Public Assessment Report

Scientific discussion

Clopidogrel/Acetylsalicylzuur Billev
75 mg/75 mg and 75 mg/100 mg
film-coated tablets

(clopidogrel/acetylsalicylic acid)

NL/H/2953/001-002/DC

Date: 16 September 2014

This module reflects the scientific discussion for the approval of Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg and 75 mg/100 mg film-coated tablets. The procedure was finalised on 9 June 2014. For information on changes after this date please refer to the module ‘Update’.

This report includes a summary, on pages 15-17.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>Adenosine Diphosphate</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic Acid</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>Area under the plasma concentration-time curve from time zero to t hours</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>Area under the plasma concentration-time curve from time zero to infinity</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;72&lt;/sub&gt;</td>
<td>Area under the plasma concentration-time curve from time zero to t=72</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CMS</td>
<td>Concerned Member State</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDOM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>HDPE</td>
<td>High-density Polyethylene</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>non-ST segment elevation myocardial infarction</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PIP</td>
<td>Paediatric Investigation Plan</td>
</tr>
<tr>
<td>PL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SA</td>
<td>Salicylic Acid</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST segment elevation myocardial infarction</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TXA2</td>
<td>Thromboxane A2</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
</tbody>
</table>
I. **INTRODUCTION**

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg and 75 mg/100 mg film-coated tablets from Billev Pharma Aps.

The product is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA).

Clopidogrel/Acetylsalicylzuur Billev is a fixed-dose combination medicinal product for continuation of therapy in:

- 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
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns an application for a fixed combination medicinal product where the individual active substances (monocomponents) have established clinical use as well as regulatory approval. For this kind of application it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

Both components of the proposed product are authorised in the Community for more than a decade. Plavix (clopidogrel) has been registered by Sanofi Clir SNC through a Centralised Procedure in July 1998. ASA has been available on the market for over a hundred years. Combination therapy with clopidogrel and acetylsalicylic acid is discussed extensively in the SmPC of the innovator Plavix. Two fixed dose combinations with the same active ingredients, DuoCover and DuoPlavin, are authorised by sanofi-aventis groupe and Sanofi Clir SNC since 2010 through a Centralised Procedure.

The concerned member states (CMS) involved in this procedure were Germany, Portugal and Spain.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

The MAH gave the following argumentation for this fixed dose combination:

In line with the requirements stated in the document CHMP/EWP/191583/2005 entitled *Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention* it has been shown that:

- Clopidogrel and acetylsalicylic acid are well known (therapeutic experience > 10 years and 40 years respectively).
- The joint application of the components is already in widespread use in the proposed dosage strengths, has proven to be efficacious and safe and thus clinically useful.
- The pharmacological rationale for the use of clopidogrel and ASA in combination is adequately justified in literature. In this respect a well founded bibliographical data analysis is presented in this application, the present application is based on this clinical overview and bioequivalence studies.

No dedicated studies in the target population have been performed with this product. This is however not necessary taking into account the substitution indication. No new non-clinical studies were performed in support of this application.

The submission includes two bioequivalence studies comparing both components to their registered products containing a single component. Both strengths were investigated.

No scientific advice was given for development of the proposed product.

No Paediatric Investigation Plan (PIP) has been submitted. On 14 June 2013 the EMA adopted a product-specific waiver for all subsets of the paediatric population from birth to less than 18 years of age (EMEA-001463-PIP01-13, waiver decision number P/0179/2013).
II. QUALITY ASPECTS

II.1 Introduction

Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg is a yellow, film-coated capsule shaped tablet, plain on both sides. Clopidogrel/Acetylsalicylzuur Billev 75 mg/100 mg is a light pink to pink, film-coated capsule shaped tablet, plain on both sides of the tablet.

The film-coated tablets are packed in Al+desiccant/Al blisters, white HDPE bottles with a green polypropylene (PP) child resistant closure or white HDPE multi-layer bottles with green polypropylene (PP) child resistant closure.

The excipients are:
- Tablet core - lactose monohydrate, microcrystalline cellulose (E460), hydroxypropyl cellulose (E463), crospovidone (type A), stearic acid, croscarmellose sodium, hydrogenated vegetable oil (type I), sodium lauril sulphate
- Tablet coating – For the 75 mg/75 mg tablet Opadry film-coating yellow: hypromellose, polydextrose, titanium dioxide, quinolone yellow aluminium lake, talc, maltodextrin, medium chain triglycerides and iron oxide yellow.
  For the 75 mg/100 mg tablet Opadry film-coating pink, 75 mg/100 mg: hypromellose, polydextrose, titanium dioxide, talc, maltodextrin, medium chain triglycerides, carmine and iron oxide red.

The different tablet strengths are not dose-proportional.

