CLOPIDOGREL 75MG FILM-COATED TABLETS
PL 24837/0016

UKPAR

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The Medicines Healthcare products Regulatory Agency granted Consilient Health Limited a Marketing Authorisation (licence) for the medicinal product Clopidogrel 75mg Film-Coated Tablets (PL 24837/0016) on 26th June 2009. This is a prescription-only medicine (POM) for the prevention of blood clots forming in hardened blood vessels, a process known as atherothrombosis, which can lead to stroke, heart attack or death.

The active ingredient is clopidogrel hydrochloride. Clopidogrel belongs to a group of medicines called anti-platelet medicinal products. Platelets are very small structures in the blood, smaller than red or white cells, which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots from forming (a process called thrombosis).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Clopidogrel 75mg Film-Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
CLOPIDOGREL 75MG FILM-COATED TABLETS
PL 24837/0016

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Clopidogrel 75mg Film-Coated Tablets (PL 24837/0016) on 26th June 2009. This is a prescription-only medicine (POM).

This is a national application for Clopidogrel 75mg Film-Coated Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended, which has been shown to be a generic medicinal product of Plavix® 75mg Film-Coated Tablets, authorised to Sanofi-Synthelabo, UK as a centralised product on 15th July 1998. The reference product has therefore been authorised in the EU for more than 10 years.

The product contains the active ingredient clopidogrel hydrochloride, a platelet aggregation inhibitor. It works by irreversibly inhibiting a receptor called P2Y12. The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. The IIb/IIIa complex functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor. Activation of this receptor complex is the "final common pathway" for platelet aggregation, and is important in the cross-linking of platelets by fibrin.

Clopidogrel is taken to prevent blood clots forming in arteries, a process known as atherothrombosis, which can lead to atherothrombotic events, such as stroke, heart attack or death.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Clopidogrel hydrochloride

INN: (+)-(S)-Methyl α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate hydrochloride

Structure:

![Structure of Clopidogrel Hydrochloride](image)

Description: White to off-white or yellowish crystalline powder

Molecular formula: C_{16}H_{16}ClNO_{2}S. HCl

Relative molecular mass: 358.28 gmol\(^{-1}\)

Solubility: practically insoluble in water, freely soluble in methanol and soluble in DMSO.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting material and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance clopidogrel hydrochloride.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The drug substance clopidogrel hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

An adequate retest period has been defined based on conducted stability studies.
DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, colloidal anhydrous silica, crospovidone (type A), macrogol 6000 and hydrogenated castor oil. All the ingredients within the tablet core comply with respective Ph Eur monographs.

The film coating contains: hypromellose (E464), titanium dioxide (E171), red iron oxide (E172), talc and propylene glycol. All ingredients within the film coating comply with relevant Ph Eur monographs with the exception of red iron oxide, in the absence of a Ph Eur monograph is controlled to the United States Pharmacopeia (USP).

Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

Dissolution and Impurity profiles
Dissolution and impurity profiles of the drug product were found to be similar to those for the reference product, PLAVIX® 75mg Film Coated Tablets.

Manufacture
A detailed description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on two batches of product and the results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is presented in blister packs consisting of cold formed OPA/Al/PVC film and heat sealing aluminium foil. Specifications and certificates of analysis for the packaging types used have been provided. These are satisfactory. The product is packaged in sizes of 7, 14, 28, 30, 50, 56, 84, 90 and 100 film-coated tablets in the box. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set. Storage conditions are to “Store in the original packaging material in order to protect from light and moisture” which is satisfactory.
Patient Information Leaflet
This is satisfactory. The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Bioequivalence
Please refer to Clinical Assessment Report.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics
The SPC is pharmaceutically satisfactory.

