Based on the results of this single study, Plavix showed an intra-subject variability of >30%. However, the CHMP considered that although these data could indicate high within-subject variability, it has not been definitely established that clopidogrel is a "highly variable" drug and the results do not justify such assumption. It is also unlikely that the power of study X-1706 could be considered acceptable to justify this conclusion, since only a limited number of subjects participated in this trial.

No SAEs occurred during the study X-1706. The AEs related to the drug such as headache, vomit, nausea, dizziness, abdominal pain, fatigue and blurred vision, were reported. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Two subjects were withdrawn due to adverse events (headache, nausea, emesis, sore throat, cough, dizziness and feeling hot). There were some post-dose blood sampling deviations greater than or equal to 1 minute and deviations from the scheduled sampling time. The handling of drop outs was performed according to the protocol requirements. Protocol deviations were not considered to have impact on the efficacy and safety evaluation.

- Conclusions

Based on the presented bioequivalence studies Clopidogrel Teva is considered bioequivalent with Plavix.

Pharmacodynamics

No studies were submitted.

Post marketing experience

No post-marketing data were provided.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system, version 5 of 29 May 2008, as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before and whilst the product is on the market.

- **Risk Management Plan**

No description of Risk Management plan has been provided by the applicant. Since the application concerns a generic with a reference medicinal product for which no safety concerns requiring additional risk management activities have been identified, this approach is considered acceptable.

Discussion on Clinical aspects

Three clinical bioequivalence trials were provided for Clopidogrel Teva (clopidogrel hydrogen sulphate). At the time of approval of the reference product Plavix (clopidogrel hydrogen sulphate), there was no reliable and validated methodology for the determination of the pharmacokinetics of the parent prodrug clopidogrel, or of the active metabolite clopidogrel thiol. Thus, the pharmacokinetic profile was established based on the pharmacokinetics of clopidogrel carboxylic acid, which is the major non-active metabolite. In the meantime, a reliable bio-analytical method for determination of clopidogrel in plasma and urine has been developed. Since the pharmacokinetic profile of the active metabolite is still not well established, the CHMP accepted the proof of bioequivalence based on the clopidogrel parent compound data. Thus, study X-1676, which determines the bioequivalence based on the data for clopidogrel carboxylic acid, is considered supportive, whereas study X-1362 is important for the confirmation of bioequivalence.

The recently published literature indicates that the bioavailability of a single oral dose of clopidogrel and the pharmacokinetic parameters of clopidogrel, especially C_{max} and AUC_{inf}, might be increased several fold in the fed condition compared to the fasted condition. The currently presented clinical studies were conducted in fasted state and thus, the CHMP requested a clarification of this approach. Adequate justification why bioequivalence for the generic product should be demonstrated only under fasting condition was provided. Bioequivalence studies in fasting conditions are normally recommended as mentioned in the Questions & Answers on the Bioavailability and Bioequivalence Guideline (EMEA/CHMP/EWP/40326/2006) document as this situation would be more sensitive to differences in pharmacokinetics. In addition the dissolution studies using clopidogrel hydrogen sulphate conducted at three different pH values (1.2, 4.5 and 6.8) and mimicking the conditions of a fed state did not show any major differences between the originator and the generic product.

The bio-analytical technique and methodology applied in the analysis of the samples during the bioequivalence studies included validation with the analysis of calibration curves and controls at various concentrations. The CHMP questioned whether there is a potential for back-conversion of the quantitatively major metabolite clopidogrel carboxylic acid to the parent drug. Considering that the plasma levels of clopidogrel carboxylic acid are considerably higher than those of the parent drug, a minimum back-conversion of the metabolite would lead to a huge over-estimation of clopidogrel plasma levels and would bias the outcome of the bioequivalence study. Demonstration of the lack of back-conversion of clopidogrel carboxylic acid metabolite to the parent drug under all conditions for sample handling and storage was requested by the CHMP. To resolve any doubts and to confirm that there is no back-conversion of the quantitatively major metabolite clopidogrel carboxylic acid to the parent-drug clopidogrel in the presence of methanol during procedures in the bioequivalence study, additional experimental data were obtained from multiple samples prepared by spiking blank human

plasma with clopidogrel carboxylic acid. Presence of clopidogrel in the analysed samples was not observed and these results show that there is no potential for the occurrence of back-conversion of clopidogrel carboxylic acid to clopidogrel during the bio-analysis in study X-1362. The CHMP considered this issue resolved.

The bioequivalence study X-1362 and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). The parameters used to establish bioavailability included the area under the plasma concentration-time curve and the maximal plasma concentration of the parent compound of clopidogrel. The 90% confidence intervals for these parameters were within the recommended 80%-125% range for clopidogrel, as required by the above mentioned guideline.

Study X-1706 aimed to demonstrate the proposed high variability of Plavix, however, the CHMP did not consider this stand alone clinical trial sufficient to establish Plavix as a drug with a highly variable pharmacokinetics due to its inadequate design and limited number of participants. Therefore, the proposed widening of the 90% confidence interval for clopidogrel C_{max} to 75%-133% on the basis that clopidogrel belongs to a group of drugs with high variability was found to be unacceptable by the CHMP. Nevertheless, since the confidence intervals for C_{max} values of clopidogrel were within the required 80%-125% range, the need for widening of the intervals was not applicable.

2.6 Overall conclusions, 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.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Clopidogrel Teva 75 mg film-coated tables in the treatment of:

"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."

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