II.2 Drug Substances

Clopidogrel

The active substance is clopidogrel hydrogen sulphate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder, which is freely soluble in water. Clopidogrel hydrogen sulfate has one chiral centre and is manufactured as an enantiomer with S configuration. The substance exhibits polymorphism and Form I is consistently manufactured.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The proposed specification is line with or tighter than the Ph.Eur. monograph and the CEP, with additional limits for residual solvents, particle size distribution, bulk and tapped density. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for four full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for seven full-scale batches stored at 2-8°C (24 months) and for three full-scale batches stored at 25°C/60% RH (6 months). Increases in related substances were observed at accelerated conditions. All other parameters examined remained relatively stable throughout the test periods at both conditions.

Based on the stability data provided, the proposed re-test period of 24 months when stored at 2-8°C can be granted.
Acetylsalicylic acid
The second active substance is acetylsalicylic acid, an established active substance described in the European Pharmacopoeia. The active substance is slightly soluble in water and appears as a white or almost white crystalline powder or colourless crystals. It does not contain chiral centres and does not show polymorphism. For acetylsalicylic acid CEP is provided.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The proposed specification is line with or tighter than the Ph.Eur. monograph and the CEP, with additional limits for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 3 years if stored at a temperature not exceeding 25°C. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the compatibility studies, formulation and manufacturing optimization studies and comparative dissolution studies between the batches used in the bioequivalence studies. The use of these batches has been adequately justified. The pharmaceutical development of het product has been adequately performed. Sufficient dissolution data is provided.

Manufacturing process
The manufacturing process mainly consists of wet granulation of clopidogrel, dry granulation of acetylsalicylic acid, mixing, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. requirements, with the exception of the film-coating. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, identification of the colorants, dissolution, content uniformity, related substances (including enantiomeric purity of clopidogrel), assay, water content and microbial quality. The release and shelf life limits are identical with the exception of related substances and water content. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches of each tablet strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two pilot-scale batches of each tablet strength stored at 25°C/60% RH (18 months) and 30°C/65% RH (12 months). Furthermore stability data was provided of one pilot scale batch stored at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed marketing packages. Stability studies indicated that a desiccant is required in the primary packaging. At accelerated conditions out-of-specification results were observed in the pilot-scale batch after 1 month of storage. Therefore, the omission of further stability studies at accelerated conditions is considered adequately justified. Variability of the assay values of acetylsalicylic acid and to a lesser extent of clopidogrel was observed. All other parameters tested remained relatively stable throughout the test periods at both test conditions. Results of photostability testing show that the drug product is sensitive to light. Based on the stability data provided the proposed shelf life of 18 months and the following storage
conditions are considered acceptable: ‘Store below 25°C’ and ‘Store in the original package in order to protect from light and moisture’.

Stability data has been provided demonstrating that the product remains stable for 30 days following first opening of the bottle, when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only substance of animal or human origin used in the manufacture of the drug product is lactose monohydrate. A BSE-statement has been provided that the lactose monohydrate is produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

For this fixed dose application, the MAH provided an overview summarising the relevant literature on the pharmacology of clopidogrel, ASA and the combination of these two active substances. The pharmacokinetics and toxicology were also reviewed. No new studies have been performed. This is acceptable, as both active substances are well known.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Clopidogrel/Acetylsalicylzuur Billev is intended for substitution of both active ingredients used in separate tablets, its use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. The Member States agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clopidogrel and acetylsalicylic are well-known active substances with established efficacy and tolerability.

The clinical development program was designed to evaluate the comparative bioavailability between Clopidogrel/Acetylsalicylzuur Billev tablets and tablets containing the separate active substances. For this application, the MAH has submitted two bioequivalence studies, which are discussed below. The pharmacological rationale for the use of clopidogrel and ASA in combination is adequately justified in the published literature. A bibliographical data analysis regarding efficacy and safety has been presented in this application. No further studies have been performed and none are considered necessary.

IV.2 Pharmacokinetics

The pharmacokinetic properties of both active substances are well known.
To support the application, the applicant has submitted the reports of two single-dose, 4-period replicate design studies. Each treatment was administered twice for estimation of the intra-individual reference variability. The replicate design was chosen as the intra-individual reference variability in Cmax for clopidogrel was \textit{a priori} estimated to be more than 30%. One study was conducted with the 75/75 mg tablets versus Plavix 75 mg (Sanofi Pharma Bristol-Myers Squib, France) and ASS 75 mg (Worwag Pharma, Germany) as reference products. The second study was conducted with the same study design, comparing Clopidogrel/Acetylsalicyliczuur Billev 75/100 mg tablets to Plavix 75 mg and Aspirin 100 mg (Bayer Vital, Germany).

Acetylsalicylic acid and salicylic acid were determined in plasma only in the first 36 subjects of the two first periods of each study.

