European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT FOR ZYLAGREN

International Nonproprietary Name:
clopidogrel

Procedure No. EMEA/H/C/1138

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 Krka, d.d., Novo mesto submitted on 25 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Zylagren, 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
- Date of authorisation: 15-07-1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/98/069/001a, EU/1/98/069/001b, EU/1/98/069/002a, EU/1/98/069/002b, EU/1/98/069/003a, EU/1/98/069/003b, EU/1/98/069/004a, EU/1/98/069/004b, EU/1/98/069/005a, EU/1/98/069/005b, EU/1/98/069/006a, EU/1/98/069/006b, EU/1/98/069/007a, EU/1/98/069/007b

■ 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(s), pharmaceutical form(s): Plavix, 75 mg, film coated tablets
- Marketing authorisation holder[4]: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-07-1998
- Marketing authorisation(s) granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/98/069/001a, EU/1/98/069/001b, EU/1/98/069/002a, EU/1/98/069/002b, EU/1/98/069/003a, EU/1/98/069/003b, EU/1/98/069/004a, EU/1/98/069/004b, EU/1/98/069/005a, EU/1/98/069/005b, EU/1/98/069/006a, EU/1/98/069/006b, EU/1/98/069/007a, EU/1/98/069/007b
- Member State of source: Germany

The Rapporteur appointed by the CHMP was:
Prof. Philippe Lechat

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

Zylagren has been given a Marketing Authorisation in the following countries using the invented name Zyllt.

Country	Date of Authorisation
Poland	30.04.04
Bulgaria	14.09.06
Albania	11.07.06
Bosnia and Hercegovina	28.09.05
Croatia	22.12.04
Former Yugoslavic Republic of Macedonia	15.10.03
Serbia	19.12.05
Russian Federation	05.08.05
Ukraine	01.04.05
Uzbekistan	25.02.08
Belarus	20.02.08

A Marketing Authorisation for Zyllt was suspended in Slovenia on 01.12.06

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 20 February 2009.
- The procedure started on 25 March 2009. The timelines were aligned with the re-start of the Zyllt procedure after the submission of the responses to the D120 List of Outstanding Issues.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 May 2009.
- During the CHMP meeting on 26 – 29 May 2009, the CHMP agreed on a List of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of outstanding issues on 03 June 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 11 June 2009
- During the meeting on 22-25 June 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 Zylagren on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 June 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Zylagren 75mg film-coated tablets are generic medicinal products containing clopidogrel as clopidogrel hydrogensulphate as active substance. The reference medicinal product is Plavix 75 mg film-coated tablets, which contains 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. Zylagren 75mg film-coated tablet contains clopidogrel hydrogesulphate. 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 hydrogensulphate.

The indication for Zylagren is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.

The therapeutic indication of Zylagren 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

Composition
Zylagren contains clopidogrel as the active substance. It is presented as film-coated immediate release tablets. Each tablet contains 97.875 mg clopidogrel hydrogen sulphate equivalent to 75 mg of clopidogrel.
Other ingredients used in the core tablet include anhydrous lactose, microcrystalline cellulose, pregelatinised starch, polyethyleneglycol 6000 and hydrogenated castor oil. The film coating consists of hypromellose 6cp, titanium dioxide, talc, red iron oxide and propylene glycol.
The tablets are packed in OPA/AL/PVC – Alu blisters.

Active Substance

The chemical name of clopidogrel hydrogen sulphate is (+)-(S)-Methyl α-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4*H*)-acetate hydrogen sulphate.
It is a white to off-white or yellowish crystalline powder practically insoluble in water at neutral pH, freely soluble in water at pH 1 and in some organic solvents like methanol. The chemical structure of clopidogrel hydrogen sulphate has been confirmed with nuclear magnetic resonance (^{1}H-NMR, ^{13}C-NMR), mass spectrometry (MS), infrared spectrometry (IR) and elemental microanalysis. Clopidogrel hydrogen sulphate exists in two polymorphic forms, form I and II. The proposed manufacturing process produces consistently the form I and this has been confirmed with X-Ray powder diffraction and FT-IR spectra. The molecule includes a chiral atom of carbon and therefore exhibits diasteromerism. The active substance is the S-, (+)- diastereomer.