MAA form
This is satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

Clopidogrel is a widely used well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. This generic application contains a different salt (clopidogrel hydrochloride) of the active substance to that used in the reference product (clopidogrel hydrogensulphate). A summary of the literature information on non-clinical data of clopidogrel and the results of two new non-clinical studies (acute and chronic toxicity) conducted with clopidogrel hydrochloride were provided. Furthermore, on the basis of the CHMP Guidance for a generic application when different salts of the active substance of the reference medicinal product are used, additional information providing proof that their non-clinical safety and/or efficacy profile is not different from that of the reference medicinal product is needed. Thus, information that the different clopidogrel salt (clopidogrel hydrochloride) does not differ significantly in non-clinical properties with regards to safety and efficacy of the reference product were requested in accordance with the relevant guideline.

The response referred to the results of the toxicity and genotoxicity studies to examine the safety profile of clopidogrel hydrochloride vs clopidogrel hydrogen sulphate. The repeated dose toxicity study reports were in accordance with GLP standards and regulatory guidelines (please see section Toxicology). The 13-week toxicity study report did not detect major differences in the safety profile for the hydrochloride and hydrogen sulphate salt; the liver was determined as the target organ in both salts. Regarding the genotoxicity testing, clopidogrel hydrochloride tested at a higher concentration level than clopidogrel hydrogen sulphate, turned out to be not clastogenic in the chromosome aberration test. In the micronucleus test, at the same dose levels, neither the hydrogen sulphate salt nor the hydrochloride salt was found clastogenic/aneugenic. Thus, based on the data provided, similar safety profile was demonstrated for clopidogrel hydrochloride and clopidogrel hydrogen sulphate.

TOXICOLOGY

Two new non-clinical studies were conducted with clopidogrel hydrochloride.

**Single-dose toxicity**

The acute toxicity study on rats was performed with clopidogrel hydrochloride. Results of single dose toxicity studies in rats revealed low toxicity of clopidogrel hydrochloride at doses of 10, 100, 1000 mg/kg. No clinical signs of toxicity and mortality were reported in rats after the administration of drug. No significant differences in body weight gain were seen between the control and treated groups. At terminal necropsy, no apparent macroscopic changes attributed to clopidogrel hydrochloride administration were observed in any animal. The majority of tissue was macroscopically unremarkable. LD₅₀ values were over 1500mg /kg for both sexes.

After a single oral administration of clopidogrel in mice, rats and baboons, toxicity occurred only at very high doses and the target organs were mainly the gastrointestinal tract, the kidney and the lung. The oral LD₅₀ values of clopidogrel were over 2 g/kg in all species.
Repeated-dose toxicity
The toxicity of clopidogrel hydrochloride was investigated in rats upon daily oral administration by gastric gavage for 13 consecutive weeks. The study was conducted with four groups of 10 males and 10 females each versus one vehicle control group and 3 test groups receiving 12.5, 125 or 250 mg/kg body weight/day. Treatment with clopidogrel hydrochloride was generally well tolerated, based on the lack of treatment related clinical signs and the normal growth of the animals. Some treatment related changes in haematology, e.g. thrombocytes, and clinical chemistry, e.g. cholesterol, triglycerides, bilirubin, total protein, etc., were revealed. Decreased thymus weights, increased adrenal, kidney, seminal vesicles and liver weights and hypertrophy of centrilobular hepatocytes were also observed. The no-observed-adverse-effect level (NOAEL) for clopidogrel hydrochloride was considered to be 12.5 mg/kg body weight/day. There appears to be no additional toxic effects of clopidogrel hydrochloride although no direct comparative data between the clopidogrel hydrochloride and clopidogrel hydrogensulphate were provided. Furthermore, any potential differences in the non-clinical toxicokinetic profile would be apparent in the clinical pharmacokinetic profile addressed by the bioequivalence studies.

Genotoxicity
The in vitro Salmonella typhimurium reverse mutation assays of clopidogrel hydrochloride was performed and revealed evidence that clopidogrel did not induce effects at either the gene or chromosome levels. In Ames test of clopidogrel’s main metabolite S-carboxylic acid derivative was also negative. The eventual mutagenic activity of clopidogrel hydrochloride was investigated in the bacterial reverse mutation assay with Salmonella typhimurium strains TA97a, TA98, TA100, TA 1535 and TA102, without and with metabolic activation. The tested substance was considered non mutagenic. Clopidogrel was not genotoxic in micronucleus test in mice. Incidence of micronucleated polychromatic red blood cells (RBs) was not elevated in mice that received clopidogrel at oral doses up to 2000 mg/kg daily, for three consecutive days. Ratio of polychromatic to normochromatic reb blood cells was also normal which indicates that there was no bone marrow cytotoxicity. There was no evidence of any clastogenic activity for clopidogrel.

