European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref.: EMEA/487789/2009

ASSESSMENT REPORT
FOR

Grepid

International Nonproprietary Name: **clopidogrel**

Procedure No. EMEA/H/C/001059

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 Pharmathen S.A. submitted on 31 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Grepid, 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: **15 July 1998**
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: **EU/1/98/069/001-7**

■ 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: **15 July 1998**
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: **EU/1/98/069/001-7**
- Bioavailability study number: **AA44502**

The Rapporteur appointed by the CHMP was Metoda Lipnik-Štangelj

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 31 July 2008.
- The procedure started on 20 August 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 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 19 December 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 February 2009.
- During the CHMP meeting on 16-19 March 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- A clarification meeting with the Rapporteur and the EMEA took place on 26 March 2009.
- The applicant submitted the responses to the CHMP list of outstanding issues on 24 April 2009.
- The Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues on 11 May 2009.
- On 20 May 2009 the applicant provided a request to change the name of the product from Clopidogrel Pharmathen (initially proposed name for which the procedure has been started) to Grepid.
- During the meeting on 26-29 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 Grepid on 29 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

Grepid 75 mg film-coated tablet is a generic medicinal product containing clopidogrel as an active substance. The application was submitted under the Article 10(1) of Directive 2001/83/EC i.e. generic application referring to a reference medicinal product.

Grepid contains different salt of clopidogrel - clopidogrel besilate in contrary to the reference medicinal product (Plavix), which contains clopidogrel hydrogensulphate as the active substance.

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. Grepid 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 for clopidogrel besilate is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.

The therapeutic indication of Grepid is:
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.

The therapeutic indication of Plavix is:
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

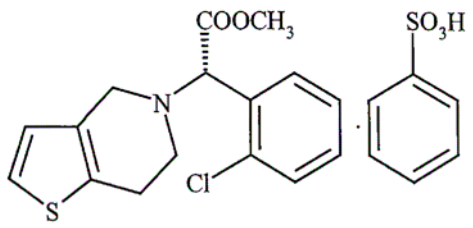
Introduction

Grepid is presented as film-coated tablets containing 75 mg of clopidogrel (active substance). The active substance is in form of besilate salt. Excipients used in the preparation of Grepid are well known excipients used in tablets preparations such as microcrystalline cellulose, hydroxypropylcellulose (E463), mannitol (E421), crospovidone (type A), citric acid, monohydrate, macrogol 6000, stearic acid, talc (present in the tablet core) and Opadry II Pink 32K14834 (coating agent) which is composed of hypromellose (E464), iron oxide red (E172), lactose monohydrate, triacetin (E1518), titanium dioxide (E171).

Grepid film-coated tablets are pink, round and biconvex and packed in polyvinyl PVC/PE/PVDC-aluminium foil or PA/ALL/PVC-aluminium foil (Alu-Alu) blisters.

Active Substance

The active substance is chemically designated as (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-yl-acetic acid methyl ester benzene sulfonate or methyl(+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate, benzene sulfonic acid (Chemical names) or methyl (2S)-2-(2-chlorophenyl)-2-(9-thia-4-azabicyclo[4.3.0]nona-7,10-dien-4-yl)acetate, benzene sulfonic acid (IUPAC Name) and has the following structure:



Clopidogrel besilate is an off-white crystalline, non-hygroscopic powder, very soluble in methanol, acetonitrile, dichloromethane and practically insoluble in water.

Clopidogrel molecule has one chiral centre. Active substance used in the manufacturing process of the drug product is a D-enantiomer. No specific form (except of amorphous and crystalline) has been found. The commercially utilised process is optimised to produce a crystalline form.

- Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure. The synthesis consists of six steps. First step involves cyanation and condensation of chlorobenzaldehyde with cyclic amine. The result of the first stage is cyanocoupled compound. In the next stage, the racemic amide is prepared. It continues to the third stage where the resolved (+) amide is isolated. The synthesis continues through camphor sulfonic acid salt of clopidogrel to clopidogrel base. In the last step of the synthesis clopidogrel base reacts with benzene sulfonic acid (besilation) to give clopidogrel besilate.