- Manufacture

Clopidogrel hydrogen sulphate is synthesised by three alternative routes from four key starting materials. The manufacturing process consists of three stages: the synthesis of clopidogrel free base (stage 1), purification of clopidogrel (stage 2) and crystallisation of clopidogrel hydrogen sulphate (stage 3). The active substance is manufactured in three manufacturing sites.
The reaction scheme, description of the manufacturing process, characterisation, test methods and specifications for all starting materials have been provided. In addition batch analysis data have been provided for 3 batches manufactured according to all alternative methods by all manufacturers. In all cases the active substance produced met the predefined specifications.
The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.The solvents used in the synthesis have been shown to be efficiently removed during the purification and drying operations and appropriate specifications have been set.
The active substance is packed into LDPE bags and then into a secondary laminated bags made of PET/Al/PE foil and is stored into cardboard drums. Suitable specifications for primary packing material have been provided together with an FT-IR spectrum of the LPDE bag. A declaration of conformity with European Regulation for food contact for the primary packing has been provided. Suitable specifications for the laminated bag have also been set.

- Specification

The active substance specification includes tests for appearance, identification (IR, sulphates), assay (HPLC),), solubility (Ph. Eur.), loss on drying (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (UPLC, HPLC,CAD), enantiomeric purity (chiral HPLC) , particle size (laser diffraction method), polymorphic form (XRPD).

- Stability

Stability studies have been carried out on three batches of the active substance in accordance with ICH requirements. Samples have been stored at long-term conditions (25°C/60 % RH) for 24 months and at accelerated conditions (40°C/75% RH) for 12 months.
The parameters tested were appearance, assay, loss on drying, related substances, and enantiomeric purity. The analytical methods used were the same as the ones used for release testing and have been shown to be stability indicating.
Photostability studies have also been performed and have demonstrated that the active substance is not sensitive to light.
Results of stress studies showed that clopidogrel hydrogensulfate is sensitive to basic hydrolysis, oxidation and to acid hydrolysis at elevated temperature. Practically no degradation occurs when clopidogrel hydrogensulfate is placed at solid state under elevated temperature.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance and exhibiting the same bioavailability as the already marketed reference product PLAVIX 75 mg film-coated tablets in order to comply with the regulations pertaining to abridged applications in the European Union.
Zylagren does not have exactly the same qualitative composition with the reference product with regards to excipients. In Zylagren lactose is used as filler and pregelatinised starch as binder compared to mannitol and hypromellose used in Plavix respectively However, the chosen excipients raise no concerns since they are well-established and commonly used in the manufacture of solid dosage forms. All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.
As clopidogrel hydrogen sulphate is unstable in the presence of excessive amounts of water direct compression was chosen for manufacturing the Zylagren tablets. In order to cover the unpleasant taste of the active ingredient the tablets are film-coated.
The immediate packaging material consists of OPA-Alu-PVC blisters and has been demonstrated through stability studies to provide a good protection from water.
Three batches of CLOPIDOGREL hydrogen sulphate 75mg, film-coated tablets have been compared to two batches of the reference PLAVIX.Related substances and enantiomeric purity results show that both products are comparable in terms of impurity profile
A discriminatory dissolution test has been developed for routine testing of the clopidogrel tablets. An acidic dissolution medium has been chosen (0.1 M HCl), because the solubility of clopidogrel hydrogen sulphate decreases as the pH values increase and the requirements for sink conditions are met only at acidic conditions (900 ml of 0.1M HCl). The influence of the particle size of the active substance (from mean 11 μm to 97 μm) on the dissolution profile has been tested and it was found that the dissolution profile is not significantly different whatever the mean particle size is within the range that is set in the active substance specifications.
Comparative dissolution profiles between the reference product and Zylagren were performed in three different dissolution media (0.1 M Hydrochloric acid, Acetate buffer solution pH 4.5 and Phosphate buffer solution pH 6.8). The results show that Zylagren expresses similar dissolution profiles in all three dissolution media and that the dissolution profiles are comparable with that of the reference product.
The bioequivalence study was performed using as reference the biobatch No. 600711 of Plavix 75 mg tablets manufactured by Sanofi-Synthelabo Limited, UK (expired date 02/2009) has been used in bioequivalence study. The biobatch No. P11092 of Clopidogrel 75 mg tablets (hydrogen sulphate salt) manufactured by Krka, Novo Mestro, d.d., Slovenia in 11/2007 has been used as the tested product in the bioequivalence study.