Although the in vitro studies did not reveal any mutagenic, genotoxic or clastogenic potential of clopidogrel, a major objection with respect to the studies on impurities, which did 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.

Introduction of the product onto the market is unlikely to result in any significant increase in the combined sales volumes for all clopidorel 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.
CLINICAL ASSESSMENT

1 BACKGROUND
Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist. It belongs to the Pharmacotherapeutic group of platelet aggregation inhibitors. 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.

2. INDICATIONS
Clopidogrel is indicated 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.

3. DOSE & DOSE SCHEDULE
- Adults and elderly
  Clopidogrel should be given as a single daily dose of 75 mg with or without food.
- Paediatric patients
  The safety and efficacy of clopidogrel in children and adolescents have not yet been established.
- Renal impairment
  Therapeutic experience is limited in patients with renal impairment (see section 4.4 of the SPC).
- Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4 of the SPC).

4. TOXICOLOGY
No new data are submitted or required. However the pre-clinical aspects of the application have been assessed separately.

5. CLINICAL PHARMACOLOGY
5.1 Pharmacodynamics
Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.
and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

5.2. Pharmacokinetics

Clopidogrel is rapidly absorbed after oral administration, with a relative bioavailability of approximately 50%.

The parent-drug (clopidogrel) is a pro-drug and its active metabolite, a thiol derivative, is formed by oxidation to 2-oxo-clopidogrel and subsequent hydrolysis, the oxidative step is mediated by CYP450 isoenzymes (CYP2B6 and 3A4 and to lesser extent by the CYP1A1). Although the pharmacological properties of the active metabolite are characterized in vitro, no in vivo pharmacokinetic data are available at present. This metabolite is still undetectable by the currently available analytical technique. Thus its PK behavior is still unknown.

Extensive hepatic metabolism of clopidogrel yield mainly an inactive carboxylic acid metabolite, referred to as SR26334. This metabolite represents approximately 85% of the drug-related compounds circulating in the plasma.

The inactive metabolite SR26334 exhibits linear PK behavior with increasing doses up to 150 mg.

The elimination half-life of SR26334 is about 8 h.

5.3 Clinical studies

The applicant has submitted one bioequivalence study. This was an open-label, randomised, single-dose, two-period, two-sequence, crossover study. 96 healthy non-smoking adult male volunteers were enrolled. Subjects were divided in two groups for dosing: Group 1 (Subject Nos. 1-48) and Group 2 (Subject Nos. 49-96). A total of 92 subjects completed the clinical phase of the study. In each period, subjects were housed from at least 10 hours before dosing until after the 28-hour post-dose events. The study compared Test product: Clopidogrel 75 mg film-coated tablets with the reference product: PLAVIX® 75 mg tablets.

On the morning of Day 1, in each period, subjects received a single oral 75 mg dose, after an overnight fast, with 240 ml of water. Doses were separated by a 7-day washout period. A total of 19 blood samples were collected in each period at pre-dose and up-to 28 hours post-dose.

Population(s) studied
A total of 96 were included in the study, among them 4 subjects were withdrawn/discontinued. 92 subjects finished the study and were included in the data set for statistical analysis.

Adequate inclusion/exclusion criteria were followed. All withdrawals/discontinuers are documented and justified.
Methods

Analytical methods

The plasma samples were assayed for clopidogrel and its carboxylic acid metabolite using LC/MS/MS method. The analytical technique was initially validated at one laboratory, and transferred afterward to another. 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 therefore the validity of the bioequivalence study was questioned. Thus, a GCP inspection was conducted. The results of the inspection were satisfactory and none of the findings affected the overall results of the trial.

Pharmacokinetic Variables

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

Statistical methods

Analysis of variance (ANOVA) was carried out on ln-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ for both analytes: clopidogrel and the main inactive metabolite. A non-parametric test was carried out to compare the $T_{\text{max}}$ values between treatments. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect. The statistical methods used were acceptable.

