European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref.: EMEA/533344/2009

ASSESSMENT REPORT
FOR

Clopidogrel 1A Pharma

International Nonproprietary Name: **clopidogrel**

Procedure No. EMEA/H/C/1054

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 Acino Pharma GmbH submitted on 18 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Clopidogrel 1A Pharma, 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 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**
- ■ Date of authorisation (yyyy-mm-dd): **1998-07-15**
- ■ Marketing authorisation granted by: **Community**
- ■ Marketing authorisation number(s): **EU/1/98/069/001a – 007b**

■ *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**
- ■ Date of authorisation (yyyy-mm-dd): **1998-07-15**
- ■ Marketing authorisation granted by: Community
- ■ Marketing authorisation number(s): **EU/1/98/069/001a – 007b**
- ■ Member State of source: **Germany**
- ■ Bioavailability study(ies) reference number(s) : *014-06*

The Rapporteur appointed by the CHMP was: Ondřej Slanař

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 application was received by the EMEA on 18 July 2009.
- The procedure started on 20 August 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2008.
- During the meeting on 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 16 February 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 April 2009.
- During the meeting on April 2009, the CHMP agreed on the List of Outstanding Issues to be sent to the applicant. The final List of Outstanding Issues was sent to the applicant on 23 April 2009.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 April 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 May 2009.
- During the meeting on 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 1A Pharma on 29 May 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 May 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 28 July 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Clopidogrel 1A Pharma 75 mg film-coated tablets is a generic medicinal product containing clopidogrel as clopidogrel besilate as active substance.

The reference medicinal product is Plavix 75 mg film-coated tablets, which contain clopidogrel hydrogensulphate.

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 1A Pharma 75mg film-coated tablet contains clopidogrel besilate. Since this application is a generic application referring to the reference medicinal product Plavix, summary of the clinical data of clopidogrel hydrogensulphate is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with clopidogrel besilate.

The indication proposed for clopidogrel besilate is the same as for the reference medicinal product.

2.2 Quality aspects

Introduction

Clopidogrel 1A Pharma is presented in the form of film-coated tablets.

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

It is packaged into blisters made of OPA/Al/PVC/Al.

Active Substance

The chemical name of clopidogrel besilate is: (S) – (2-chlorophenyl)-6, 7-dihydrothieno [3,2-c]-pyridine -5 (4H) – acetic acid methyl ester benzene sulphonate, corresponding to the molecular formula $C_{16}H_{16}ClO_2NS$ *$C_6H_5SO_3H$ and relative molecular mass 479.06. It is a white to off-white crystalline, non-hygroscopic powder, practically insoluble in water. The pKa value was determined to 9.67. No polymorphism of clopidogrel besilate is known.

- Manufacture

Clopidogrel besilate is manufactured in either of two manufacturing sites by a six step chemical synthesis. An ASMF has been submitted. Critical process parameters of all stages with appropriate justification have been described. Starting materials are described in sufficient detail as well as synthetic intermediates.
The active substance has one chiral centre therefore it exhibits chirality - clopidogrel besilate is synthesized as the S-enantiomer. No racemisation was observed under the commercial manufacturing process and proposed storage conditions and also under conditions for drug product manufacture.

- Specification

The drug substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (IR and HPLC), solubility (in-house), loss on drying (in-house), residue on ignition (in-house), heavy metals (Ph.Eur), specific optical rotation (polarimetry), assay (HPLC), related substances (HPLC), residual solvents (GC), methyl ester of benzene sulphonic acid (GC/MS, non-routine test).
Registration batches of clopidogrel besilate have been submitted. Data were in compliance with the specifications. Three registration batches of clopidogrel besilate for each manufacturing site have been submitted. Data of these six batches were in compliance with the specifications.

- Stability

Stability was studied in accordance with ICH guidelines under normal (25°C/60% RH), accelerated (40°C/75%RH) and intermediate (30°C/65%RH) conditions for three registration batches. Results of primary long term studies for up to 18 months have been provided.
Overall the obtained results support the proposed re-test period and storage conditions.