- Manufacture of the Product

The manufacturing process is a standard direct compression process and consists of the following steps: screening, mixing, compression to tablets and film-coating.
All critical process parameters have been identified and controlled by appropriate in process controls.
The validation report from 3 production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, uniformity of dosage units, identification (HPLC, TLC), assay (HPLC), identification of titanium dioxide and iron oxides, related substances, microbiological quality, enantiomeric purity, dissolution, hardness, , disintegration and water content.
All tests included in the specification have been satisfactorily described and validated.
Batch analysis data from 3 production scale and 6 supportive batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out on 3 production scale batches of tablets according to the ICH requirements. Samples were packaged in the same immediate packaging as the one intended for marketing. were stored at 25°C/60 % RH for 24 months and in 40°C/75 % RH for 6 months.
The parameters tested were appearance, assay, water content, hardness, related substances, enantiomeric purity, dissolution, and microbiological tests. The analytical procedures used were the same as those used for routine testing and have been shown to be stability indicating.
In addition photostability tests have been performed in accordance with ICH guideline Q 1 B.
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 Zylagren is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

In comparison with the EU reference product Zylagren has been shown to have the same qualitative and quantitative composition in terms of the active substance. The excipients used are mostly the same with some minor modifications. Both the EU reference product (Plavix) and Zylagren exhibit similar dissolution profiles.

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 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 hydrogensulphate were provided. Further studies are not required, because the active substance used in reference product and the generic product are the same and the overview based on the literature is, thus, appropriate. Although the *in vitro* studies did not reveal any mutagenic, genotoxic or clastogenic potential of clopidogrel, the CHMP raised a major objection with respect to the studies on impurities, which did do not follow recommendations of the OECD guideline, protocol 471 (*OECD, 1997, Test Guideline 47:Bacterial Reverse Mutation Test. In: OECD Guideline for Testing of Chemicals. Paris, Organization for Economic Cooperation & Development*) and of the *Question & Answers on the CHMP guideline on the limits of genotoxic impurities* (EMEA/CHMP/SWP/431994/2007). In response, adequately conducted reverse mutation assays in accordance with GLP standards and OECD guideline protocol number 471 was provided. The results of the Ames test performed with potassium ethyl sulphate and clopidogrel isopropyl sulphate indicated that these two substances do not hold a mutagenic potential. Thus, the content limit for monoalkylsulphates as proposed by the applicant is acceptable to the CHMP.

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 provided in support of the application was performed by CROs in Canada. A statement was provided that the clinical part of these studies was conducted according to the ICH Note for Guidance on Good Clinical Practices.

During the evaluation of the dossier, the CHMP considered that in the view of the reported discrepancies that occurred during clopidogrel plasma analysis, it was necessary to inspect the conduct of the bioequivalence study 08-210. The results of this triggered inspection and the satisfactory responses to its findings are an integral part of the procedure.

Clinical study

One bioequivalence study comparing Zylagren 75 mg film-coated tablets with the originator Plavix 75 mg film-coated tablets was provided. The study was performed in fasting subjects and measured the parent drug and the major (inactive) metabolite, clopidogrel carboxylic acid.