Critical parameters and accompanying in-process controls, to ensure quality of the final compound, have been defined.

Confirmation of the chemical structure of clopidogrel besilate was provided by elemental analysis (confirmation of the determined elementary composition), spectroscopic methods as FT-IR, NMR (^{1}H-NMR and ^{13}C-NMR), mass spectrum, X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC). X-ray diffraction studies and DSC confirmed the morphology of clopidogrel besilate and confirm the proposed crystalline form.

Potential impurities have been well discussed in relation to their origin and potential carry-over into the final drug substance, including potential for the formation of alkyl besilates (genotoxic impurities).

- Specification

The drug substance specification includes tests for appearance and solubility, identification (IR and HPLC), besilate content, water content, sulphated ash, heavy metals, related substances (HPLC), assay (HPLC), specific optical rotation and residual solvents (GC). The drug substance is also routinely tested for particle size.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (in-house) analytical methods: HPLC methods for identification of clopidogrel, assay, chromatographic purity and related substances and GC method for residual solvents.

The HPLC methods have been validated for specificity, absorptivity factor (i.e. RRF), linearity and range, limit of quantitation, limit of detection, accuracy, precision (system precision, method precision i.e. repeatability, intermediate precision), robustness, solution stability, forced degradation and peak purity.

The GC method has been validated for specificity, linearity, limit of quantitation, limit of detection, accuracy, precision (method precision i.e. repeatability, intermediate precision) and robustness with regards to specified solvents. All acceptance criteria were in line with ICH recommended limits

In general analytical methods proposed are suitable to control the quality of the drug substance.

Data on three consecutive batches of clopidogrel besilate manufactured according to the proposed manufacturing process as described in the ASMF was provided by the ASMF Holder. In addition data on three batches of the drug substance used for commercial scale-up and stability studies has been provided by the applicant. All batches represented full scale production and complied with the requirements in the drug substance specification.

- Stability

Stability studies were carried out according to ICH guidelines for real time (25°C/60% RH) and accelerated conditions (40°C/75% RH). Data for three commercial scale batches were given with 12 months real time and 6 months accelerated data. No trends were found at long-term and accelerated conditions for tested parameters.

In addition forced degradation studies were performed. Results form this study proved that clopidogrel besilate degrades under stress conditions (acidic and alkaline conditions, oxidation, UV irradiation, sun light and thermal treatment) to the known impurities. No unknown impurities were detected during stability testing.

The stability studies confirmed the proposed re-test period.

Medicinal Product

- Pharmaceutical development

The aim of the pharmaceutical development was to obtain, using different salt of clopidogrel (clopidogrel besilate) as active substance, a robust and stable immediate release tablet formulation that is comparable in terms of dissolution and stability to the reference medicinal product, and to be bioequivalent.

Similarity with the reference medicinal product was addressed by way of composition comparisons, dissolution studies and comparative impurity profiles.

After intensive tests performed with the reference product the target characteristics for formulation were defined as disintegration time, dissolution, loss on drying and impurities.

Based on results from the pre-formulation studies two issues requiring addressing specifically during the development program were solubility of the active substance and consequently the dissolution profiles of the finished product in different media and the stability of the active substance since the pre-stability results indicated degradation of the active substance in acidic, alkaline and peroxide treatment and slight degradation in high temperatures and light presence.

Based on the excipients compatibility study and knowledge of the reference products, different small-scale laboratory trial formulations were prepared and tested for the physical (pharmacotechnical) characteristics against the reference product in order to find appropriate formulae with satisfactory pharmacotechnical characteristics, dissolution profile and stability results (pre-stability studies were conducted with regard to impurity profile). The study also included different manufacturing processes (dry mixing, wet granulation with water and wet granulation with absolute ethanol).
Discriminatory nature of the dissolution method due to the ability to distinguish between batches with different composition was demonstrated by dissolution testing carried out on different formulations. Results from these studies allowed developing the final optimised composition of the finished product, in terms of excipients, and choosing the most appropriate manufacturing process.