Results

Pharmacokinetic parameters for clopidogrel ($AUC$ and $C_{\text{max}}$; arithmetic mean ± SD, $T_{\text{max}}$: median, range) following a single 75 mg oral dose (n=92) in study 07-197 are presented below.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ pg*h/ml (S.D.)</th>
<th>$AUC_{0-\infty}$ pg*h/ml (S.D.)</th>
<th>$C_{\text{max}}$ pg/ml (S.D.)</th>
<th>$T_{\text{max}}$ h (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2257.6 (3482.8)</td>
<td>2579.1 (3891.4)</td>
<td>1106.7 (873.3)</td>
<td>1 (0.33-16)</td>
</tr>
<tr>
<td>Reference</td>
<td>1909.7 (1575.7)</td>
<td>1983.4 (1649.5)</td>
<td>981.4 (1001)</td>
<td>1 (0.33-5)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>[90;110]%</td>
<td>[87; 109]%</td>
<td>[84;108]%</td>
<td></td>
</tr>
<tr>
<td>*Point estimate</td>
<td>100 %</td>
<td>98 %</td>
<td>95 %</td>
<td></td>
</tr>
<tr>
<td>Intra-subject CV (%)</td>
<td>43.3 %</td>
<td>43.5 %</td>
<td>54.6 %</td>
<td></td>
</tr>
</tbody>
</table>

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
$C_{\text{max}}$ maximum plasma concentration
$T_{\text{max}}$ time for maximum concentration : median, min and max

*log-transformed values
Pharmacokinetic parameters for clopidogrel carboxylic acid (AUC and $C_{\text{max}}$; arithmetic mean $\pm$ SD, $t_{\text{max}}$: median, range) following a single 75 mg oral dose ($n=92$) in study 07-197 are presented below.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng*h/ml (S.D.)</th>
<th>AUC$_{0-\infty}$ ng*h/ml (S.D.)</th>
<th>$C_{\text{max}}$ ng/ml (S.D.)</th>
<th>$t_{\text{max}}$ h (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>6632.4 (1372.7)</td>
<td>7105.8 (1452.4)</td>
<td>2545.7 (873.3)</td>
<td>0.685 (0.5-3)</td>
</tr>
<tr>
<td>Reference</td>
<td>6674.7 (1435.9)</td>
<td>7229.6 (1536.3)</td>
<td>2608.9 (854.9)</td>
<td>0.775 (1-5)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

Point estimate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (%)</th>
<th>AUC$_{0-\infty}$ (%)</th>
<th>$C_{\text{max}}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>[96;100]%</td>
<td>[97;100]%</td>
<td>[91;104]%</td>
</tr>
<tr>
<td>Reference</td>
<td>98%</td>
<td>98%</td>
<td>97%</td>
</tr>
</tbody>
</table>

Intra-subject CV (%) 8.4 % 7.8 % 26 %

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$_{0-\infty}$ 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 $C_{\text{max}}$ should be within 75-133%.

The proposed 90% confidence intervals for AUC$_t$ and AUC$_{\infty}$ 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 $C_{\text{max}}$ values, although not in line with the current CHMP recommendations, was not considered necessary since the $C_{\text{max}}$ results of the study are within the standard 80-125% limits required by the N/G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. No significant difference in $T_{\text{max}}$ 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 aminosalicyclic acid (ASA). No significant changes in the subjects' state of health were observed and it is believed that Clopidogrel 75mg 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 were included in the data set for statistical analysis. All withdrawn and discontinued subjects are documented and validity is justified.

**Discussion on Clinical aspects**

One clinical bioequivalence study was provided for Clopidogrel 75mg Film Coated Tablets application, analysing the parent prodrug clopidogrel. The demonstration of the unchanged safety/efficacy profile of clopidogrel hydrochloride when compared with Plavix® (clopidogrel hydrogensulphate) was raised as a major issue for this
generic product. In response, further discussion on the comparability of the efficacy and safety profiles of clopidogrel hydrogen sulphate and clopidogrel hydrochloride was provided. Pharmacokinetics, dissolution, adverse events profile and other clinical data were considered and it was concluded that the two salts of clopidogrel have a comparable safety/efficacy profile.