Pharmacokinetic, statistical and bioanalytical methods are acceptable for these studies. For both studies the overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. As this product can be taken regardless food intake, studies under fasting conditions are justified.

\textbf{Bioequivalence study I – 75 mg/75 mg tablets}

\textbf{Design}

The study was conducted as a single dose, 4 period replicate design study in 60 healthy male (35) and female (25) subjects (aged 21-55 years) under fasting conditions. The test product Clopidogrel/Acetylsalicyliczuur Billev and reference products Plavix 75 mg and ASS 75 mg were administered after an overnight fast with 240 ml water. The two reference products were administered concomitantly.

Blood samples were taken for ASA and SA determination in plasma after 0.167, 0.333, 0.5, 0.583, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after dosing (Periods 1 & 2 only) and for clopidogrel: 0.167, 0.333, 0.5, 0.583, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after dosing (all periods).

The washout period between the treatments was 7 days.

\textbf{Results}

Four subjects dropped out: two in period I, one of them due to adverse events and the other one for personal reasons, one in period 3 for non compliance and one in period 4 for personal reasons.

\textbf{Table 1.} Pharmacokinetic parameters of clopidogrel after oral administration of 75 mg: non-transformed values; arithmetic and geometric means, intra-subject CV, tmax median, tmax range

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
Parameter & Trt & n & Arithmetic Mean (\%) & Geometric Mean & Contrast & Ratio (\%) & 90\% Confidence Interval & Intra-Sbj CV(\%) & Intra-Sbj CV(\%) \tabularnewline
\hline
Cmax (ng/mL) & A1 & 50 & 1.8019 (49) & 1.0940 A vs B & 100.03 & 91.91-109.47 & 39 & 38 & 75.08-132.14 \tabularnewline
& A2 & 50 & 2.0554 (110) & & & & & & \\
& B1 & 50 & 2.0150 (166) & & 1.0848 & & & & \\
& B2 & 50 & 2.0630 (135) & & & & & & \\
\hline
AUCt (ng/h/mL) & A1 & 50 & 2.8128 (133) & 1.5527 A vs B & 99.82 & 91.35-107.47 & 50 & N/A & N/A \tabularnewline
& A2 & 50 & 2.5505 (136) & & & & & & \\
& B1 & 50 & 2.6386 (136) & & 1.5586 & & & & \\
& B2 & 50 & 2.7270 (123) & & & & & & \\
\hline
Tmax (h) & A1 & 50 & 0.71 (97) & & & & & & \\
& A2 & 50 & 0.61 (30) & & & & & & \\
& B1 & 50 & 0.76 (43) & & & & & & \\
& B2 & 50 & 0.74 (23) & & & & & & \\
\hline
\end{tabular}
\end{table}
Table 2. Pharmacokinetic parameters of acetylsalicylic acid: non-transformed values; arithmetic and geometric means, intra-subject CV, t\text{max}, median, t\text{max} range

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trt</th>
<th>n</th>
<th>Arithmetic Mean (CV%)</th>
<th>Geometric Mean</th>
<th>Contrast</th>
<th>Ratio (%)</th>
<th>95% Confidence Interval</th>
<th>Intra-Sbj CV (%)</th>
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</thead>
<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>A</td>
<td>36</td>
<td>1234.2 (27)</td>
<td>1199.1</td>
<td>A vs B</td>
<td>118.65</td>
<td>110.34 - 127.59</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>1084.3 (38)</td>
<td>1010.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AUC\text{t} (ng h/mL)</td>
<td>A</td>
<td>36</td>
<td>1071.0 (27)</td>
<td>1015.7</td>
<td>A vs B</td>
<td>102.02</td>
<td>97.40 - 106.86</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>1050.2 (26)</td>
<td>1015.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>A</td>
<td>36</td>
<td>0.55 (26)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>0.64 (34)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Median and Range

<table>
<thead>
<tr>
<th>T\text{max} (h)</th>
<th>Trt</th>
<th>n</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>36</td>
<td>0.38</td>
<td>0.17 - 0.83</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>36</td>
<td>0.38</td>
<td>0.30 - 1.75</td>
<td>-</td>
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</table>

Treatment A: Clopidogrel and Acetylsalicylic acid 75/75 mg Tablets
Treatment B: ASS 75 mg Tablets (Warwag Pharma GmbH & Co. KG, Germany) with Plavix 75 mg Tablets (Sanofi Pharma)

Table 3. Pharmacokinetic parameters of salicylic acid: non-transformed values; arithmetic and geometric means, intra-subject CV, t\text{max}, median, t\text{max} range