Impurity profile comparisons and assay values of test product and reference medicinal product from different EU markets showed that Grepid and the reference product have comparable assay values and impurity profile.

Similarity between two products was also shown by dissolution testing. Comparative dissolution profiles of Grepid 75 mg film-coated tablets and reference product Plavix 75 mg film-coated tablets in three different media: 0,1 M HCl, phosphate buffer pH 4,5 and phosphate buffer pH 6,8 have been conducted. The dissolution profiles of test product and reference product are considered similar in all three media. All calculated F_2-values are above 50.

A bioequivalence study was conducted, under fasting conditions, in order to prove in-vivo bioequivalence between Grepid 75 mg film-coated tablets and the reference product Plavix 75 mg film-coated tablets.

- Adventitious Agents

Among excipients used in the drug product only lactose monohydrate present in coating agent (Opadry II Pink 32K14834) is of animal origin. Declarations from lactose suppliers were provided stating that milk used for production of lactose is sourced from healthy animals under the same conditions as milk collected for human consumption.
Stearic acid used in the formulation is of vegetable origin.

- Manufacture of the Product

The proposed manufacturing process is dry, direct-compression. This standard manufacturing process has been sufficiently characterised and includes weighing, sieving, mixing, compressing and film-coating as steps during manufacture. A flow diagram and detailed description of the manufacturing process have been provided.

The critical steps and in-process controls have been identified. Mixing, lubrication, compression and coating were found to be critical steps. Mixing is considered essential to produce a homogenous powder/granule, which is critical for batch-to-batch reproducibility. Lubrication is necessary to overcoming abrasiveness of powder before compression. Tabletting (compression) is essential for uniformity of content, uniformity of tablet mass and good disintegration characteristics. Coating is essential for the pharmaceutical form of film-coated tablets in order to ensure that the solvent that is selected for the application of the coating is suitable and does not affect the uncoated tablets and that the film coating is applied appropriately on uncoated tablets and consequently the produced film-coated tablets present no defects.

- Product Specification

The product specification is a standard one for tablets and contains tests with suitable limits for appearance, identification (HPLC and UV), average mass and uniformity of mass, loss on drying, disintegration, hardness, uniformity of dosage units, assay (HPLC), related substances, including chiral purity and genotoxic impurities (HPLC), residual solvents (GC), dissolution, microbial

contamination, identification of colouring agent (titanium dioxide and iron oxide) and tightness of blister.

Full details of all analytical methods have been provided. All non pharmacopoeial methods have been satisfactory validated.

The HPLC methods for assay, dissolution and related substances have been suitably validated with respect to stability of the standard and sample solutions, specificity, linearity and range, accuracy, precision (system and method precision/repeatability, intermediate precision) and robustness. Relevant chromatograms have been provided.

The GC method for determination of residual solvents has been validated with respect to stability of the standard and sample solutions, linearity and range, specificity, limit of quantitation, limit of detection, accuracy, precision (system and method precision/repeatability, intermediate precision) and robustness.

Batch analysis data was provided on three pilot scale batches of the finished product. Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. It has been shown that tablets can be manufactured reproducibly according to the finished product specifications.

- Stability of the Product

Stability studies under ICH conditions of 25ºC/60%RH (long term, 12 months), 30ºC/65%RH (intermediate, 12 months) and 40ºC/75%RH (accelerated, 6 months) were carried out on three pilot scale batches (the same as used for process validation and quality control of finished product). Containers used in the stability studies were the same as those proposed for commercialisation.
Photostability and degradation studies have also been included in the stability program. The results proved a stability indicating properties of the method used for determination of impurities.