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 data presented on the clopidogrel parent compound data in the bioequivalence study submitted with this application was accepted as proof of bioequivalence. 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 Clopidogrel 75mg Film Coated Tablets is different from that of the reference medicinal product, Plavix®. 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 \( C_{\text{max}} \) and \( \text{AUC}_{\text{inf}} \), 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, a clarification of this approach was requested 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 the drug product is to be administered under fasting as well as fed conditions. In addition the dissolution studies using clopidogrel hydrogen sulphate, conducted at three different pH values (1.2, 4.5, 6.8), the applicant provided an additional \textit{in vivo} bioequivalence study conducted under fed conditions. The comparative \textit{in vitro} dissolution studies under conditions mimicking the fed state as well the fed state bioequivalence study did not reveal any major differences when compared to the reference drug 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. A potential for back-conversion of the quantitatively major metabolite clopidogrel carboxylic acid to the parent drug was questioned. 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
clopидогрел родительское вещество было обнаружено в присутствии метанола. В целях избежания этого процесса, методика экстракции была изменена и использовались безметанольные условия. Хотя было указано, что проведены испытания на стабильность для проверки воспроизводимости и точности измерений концентрации clopidogrel, эти результаты были подвергнуты сомнениям, так как не были даны ясные описания аналитической техники, включая методику экстракции, используемую в начальном предварительном валидационном процессе. Информация о процедурах валидации проведенного биоэквивалентного исследования была запрошена. В ответ были представлены детали биоаналитического метода и полные детали валидации, демонстрирующие, что метanol, который необходим для переработки кислотного метаболита в clopidogrel, не использовался, поэтому нет источника метилирования в течение всего метода, включая подготовку всех растворов, обработку плазменных образцов, хранение и определение LC-MS/MS. Этот вопрос считается разрешенным.

Биоэквивалентное исследование и его статистическая оценка были в соответствии с принятыми стандартами биоэквивалентности, как указано в Примечании к руководству по Ведению Исследований по Биодоступности и Биоэквивалентности (CPMP/EWP/QWP/1401/98). Параметры, используемые для оценки биодоступности, это площадь под кривой концентрации в плазме и максимальная концентрация родительского компонента clopidogrel. 90% доверительные интервалы для этих параметров были в пределах рекомендуемого диапазона 80-125% для clopidogrel, требуемого в вышеупомянутом руководстве. Предложенное удлинение доверительного интервала для Cmax clopidogrel до 75%-133% было признано неприемлемым; однако, поскольку доверительные интервалы для Cmax значения clopidogrel были в пределах рекомендуемого 80-125% диапазона, не было необходимости в удлинении интервалов. Биоэквивалентность с Plavix® была доказана.

**Conclusions**

На основании представленного биоэквивалентного исследования, Clopidogrel 75mg Film Coated Tablets считается биоэквивалентным с Plavix®.

**Pharmacodynamics**

Нет данных, которые были представлены.

**Post marketing experience**

Было представлено нет данных по постмаркетинговому анализу представленного продукта. Есть широкий опыт постмаркетингового анализа с clopidogrel.

**PHARMACOVIGILANCE**

**PSUR**

Схема подачи PSUR для Clopidogrel 75mg Film Coated Tablets будет следовать схеме подачи PSUR для исходного лекарственного средства.