Medicinal Product

- Pharmaceutical Development

The tablets have been developed with the objective of developing a conventional release film coated tablets bioequivalent with the innovator's product Plavix tablets. Clopidogrel 1A Pharma product represents an alternative to the originator since it contains the same active substance (clopidogrel base) different in the salt (besilate instead of bisulphate) with the same dosage strength and dosage form.
The potential risk of occurrence of contamination with benzene sulphonic acid methyl ester in clopidogrel besilate was further elucidated in the documentation. A GC/MS method has been established and LOD of benzene sulphonic acid methyl ester is far below the TTC value of 1.5 µg/day intake of a genotoxic impurity mentioned in the Guideline on the Limits of Genotoxic Impurities.
Results of batch analysis provided on several batches of clopidogrel besilate from both active substance manufacturing sites, and the possible genotoxic impurity in question was below LOD. The content of benzene sulphonic acid isopropyl ester in the drug product is controlled by a validated method and a specification limit has been set by the finished product manufacturer.
The manufacture of the newly developed conventional-release film-coated tablet is based on granulation followed by blending of the resulting granules with an external phase, compression to tablet cores and film-coating. The drug substance clopidogrel besilate is uniformly distributed in the film-coated tablet. Bioequivalence study of Clopidogrel 1A Pharma and Plavix has been provided.
During pharmaceutical development different clopidogrel salts were considered and tested and the free base as well as formulations with or without stabilizing agents to get the most stable composition. Based on the stability results besilate salt has been chosen with respect to total impurities. Several polymorphic forms of the clopidogrel hydrogen sulphate (bisulphate) salt contained in Plavix are known. In contrast, up to now no polymorphs of the besilate salt are known.
Widely used, common excipients have been chosen and compatibility with the active substance was demonstrated.
The developed formulation provides rapid disintegration of the tablets and rapid clopidogrel release and therefore particle size was not considered to be an important factor.
Comparative dissolution profiles of four different batches including bio-batch of the tested product with the similar results and release of more than 85 % within 15 minutes have been submitted.
Comparative dissolution profiles of the bio-batch of the tested product and reference products from different European countries including bio-batch have been submitted. Results demonstrate similar profiles for test and reference.
Impurity profiles of a number of reference products sourced from different European countries (the same as for the comparative dissolution profiles experiment) and three batches of the tested product have been evaluated on impurity and active substance assay. The amount of impurities is negligible for all batches.

- Manufacture of the Product

The manufacturing process comprises four main steps: granulation, blending, compression, film-coating.
A number of process parameters have been identified as potentially critical for the quality of the finished product and appropriate in-process controls is performed during the manufacture of the film-coated tablets.

- Product Specification

The product release and shelf-life specifications include tests for appearance (visual), identification (clopidogrel besilate: HPLC, UV, titanium dioxide: chemical reaction, non-routine test), uniformity of dosage units-mass variation (PhEur), dissolution (PhEur), assay (HPLC), degradation products (HPLC), water content (PhEur), enantiomeric purity (HPLC, non-routine test), benzene sulphonic acid isopropyl ester (GC/MS- non-routine test), residual solvent (GC, non-routine test) and microbiological quality (PhEur- Non-routine test).
Validation data for three production and four pilot scale batches of the finished product have been submitted. Validation plan for three production scale batches has been described including risk analysis.
All presented batches comply with the proposed specification and demonstrate consistent manufacture.

- Adventitious Agents

None of the starting materials and excipients used for the manufacture Clopidogrel 1A Pharma film-coated tablets do contain materials that are of animal or human origin.

- Stability of the Product

Four pilot scale batches of Clopidogrel 1A Pharma film-coated tablets were put on long-term (25±2°C/60±5%RH) for up to 24 months, intermediate (30±2°C/65±5%RH) for up to 12 months and accelerated (40±2°C/75±5%RH) stability testing conditions for up to six months.
The product shows no trends in any controlled parameter except the slight increase of water content, tablet hardness and of one impurity content at any of the storage conditions. However these changes did not present any significant change in the overall quality over time.
All the results remained well within the specification limits during all the stability studies.

Photostability study as per the relevant guideline has been performed and the obtained data show that the product is not sensitive to light.

In conclusion the proposed shelf-life and storage conditions as stated in the SPC are accepted.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug 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.

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 on request of the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary. The excipients used in drug formulation are conventional, known and already used in other medicinal products.

The environmental risk assessment (ERA) in line with the CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00) was not submitted; however, a justification for omission of environmental risk assessment was provided. This was based on the fact the generic medicinal product is intended to substitute the reference product and it will not result in additional hazard to the environment. The supplied justification for the lack of a full ERA was considered acceptable by the CHMP.

2.4 Clinical Aspects

Introduction

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

GCP

The bioequivalence study 014-06 as well as the relevant analytical procedures was conducted by a CRO in India. It was stated that the clinical part of the clinical study was carried out in accordance which the principles and requirements described in the ICH guideline on Good Clinical Practice.

Clinical studies

To support the application for Clopidogrel 1A Pharma , one bioequivalence study 014-06 comparing the bioavailability of Clopidogrel 75 mg Tablet and Plavix following a 75 mg dose in healthy subjects under fasting conditions was presented. The study was conducted under fasting conditions. In addition, this generic product contains a different salt of clopidogrel (clopidogrel besilate) in comparison with the reference medicinal product. Thus, the CHMP raised a major concern, since 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.