Stability results showed no increase of the impurities (known and unknown). The results are well within the specifications. Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

In summary the stability data provided support the proposed shelf-life and storage conditions.

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, 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 clopidorel 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

Introduction

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

GCP

The bioequivalence study AA44502 was performed by a Clinical Research Organisation (CRO) in Canada (clinical part) and a CRO in Switzerland (analytical part). It was stated that the clinical part of the study was carried out in accordance with Standard Operating Procedures (SOPs) which are written based on the principles and requirements described in the ICH guideline on Good Clinical Practice.

The CHMP has requested a routine GCP inspection of the clinical study AA44502. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure.

Clinical studies

Two bioequivalence studies comparing Grepid 75 mg film-coated tablets (clopidogrel besilate) with the originator Plavix 75 mg film-coated tablets (clopidogrel hydrogensulphate) marketed in Greece by Sanofi Pharma Bristol-Myers Squibb SNC. The study was performed in fasting subjects, measuring both the parent drug and the major (inactive) metabolite, clopidogrel carboxylic acid. 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: AA44502
Single-dose, Randomised, 2-way Crossover Bioavailabiliy Study Comparing Pharmathen SA Clopidogrel Besilate 75 mg Tablets with Sanofi Pharma Bristol –Myers Squibb SNC (Plavix) Clopidogrel Bisulphate 75 mg Tablets in Healthy Adult Volunteers under Fasting Conditions

The objective of this study was to assess the single-dose relative bioavailability of Pharmathen SA clopidogrel besilate 75 mg tablets and Sanofi Pharma Bristol-Myers Squibb SNC (Plavix) 75 mg clopidogrel bisulphate tablets. This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence, comparative bioavailability study performed on 64 healthy adult non-smoking volunteers (41 males and 23 females). The study was performed in fasting subjects, measuring both the parent prodrug and the major (inactive) metabolite, clopidogrel carboxylic acid. The protocol and informed consent forms (ICFs) were reviewed and approved by an Institutional Review Board (IRB) convening at the CRO in Canada, prior to study initiation on 18/Sep/2007 and 16/Oct/2007. The study was conducted between 12/Oct/2007 and 3/Nov/2007.

TEST AND REFERENCE PRODUCTS

Clopidogrel/Pharmathen 75 mg (clopidogrel besilate), manufactured by Pharmathen SA (batch No.333037)
Plavix 75 mg Clopidogrel (clopidogrel bisulphate), manufactured by Sanofi Winthrop Ind., Sanofi Pharma Bristol-Myers Squibb SNC (batch No. 7Y082)

POPULATION(S) STUDIED

The population studied in trial AA44502 included male and female, non-smoking healthy adult subjects, between 18 and 55 years of age of black and Caucasian race and with a body mass index of 18.0-28.0 kg/m^2. Subjects were divided into two groups for dosing of the two treatments. Sixty two (62) subjects completed the study and data of all 62 is included in the statistical analysis. Inclusion and exclusion criteria are acceptable and drop outs handling performed according to the protocol requirements. The selected population is in accordance with the N*f*G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98.

ANALYTICAL METHODS

Determination of clopidogrel and clopidogrel acid metabolite in human plasma (EDTA) samples was performed by LC/MS/MS. Clopidogrel hydrochloride-d6 and Clopidogrelat hydrochloride-d6 were used as internal standard. The method was validated at a CRO in Switzerland.

PHARMACOKINETIC VARIABLES

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

STATISTICAL METHODS

The ANOVA model included group, sequence, period nested within group, formulation and formulation group interaction as fixed affects and subject nested within group sequence as a random effect. The ANOVA model included group, sequence, period nested within group, formulation, and formulation group interaction as fixed effects, and subject nested within group sequence as a random effect. Sequence was tested using subject nested within group sequence as the error term, at a 10% level of significance. The 90% confidence intervals for the ratios of drug formulation least-squares means (LSM) were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed AUC_{0-t}, AUC_{inf} and C_{max} pharmacokinetic parameters. The ratios of LSM and confidence intervals were expressed as a proportion relative to the reference formulation. Non-parametric analysis of t_{max} was performed using the methods of Koch and Hauschke.