Pharmacokinetics

- Methods

STUDY DESIGN

Study code: 08-210
Randomized, open-label, 2-way crossover, bioequivalence study of Clopidogrel75 mg film-coated tablet and Plavix (reference) following a 75 mg dose in healthy subjects under fasting conditions
The objective of this study was to compare the rate and extent of absorption of clopidogrel originating from KRKA d.d. Novo mesto, Slovenia and Plavix, Sanofi-Synthelabo Limited, U.K., administered as a 1 x 75 mg film-coated tablet, under fasting conditions. This was a single centre, bioequivalence, open-label, single-dose, randomised, 2-way crossover study, performed in 96 healthy volunteers. Subjects were confined to Clinical Research Facility from at least 10 hours prior to drug administration, until after the 28.0-hour post dose blood sample in each period. The treatment phases were separated by a washout period of 7 days. The study protocol and Informed Consent Form (ICF) were approved by the Institutional Review Board and approved in March 2008. The clinical study was conducted between 25 March 2008 and 6 April 2008.

TEST AND REFERENCE PRODUCTS

Clopidogrel 75 mg film-coated tablets, manufactured by KRKA, d.d. Novo Mesto. Slovenia, batch: P11092.

Plavix 75 mg tablets manufactured by Sanofi-Synthelabo, United-Kingdom, batch: 600711.

POPULATION(S) STUDIED

In total, 96 subjects were included in the study, out of which 92 subjects finished the study and 91 subjects were included in the data set for statistical analysis. Subjects were healthy, male non-smokers, aged $\geq$ 18 and $\leq$ 55 years; with BMI $\geq$ 19.0 and $<$ 28.0 kg/m2. Adequate inclusion and exclusion criteria were followed. The withdrawal or discontinuation of all subjects are documented and their validly is justified. The choice of the selected population in this clinical trial was considered appropriate.

ANALYTICAL METHODS

The plasma samples were assayed for clopidogrel and its carboxylic acid metabolite using LC/MS/MS method using the calibration range from 5.04 pg/mL – 5040 pg/mL (clopidogrel) and 4.02 ng/mL – 4016 ng/mL (clopidogrel carboxylic acid). The analytical technique was validated. A partial validation was conducted successfully in order to allow this transfer. However, there were insufficient data submitted with respect to the pre-study validation and validation of the bio-analytical technique used for determination of clopidogrel, and the CHMP questioned the validity of the bioequivalence study. Thus, a GCP inspection was requested.

PHARMACOKINETIC VARIABLES

The main investigated pharmacokinetics parameters for clopidogrel and clopidogrel carboxylic acid were AUC_{0-t}, AUC_{0-inf} and C_{max}.

STATISTICAL METHODS

Parametric ANOVA analysis on ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} was carried out for analytes, clopidogrel and clopidogrel carboxylic acid. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect. A non parametric test was carried out to compare T_{max}.

- Results

Pharmacokinetic parameters for clopidogrel (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range) following a single 75 mg oral dose (n=91) in study 08-210 are presented below.

Treatment	**AUC_{0-t}** pg*h/ml	**$AUC_{0-\infty}$** pg*h/ml	**C_{max}** pg/ml	**t_{max}** h
Test **(S.D.)**	3815.1 (5072.6)	3811.7 (4944.3)	3424.5 (5538)	0.667 (0.33-3)
Reference **(S.D.)**	3755.2 (4370.3)	3792.3 (4251.5)	3098.6 (4823.4)	0.667 (0.33-3)
***Ratio (90% CI)** **Point estimate**	[84; 107]% 95 %	[81; 104]% 92 %	[89; 117]% 102 %	-
Intra-subject CV (%)	52.2 %	52.2 %	58.8 %	
$AUC_{0-\infty}$ 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: median, min and max				

**log-transformed values*

Pharmacokinetic parameters for clopidogrel carboxylic acid (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range) following a single 75 mg oral dose (n=91) in study 08-210 are presented below.