Pharmacokinetics

- Methods

STUDY DESIGN

Study code: 014-06
An open-label, randomized, two-treatment, two-period, two sequence single dose, crossover pivotal study to compare the bioavailability of Clopidogrel 75 mg CD film-coated tablets-Cimex AG, Switzerland with Plavix 75 mg film-coated tablets-Sanofi-Synthelabo, Germany in healthy, adult, male, human subjects under fastening conditions.
The objective of this study was to compare the bioavailability and characterise the pharmacokinetic profile of the generic clopidogrel 75 mg tablets with respect to the reference formulation of Plavix 75 mg clopidogrel film-coated tablets in healthy, adult, male population under fasting conditions and to assess the bioequivalence. This was an open-label, randomised, two-treatment, two-period, two-sequence single dose crossover pivotal study performed on 46 healthy adult male non-smokers or light smokers. The study was performed in fasting subjects, measuring the parent prodrug clopidogrel. The protocol and informed consent forms (ICFs) were reviewed and approved by an Ethics Committee on 14 March 06. The study was conducted between 16 March 06 and 26 March 06.

TEST AND REFERENCE PRODUCTS

Clopidogrel 75 mg tablet, batch No. 060281-75FT; Cimex AG, 4253 Liesberg, Switzerland.

Plavix 75 mg, batch No. 501252; Sanofi Synthelabo GMBH, Germany.

POPULATION(S) STUDIED

The study population included healthy, adult males non-smokers or light smokers (up to 10 cigarettes per day), aged > 18 and < 45 years and with BMI between 18.5 and 24.9 kg/m^2. All subjects had to comply with the inclusion and exclusion criteria pre-specified in the protocol and were judged eligible for enrolment in this study, based on medical and medication histories, demographic data, vital signs measurements, 12-lead ECG, physical examination, a chest X-ray, and clinical laboratory tests. Of the 48 subjects dosed, 46 completed the trial and were included in the statistical analysis.

The selected population is in accordance with the N*f*G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. The study has been conducted in a population of Indian subjects, which is considered acceptable by the CHMP, since there is no concern that this study population would be less sensitive than European subjects with respect to the detection of formulation-specific differences. The selection of the population as well as enrolment of light smokers has been appropriate.

ANALYTICAL METHODS

Plasma concentration of clopidogrel was determined by liquid chromatographic tandem mass spectrometric method. The method was validated in the studied range. Samples were analysed between 13 April 06 to 30 April 06. Analyses were conducted at a bioanalytical laboratory in India.

PHARMACOKINETIC VARIABLES

The primary pharmacokinetic parameters defined in the protocol were AUC_{0-t}, AUC_{0-inf} and maximal plasma clopidogrel concentration C_{max}.

STATISTICAL METHODS

Analysis of variance (ANOVA) was carried out on ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and untransformed $t_{1/2}$ values. Factors of subjects, treatments, sequence, and period were also evaluated in the model. A non-parametric test was carried out to compare the T_{max} values between treatments. Individual data were presented, logarithmic transformation used, individual plasma concentration-time profiles were shown. Descriptive statistics was used to summarize the results. The statistical methods used were acceptable.

- Results

The results for the pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median) and for the mean ratios of the 90%CI for AUC_{0-t}, AUC_{0-inf}, C_{max} are summarised in the tables below. The pharmacokinetic parameters were not reported for subjects whose extrapolation area was found to be >20%. However, the CHMP did not consider this acceptable, since subjects should not be excluded from the analysis on this ground. Therefore the submission of complete statistical analysis in which the data of all subjects are included was requested. This is presented below as an appendix to the table.

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median), study 014-06.

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product-A	Test Product-B
#T_{max} (h)	0.915	0.830
C_{max} (pg / mL)	900.993 ± 1096.0805	815.114 ± 985.7684
AUC_{0-t} (pg.h / mL)	1677.306 ± 2098.6599	1542.658 ± 1676.4121
$AUC_{0-\infty}$ (pg.h / mL)	1868.027 ± 2216.7801*	1721.661 ± 1791.0150*
λ_z (1 / h)	0.3042 ± 0.20058*	0.2812 ± 0.19754*
t½ (h)	3.514 ± 2.4931*	3.991 ± 2.9720*

Note: *n = 41 # Median values reported for T_{max}.

Appendix, table 1: The mean pharmacokinetic parameter of clopidogrel for Reference Product-A and Test Product-B of forty-six subjects in study 014-06.

Descriptive Statistics of Formulation Means for Clopidogrel (n=46)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product-A	Test Product-B
$AUC_{0-\infty}$ (pg.h / mL)	1794.274 ± 2120.3225	1670.525 ± 1700.0842

Table 2. The mean ratios of the 90%CI for AUC_{0-t}, AUC_{0-inf}, and C_{max}, study 014-06.