- Results

Pharmacokinetic parameters of clopidogrel (non-transformed values; arithmetic mean ± SD, t_{max} median)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**Tmax** h	**$T_{1/2}$** h
Test	1.358.98	1.54862	0.773251	1.0229	4.3251
Mean CV	135.8	131.6	154.9	65.7	62.1
n	62	53	62	62	53
Reference	1.41228	1.53756	0.793657	0.9405	4.6727
Mean CV	110.1	96.3	122.8	46.5	52.8
n	62	49	62	62	49
***Ratio (90% CI)**	0.96 (0.88-1.05%)	0.99 (0.89-1.11%)	0.97 (0.86-1.10%)		

Intra – subject CV (%)	30.9	31.0	44.1		

$AUC_{0-\infty}$ 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*

Pharmacokinetic parameters of clopidogrel carboxylic acid (non-transformed values; arithmetic mean ± SD, t_{max} median)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	Tmax h	$T_{1/2}$ h
Test Mean CV n	7564.17 23.9 62	8027.39 24.1 62	2734.052 37.7 62	0.8807 38.6 62	9.048 24.1 62
Reference Mean CV n	7793.82 24.5 62	8304.70 24.4 62	3022.353 36.9 62	0.7985 37.8 62	9.205 24.2 62
***Ratio (90% CI)**	0.97 (0.95-0.99%)	0.97 (0.95-0.99%)	0.91 (0.84-0.97%)		
Intra-subject CV (%)	7.4	7.2	24.4		

$AUC_{0-\infty}$ 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 criterion for the conclusion of bioequivalence was defined in the study protocol:

- The 90% confidence interval for the exponential of the difference between the test and the reference product for the ln-transformed parameters C_{max}, AUC_{0-t} and AUC_{inf} should be within **80-125%.**

The calculated 90% confidence intervals for all defined parameters for both parent prodrug and the metabolite lie within the acceptance range of 80-125% defined in the protocol for AA44502 trial for acceptance of bioequivalence. No pre-dose levels of clopidogrel and clopidogrel 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 insignificantly different between the test and reference products. The extrapolated AUC of clopidogrel acid is below 20% in each individual subject except for one subject and this single exception is not likely to affect the evaluation of bioequivalence. However, the calculated intra-subject variabilities are higher for clopidogrel in comparison with clopidogrel acid and several study subjects did not exhibit a terminal log-linear phase in their concentration *vs* time profiles for clopidogrel or had a below limit of quantification (BLQ) concentration for clopidogrel. These results were consequently not included in the pharmacokinetic and statistical analysis. The suitability of the proposed Lower Limit of Quantification for the determination of clopidogrel was questioned by the CHMP. In response, it was argued that this LLOQ allows a good characterisation of the plasma concentration-time profile of clopidogrel, since the

sampling schedule covers sufficient number of elimination half-lives post-C_{max} in the majority of subjects. Although some subjects did not exhibit a terminal log-linear phase in their concentration versus time profiles for clopidogrel and some subjects had occasionally BLQ values flanked by measurable concentrations, the proposed LLOQ for clopidogrel was deemed adequate to characterise the pharmacokinetics of clopidogrel. Since this study has a rich sampling design, the missing samples of some subjects were excluded from the analysis and this is considered the least biased method of calculating AUC_{0-t}. The missing time points occurred mainly near the end of the pharmacokinetic profile where concentrations are low and of limited contribution to the overall value of the AUC.

The following safety parameters have been evaluated in study AA44502: adverse events (AEs), vital signs, pre-study 12-lead ECG, laboratory parameters, physical examination. No serious adverse events (SAEs) occurred during the study. One subject experienced an adverse event (headache) after receiving the test and no subjects experienced any AEs after receiving the reference product. The tolerability of the test product is acceptable and not significantly different from reference product.