**Description of the Pharmacovigilance system**

Система ведения побочных эффектов, как описана компанией-производителем, соответствует всем требованиям законодательства.
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.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Clopidogrel 75mg Film Coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
Two new non-clinical studies were conducted with clopidogrel hydrochloride. Results of single dose toxicity studies in rats revealed low toxicity of clopidogrel hydrochloride. Repeated dose toxicity also showed no additional toxic effects. In vitro Salmonella typhimurium reverse mutation assays of clopidogrel hydrochloride revealed evidence that clopidogrel did not induce effects at either the gene or chromosome levels. In Ames test of clopidogrel’s main metabolite S-carboxylic acid derivative was also negative.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Clopidogrel 75mg Film Coated Tablets and Plavix® 75mg Film-Coated Tablets (Clopidogrel) (Sanofi-Synthelabo).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with clopidogrel hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
CLOPIDOGREL 75MG FILM-COATED TABLETS
PL 24837/0016

STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 21\textsuperscript{st} July 2008</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 25\textsuperscript{th} July 2008.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 6\textsuperscript{th} January 2009, and further information relating to the quality dossiers on 9\textsuperscript{th} January and 10\textsuperscript{th} June 2009.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 30\textsuperscript{th} January 2009 for the clinical sections, and again on 30\textsuperscript{th} January 2009 and 11\textsuperscript{th} June 2009 for the quality sections.</td>
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<tr>
<td>5</td>
<td>The application was determined on 26\textsuperscript{th} June 2009.</td>
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CLOPIDOGREL 75MG FILM-COATED TABLETS
PL 24837/0016

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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CLOPIDOGREL 75MG FILM-COATED TABLETS
PL 24837/0016

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Clopidogrel 75 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 75 mg clopidogrel (as hydrochloride).

Excipient:
Each film-coated tablet contains 13.00 mg hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pink, round and slightly convex film-coated tablets.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
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.

For further information please refer to section 5.1.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
• Adults and elderly
  Clopidogrel should be given as a single daily dose of 75 mg with or without food.

• Paediatric patients
  The safety and efficacy of clopidogrel in children and adolescents have not yet been
  established.

• Renal impairment
  Therapeutic experience is limited in patients with renal impairment (see section 4.4).

• Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have
  bleeding diatheses (see section 4.4).

4.3 CONTRAINDICATIONS
• Hypersensitivity to the active substance or to any of the excipients.
• Severe liver impairment.
• Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs including Cox-2 inhibitors. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section 4.2).

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

This product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4).

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

Acetylsalicylic acid (ASA): ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).
Heparin: in a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

Thrombolytics: the safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

Other concomitant therapy: a number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the coadministration of phenobarbital, cimetidine, or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P450 2C9. This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by Cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

4.6 PREGNANCY AND LACTATION
As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel 75 mg Tablets.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Clopidogrel has no or negligible influence on the ability to drive and use machines.
4.8 UNDESIRABLE EFFECTS

Clopidogrel has been evaluated for safety in more than 42,000 patients, who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for ASA.

In CURE, the major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (<100 mg: 2.6%; 100-200 mg: 3.5%; >200 mg: 4.9%) as was the major bleeding event rate for placebo+ASA (<100 mg: 2.0%; 100-200 mg: 2.3%; >200 mg: 4.0%). The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%). There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel+ASA vs. 5.3% placebo+ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel+ASA, and 6.3% for placebo+ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + ASA group (17.4%) vs. the placebo + ASA group (12.9%). The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups (0.6% versus 0.5% in the clopidogrel + ASA and the placebo + ASA groups, respectively).

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Thrombocytopenia, leucopenia, eosinophilia</td>
<td>Neutropenia, including severe neutropenia</td>
<td>Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Serum sickness, anaphylactoid reactions</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Hallucinations, confusion</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness</td>
<td>Taste disturbances</td>
<td></td>
<td></td>
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<tr>
<td>--------------------------</td>
<td>---------------------------------------------------------------</td>
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<td></td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td>Eye bleeding (conjunctival, ocular, retinal)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td>Vertigo</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>Haematom a</td>
<td>Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
<td>Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia</td>
<td>Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence</td>
<td>Retroperitoneal haemorrhage</td>
<td></td>
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<td></td>
<td></td>
<td>Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis</td>
<td></td>
<td></td>
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<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Acute liver failure, hepatitis, abnormal liver function test</td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>Rash, pruritus, skin bleeding (purpura)</td>
<td>Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td></td>
<td>Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Haematuria</td>
<td>Glomerulonephritis, blood creatinine increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Bleeding at puncture site</td>
<td>Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Bleeding time prolonged, neutrophil count decreased, platelet count decreased</td>
<td></td>
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</table>
4.9 OVERDOSE
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC code: B01AC04.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

The safety and efficacy of clopidogrel have been evaluated in 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease
The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p = 0.045), which corresponds, for every 1000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be stronger (achieving statistical significance at p = 0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%; CI: -5.7 to 18.7 [p=0.258]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = 4.0%; CI: -22.5 to 11.7 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤75 years. Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.
5.2 PHARMACOKINETIC PROPERTIES

After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative, which represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3 mg/l after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

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

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94% respectively). The binding is non-saturable in vitro over a wide concentration range.