Parameters (Units)	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Reference Product-A	Test Product-B	(B / A)%	
C_{max} (pg / mL)	564.303	533.262	94.5 %	84.64-105.50 %
AUC_{0-t} (pg.h / mL)	1073.132	1076.247	100.3 %	90.43-111.22 %
$AUC_{0-\infty}$ (pg.h / mL)	1184.640*	1174.274*	99.1 %*	88.75-110.71 %*

Note: *n = 41

Appendix, table 2: The mean pharmacokinetic parameter of clopidogrel for Reference Product-A and Test Product-B of forty-six subjects in study 014-06.

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Clopidogrel (n=46)

Parameters (Units)	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Test Product-B	Reference Product-A	Ratio (B / A)%	
$AUC_{0-\infty}$ (pg.h / mL)	1198.666	1187.274	101.0%	89.81-113.49%

The AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were considered as primary parameters for bioequivalence conclusion with the proposed acceptance range of 80-125% for the AUC and 75-133% for the C_{max} defined in the study protocol. However, widening of the limits for bioequivalence conclusions for C_{max} values was not acceptable according to the current CHMP recommendations. Nevertheless, since the C_{max} 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, lack of appropriate justification for widening the limits is of no importance.

In total, seven adverse events (AEs) occurred during the conduct of the study 014-06. All were mild in nature and were resolved. There were no serious adverse events or deaths reported. Two significant, possibly related events were reported: vomiting with indigestion and diarrhoea, but were resolved. No additional safety concerns were identified.

Out of the 48 subjects dosed, 46 were included in the statistical analysis. Two study participants dropped out; one due to medical reasons one elected to withdraw on day 0 of period 2. Two drop-out subjects are acceptable and it is considered to have no relevant impact on the results of the study. There were no major deviations from the study protocol and the minor deviations, such as blood sample timing, vital recordings, use of concomitant medication, were well documented.

- Conclusions

Based on the presented bioequivalence study 014-06, Clopidogrel 1A Pharma is considered bioequivalent with Plavix.

Pharmacodynamics

No studies were submitted.

Post marketing experience

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

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Clopidogrel 1A Pharma should follow the PSUR submission schedule of the reference medicinal product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

Risk Management Plan has not been submitted. Since the application concerns a generic of a respective reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified, this is considered acceptable.

Discussion on Clinical aspects

One clinical bioequivalence trial 014-06 was provided for Clopidogrel 1A Pharma application, analysing the parent prodrug clopidogrel. The demonstration of the unchanged safety/efficacy profile of clopidogrel besilate when compared with Plavix (clopidogrel hydrogensulphate) was raised by the

CHMP as a major issue for this generic product. Apart from this general concern, it is particularly important to evaluate the safety of the besilate moiety, since salification agents, such as benzenelsulfonic acid, could impact the antiaggregation effects of platelets considering that their chemical structure may be in relation with a pharmaceutical activity. In response, the following facts were addressed: the physical-chemical properties of clopidogrel besilate, the behaviour of benzenesulphonate in various parts of the gastrointestinal tract with different pH ranges, the use of benzensulphonic acid as an excipient and the clinical experience with besilate salts present in medicinal products on the market. It was emphasized that the properties of this moiety undergo fast elimination from human body and the use of other medicinal products containing besilate moiety has not shown any safety signals. Therefore, it was felt that the potential for an adverse interaction between platelets and the besilate moiety is unlikely and the CHMP considered the issue resolved.

At the time of approval of the reference product Plavix, 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 non-active metabolite. In the meantime, a reliable bioanalytical method for determination of clopidogrel in plasma and urine was 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 in study 016-04.

The recently published literature data indicate 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 by several folds in the fed condition compared to the fasted condition. The currently presented clinical study was 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 besilate 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 study 014-06 were described. 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 quality 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, the results of an experiment conducted with this purpose were provided during the procedure. Following the sample work up and the chromatographic analysis of multiple samples prepared by spiking blank human plasma with clopidogrel carboxylic acid immediately and after several hours, no area response at retention time relevant to clopidogrel was observed in samples of clopidogrel carboxylic acid. Hence, these results show that there is no potential for the occurrence for back-conversion of clopidogrel carboxylic acid to clopidogrel during the bioanalysis in study 014-06. The CHMP considered this issue resolved.

The bioequivalence study and 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. Bioequivalence has been established as the calculated 90% confidence intervals for ln-transformed AUC_t, AUC_{inf} and C_{max} fell within the acceptance range of 80-125% for the parent drug clopidogrel as required by the above mentioned guideline.

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 1A Pharma in 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.