Two subjects were withdrawn from the clinical trial due to personal reasons. The majority of protocol deviations were, amongst others, related to the sampling procedures such as timing, sample storage and volume of blood taken. The protocol deviations were not considered to have a significant impact on efficacy and safety evaluation.

- Conclusions

Based on the presented bioequivalence study Grepid 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 should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

The MAH must ensure that the system of pharmacovigilance, as described in version 03.02 dated 5 September 2008 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

- **Risk Management Plan**

Not applicable as the application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified.

Discussion on Clinical aspects

One clinical bioequivalence trial AA44502 was provided for Grepid application, analysing the parent prodrug clopidogrel as well as the inactive metabolite clopidogrel carboxylic acid. 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 with respect to dissolution profiles at different pH values, the lack possible interactions of the besilate moiety with the platelets, the behaviour and absorption pattern of clopidogrel besilate in the gastrointestinal tract and the use of besilates in medicinal products and the clinical experience with besilate salts present in medicinal products on the market. It was emphasized that the use of other medicinal products containing besilate moiety has not shown any safety signals. The absorption of benzenesulfonic acid and its non-specific binding was assessed by evaluating the bi-directional permeability of benzenesulfonic acid through a Caco-2 monolayer system. The results confirmed that benzenesulfonic acid is not absorbed to any meaningful extent and thus, would not have the capacity to show aggregatory or antiaggregatory effects. Nevertheless, in order to assess the potential antiaggregatory activity of benzenesulfonic acid, *in vitro* ADP-induced platelet aggregation studies were performed by employing optical aggregometry in plasma samples spiked with benzenesulfonic acid. It was evident that benzenesulfonic acid had no significant effect on prothrombin time even at the high concentrations and did affect fibrin clot formation. The potential for an adverse interaction between platelets and the besilate moiety is thus unlikely and the CHMP considered the issue resolved.

The indication of Grepid is different from that of the reference medicinal product, Plavix (please see section 3.1). Thus, the Product Information has been adequately amended to reflect this change and this is considered acceptable.

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 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, evaluation of the pharmacokinetic profile of clopidogrel carboxylic acid is considered supportive and clopidogrel pharmacokinetic data are essential for the establishment of bioequivalence.

Furthermore, 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 studies were conducted in fasted state and thus, the CHMP requested a clarification of this approach and 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, 6.8) and mimicking the conditions of a fed state did not reveal any major differences when compared to the reference product.

The bio-analytical technique and methodology applied in the analysis of the samples during the bioequivalence study AA44502 were described. However, the CHMP requested further details on validation including stability results of the analyte and metabolite in the biological matrix and stock solution, specificity, accuracy, precision, limit of quantification and response function, since the presented summary results for clopidogrel and clopidogrel carboxylic acid were not sufficient to claim that the method was validated. It was also questioned whether there is a potential for the 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. In response, details of the bio-analytical methodology and full validation report were provided demonstrating that no methanol, which is needed for the conversion the acid metabolite to clopidogrel, was used and thus, no source of methylation exists within the entire methodology, including all solution preparation, plasma sample processing, handling storage and LC-MS/MS determination. The CHMP considered this issue resolved.

The CHMP has requested a routine GCP inspection of the clinical study AA44502, which revealed no major or critical deviation from GCP. Two observations were found to be of major importance during the inspection of the bioanalytical part of the trial. The first observation was related to the absence of the validation report, which was also requested by the CHMP during the evaluation of the dossier. The second observation was related to the management and quality control in sample preparation. Following the submission of the requested report and based on the conclusions from the GCP inspection the data obtained from the bioequivalence study AA44502 are acceptable and the conclusions of the study are valid.

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 required acceptance range of 80-125% for the parent drug clopidogrel and for the clopidogrel carboxylic acid metabolite.

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 decision that the benefit/risk ratio of Grepid 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 was favourable and therefore recommended the granting of the marketing authorisation.