Following an oral dose of 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 ml/min) and to levels observed in other studies with healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75 mg/day was safe and well tolerated. Clopidogrel Cmax for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

5.3 PRECLINICAL SAFETY DATA

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon. There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity. Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats,
clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:
- Microcrystalline cellulose
- Colloidal anhydrous silica
- Crospovidone (type A)
- Macrogol 6000
- Hydrogenated castor oil

Film coating:
- Hypromellose (E464)
- Titanium dioxide (E171)
- Red iron oxide (E172)
- Talc
- Propylene glycol

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package in order to protect from moisture and light.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister of OPA/Al/PVC-Al containing 7, 14, 28, 30, 50, 56, 84, 90 and 100 film-coated tablets in the box.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Consilient Health Limited,
5th Floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 24837/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/06/2009

10 DATE OF REVISION OF THE TEXT

26/06/2009
CLOPIDOGREL 75MG FILM-COATED TABLETS
PL 24837/0016

PATIENT INFORMATION LEAFET

1. WHAT CLOPIDOGREL 75 MG FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Clopidogrel belongs to a group of medicines called antiplatelet medicinal products. Plaques are very small structures in the blood, smaller than red or white blood cells, which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chance of blood clot forming (a process called thrombosis).

Clopidogrel is taken to prevent blood clotting in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed (Clopidogrel) to help prevent blood clotting and reduce the risk of these severe events because:
- You have a condition of hardening of the arteries (also known as atherothrombosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease.

2. BEFORE YOU TAKE CLOPIDOGREL 75 MG FILM-COATED TABLETS

Do not take Clopidogrel:
- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of Clopidogrel 75 mg film-coated tablets.
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- If you suffer from severe liver disease.

If you think any of these apply to you or if you are in any doubt at all, consult your doctor before taking Clopidogrel.

Take special care with Clopidogrel:
Many of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel:
- If you have a risk of bleeding such as:
  - A medical condition that puts you at risk of internal bleeding (such as a stomach ulcer)
  - A blood disorder that makes you prone to internal bleeding (bleeding inside any tissue, organ or joint of your body).
  - A recent serious injury
  - A recent surgery (including dental)
  - A planned surgery (including dental) in the next seven days.
  - If you have had a stroke or if you have a history of heart attack.
  - If you are taking another type of medicine (see Taking other medicines).
  - If you have kidney or liver disease.

While you are taking Clopidogrel:
- You should tell your doctor if a surgery (including dental) is planned.
- You should also tell your doctor immediately if you develop a new medical condition that includes fever and bruising under the skin that appears as a red or purplish spot (see "Possible side effects").
- If you cannot stand up, it is safer than usual for bleeding or purpura.
- It is linked to the way your medicine works so it may prevent the ability to stop bleeding.
- Do not use any alcohol and take care to prevent bleeding from minor cuts and injuries, such as shaving, that are usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straight away (see "Possible side effects").
- Your doctor may order blood tests.

- You should tell your doctor or pharmacist if you notice any side effect not listed in the "Possible side effects" section of this leaflet or if you notice that a side effect gets serious.
- Clopidogrel is not intended for use in children or adolescents.

Taking other medicines
Some other medicines may influence the use of Clopidogrel or vice versa. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including dental medicine, obtained without a prescription.

The use of oral anticoagulants (medicines used to reduce blood clotting) with Clopidogrel is not recommended.