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test **(S.D.)**	7902.6 (1837)	8470.5 (2051.3)	3251.2 (969.5)	0.667 (0.33-3)
Reference **(S.D.)**	7792.6 (1807.3)	8355.5 (1972.8)	3092.1 (873)	0.667 (0.33-4)
***Ratio (90% CI)** **Point estimate**	[99;104]% 101.4 %	[99; 103]% 101.3 %	[100;111]% 105.4%	-
Intra-subject CV (%)	8.7 %	8 .8%	21.5 %	
$AUC_{0-\infty}$ 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: mediane, min and max				

**log-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 proposed 90% confidence intervals for AUC_t and AUC_{inf} 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, the widening of the limits for bioequivalence conclusions for C_{max} values, although not in line with the current CHMP recommendations, was not considered necessary 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. No significant difference in T_{max} was evidenced by the non parametric test.

No serious adverse events (SEAs) were reported during this study. Overall, clopidogrel demonstrated a good safety profile. The risk of bleeding is the most important adverse effect of clopidogrel, which might be even increased when clopidogrel is concomitantly used with ASA. No significant changes in the subjects' state of health were observed and it is believed that Zylagren 75 mg film coated tablet is safe when used according to the SmPC.

From the 96 subjects included in the study, four were withdrawn for personal reasons or non-compliance. 92 subjects finished the study and 91 subjects were included in the data set for statistical analysis, since one subject was excluded from the statistical analysis because clopidogrel carboxylic acid was detected pre-dose in period one of the trial. All withdrawn and discontinued subjects are documented and validity is justified.

- Conclusions

Based on the presented bioequivalence study 08-210, Zylagren is considered bioequivalent with Plavix.

Pharmacodynamics

No studies were submitted.

Post marketing experience

There were no post-marketing data submitted.

Discussion on Clinical aspects

One clinical bioequivalence trial (08-210) was provided for Zylagren (clopidogrel hydrogensulphate). At the time of approval of the reference product Plavix (clopidogrel hydrogensulphate), 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, data related to pharmacokinetics of clopidogrel carboxylic acid are considered supportive, whereas data on clopidogrel parent drug is important for the confirmation of bioequivalence.

The indication of Zylagren is different from that of the reference medicinal product, Plavix (please see section 2.1). Thus, the Product Information has been adequately amended to reflect this change and this is considered acceptable.

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 hydrogen sulphate 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 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 significant over-estimation of clopidogrel plasma levels and would bias the outcome of the bioequivalence study. The back-conversion could occur in the presence of alcohol used in sample preparation and analysis. It was, indeed, reported that a possible back-conversion of clopidogrel metabolite to clopidogrel parent drug was evidenced in the presence of methanol. In order to avoid this process, the extraction procedure was changed and methanol-free conditions employed. Although it has been indicated that stability tests were performed in order to prove the reproducibility and accuracy of clopidogrel concentration measurements, the CHMP questioned these results since no clear description of the analytical technique including extraction procedure actually used in the initial pre-study validation process was provided. Information on the validation procedures in study 08-210 was requested by the CHMP. In response, details of the bio-analytical methodology and full validation details 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.

Considering the above difficulties in the determination of clopidogrel in plasma especially the issue related to the possible back-conversion of the metabolite to the parent drug, a triggered GCP inspection of the bioequivalence study was requested by the CHMP, which was of the opinion that results of this inspection and the satisfactory responses to its findings were an integral part of the evaluation procedure. The inspection identified major and minor findings that seem not to affect the overall results of the trial.

The bioequivalence study 08-210 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, required by the above mentioned guideline. The proposed widening of the 90% confidence interval for clopidogrel C_{max} to 75%-133% 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. The bioequivalence with Plavix was proven.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Zylagren should follow PSURs submission schedule for the reference medicinal product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system (DescPhSys 000001/16 (09 January 2009) 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 generics of respective reference medicinal products for which no safety concerns requiring additional risk minimization activities have been identified, this considered acceptable.

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 that by consensus the benefit/risk ratio of Zylagren 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.”

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