You should specifically tell your doctor if you take a non-steroidal anti-inflammatory medicinal product, usually used to treat pain and/or inflammatory conditions of muscle or joint, or if you take aspirin, ibuprofen or any other medicine that reduces blood clotting.

An occasional use of acetylsalicylic acid (no more than 1000 mg in any 24 hour period), a substance present in many medicines most to relieve pain and reduce fever, should generally not cause a problem, but prolonged use in other circumstances should be discussed with your doctor.

Taking Clopidogrel with food and drink
Food and drinks may have an influence. Clopidogrel may be taken with or without food.

Pregnancy and breast-feeding
It is preferable not to use this product during pregnancy and breast-feeding.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel. If you become pregnant while taking Clopidogrel, consult your
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3. HOW TO TAKE CLOPIDOGREL 75 MG FILM-COATED TABLETS

Always take Clopidogrel exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one 75mg tablet of Clopidogrel per day to be taken orally with or without food and at the same time each day.

You should take Clopidogrel as long as your doctor continues to prescribe it.

If you take more Clopidogrel than you should:

Contact your doctor or the nearest emergency department because of the increased risk of bleeding.

If you forget to take Clopidogrel:

If you take more than 12 hours of your usual time, take your next tablet straightaway and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clopidogrel can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:

- signs of infection or unusual tiredness. These may be due to a rare disease called blood cancer.
- signs of liver problems such as yellowing of the skin and discoloration of the urine, whether or not associated with bleeding which appears under the skin or as pinpoint red dots and/or confusion (see section Special Cautions with Clopidogrel)
- swelling in the mouth or skin disorders such as rash and itching blisters of the skin. These may be signs of an allergic reaction.

The most common side effect affects 1 to 10 patients in 100 is bleeding. Bleeding may occur as a bleeding in the stomach or bowels, bruising hemorrhage (red pinpoint bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the area inside the head, the lungs or the joints has also been reported.

If you experience prolonged bleeding when taking Clopidogrel:

If you cut or injure yourself, it may take slightly longer than usual for your body to stop bleeding. This is linked to the way your medicine works as it means the ability of your blood to clot for minor cuts and injuries such as a bruise, cutting yourself shaving, this is of no concern.

However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section Special Care with Clopidogrel).

Other side effects reported are:

Common side effects (affect 1 to 10 of 100): headache, stomach pain, vomiting nausea, constipation, excessive gas in the stomach or intestines, diarrhea, abdominal pain, indigestion or heartburn.

Uncommon side effects (affect 1 to 10 per 1,000): abdominal pain, rash, itching, redness, skin irritation, chest pain, shortness of breath.

Rare side effects (affect 1 to 10 of 10,000): vertigo, nausea, vomiting.

Very rare side effects (affects less than 1 patient in 10,000):

jaundice, severe abdominal pain with or without back pain, fever, severe skin reaction, sometimes associated with cold, generalised allergic reactions, swelling in the mouth, closed sinuses, irritation of the skin, skin inflammation of the mouth (tromatitis), decrease in blood pressure, vomiting, vertigo, fainting, etc.

In addition, your doctor may identify changes in your blood or urine test results.

If any of these effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CLOPIDOGREL 75 MG FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not use Clopidogrel after the expiry date which is stated on the carton and blister packs. The expiry date refers to the last day of that month.

Store in the original packaging in order to protect from moisture and light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Clopidogrel contains

- the active substance is clopidogrel. Each film-coated tablet contains 75 mg clopidogrel (as hydrochloride). The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone (type A), magnesium stearate, hydroxypropyl cellulose (E464), titanium dioxide (E171), red iron oxide (E172), talc and propylene glycol in the film-coating.

What Clopidogrel looks like and contents of the pack

The film-coated tablets are pink, round and slightly convex. Boxes of 7, 14, 28, 30, 50, 64, 90 and 100 film-coated tablets in blisters are available.

NDC code may be marketed.

Marketing Authorisation Holder

Consilient Health Ltd, 5th Floor, Bear Lane House, Mercer Street Lower, Dublin 2, Ireland.

Manufacturer

KRKA d.d., Novo mesto, Smetanova cesta 6, 6291 Novo mesto, Slovenia.

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