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trt</th>
<th>n</th>
<th>Arithmetic Mean (CV%)</th>
<th>Geometric Mean</th>
<th>Contrast</th>
<th>Ratio (%)</th>
<th>95% Confidence Interval</th>
<th>Intra-Sbj CV (%)</th>
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<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>A</td>
<td>36</td>
<td>4571.9 (21)</td>
<td>4468.8</td>
<td>A vs B</td>
<td>104.96</td>
<td>100.75 - 109.34</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>4365.3 (23)</td>
<td>4257.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AUC\text{t} (ng h/mL)</td>
<td>A</td>
<td>36</td>
<td>17774.1 (31)</td>
<td>17005.8</td>
<td>A vs B</td>
<td>101.11</td>
<td>98.50 - 103.79</td>
<td>7</td>
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<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>17585.5 (32)</td>
<td>16818.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>T\text{max} (h)</td>
<td>A</td>
<td>36</td>
<td>1.18 (20)</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>1.41 (34)</td>
<td>-</td>
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Median and Range

<table>
<thead>
<tr>
<th>T\text{max} (h)</th>
<th>Trt</th>
<th>n</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>A</td>
<td>36</td>
<td>1.25</td>
<td>0.83 - 1.75</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>36</td>
<td>1.25</td>
<td>0.83 - 2.50</td>
<td>-</td>
</tr>
</tbody>
</table>

Treatment A: Clopidogrel and Acetylsalicylic acid 75/75 mg Tablets
Treatment B: ASS 75 mg Tablets (Warwag Pharma GmbH & Co. KG, Germany) with Plavix 75 mg Tablets (Sanofi Pharma)

Bioequivalence study II – 75 mg/100 mg tablets

Design
The study was conducted as a single dose, 4 period replicate design study in 60 healthy male (30) and female (30) subjects (aged 21-54 years) under fasting conditions. The test product Clopidogrel/Acetylsalicyliczuur Billev and reference products Plavix 75 mg and Aspirin 100 mg were administered after an overnight fast with 240 ml water. The two reference products were administered concomitantly.

Blood samples were taken for ASA and SA determination in plasma after 0.167, 0.333, 0.5, 0.583, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after dosing (Periods 1 & 2 only) and for clopidogrel: 0.167, 0.333, 0.5, 0.583, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after dosing (all periods). The washout period between the treatments was 7 days.

Results
Eight subjects dropped out: three in the first period, two of which due to non compliance and one for personal reasons, two in the second period for personal reasons and three in period 3, two of which for non compliance and one due to an adverse event.
Table 4. Pharmacokinetic parameters of clopidogrel: non-transformed values; arithmetic and geometric means, intra-subject CV, t<sub>max</sub> median, t<sub>max</sub> range

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trt</th>
<th>n</th>
<th>Arithmetic Mean (CV%)</th>
<th>Geometric Mean</th>
<th>Contrast</th>
<th>Ratio (%)</th>
<th>90% Confidence Interval (A-B)</th>
<th>Intra-Sbj CV(%) (B1-B2)</th>
<th>Wider BE Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>A1</td>
<td>57</td>
<td>1.5607 (149)</td>
<td>0.8929</td>
<td>A vs B</td>
<td>102.29</td>
<td>93.06-111.44</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>55</td>
<td>1.5755 (142)</td>
<td>0.8929</td>
<td>A vs B</td>
<td>102.29</td>
<td>93.06-111.44</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>B1</td>
<td>57</td>
<td>1.4285 (122)</td>
<td>0.8729</td>
<td>A vs B</td>
<td>102.29</td>
<td>93.06-111.44</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>52</td>
<td>1.7725 (184)</td>
<td>0.8729</td>
<td>A vs B</td>
<td>102.29</td>
<td>93.06-111.44</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt; (ng.h/mL)</td>
<td>A1</td>
<td>57</td>
<td>2.0910 (176)</td>
<td>1.2107</td>
<td>A vs B</td>
<td>95.90</td>
<td>88.30-104.01</td>
<td>38</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>55</td>
<td>2.1495 (127)</td>
<td>1.2107</td>
<td>A vs B</td>
<td>95.90</td>
<td>88.30-104.01</td>
<td>38</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>B1</td>
<td>57</td>
<td>1.9880 (121)</td>
<td>1.2627</td>
<td>A vs B</td>
<td>95.90</td>
<td>88.30-104.01</td>
<td>38</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>52</td>
<td>2.1138 (116)</td>
<td>1.2627</td>
<td>A vs B</td>
<td>95.90</td>
<td>88.30-104.01</td>
<td>38</td>
<td>N/A</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>A1</td>
<td>57</td>
<td>0.67 (30)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>55</td>
<td>0.64 (40)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B1</td>
<td>57</td>
<td>0.76 (31)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>52</td>
<td>0.73 (28)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Median, Range)

Table 5. Pharmacokinetic parameters of acetyl salicylic acid: non-transformed values; arithmetic and geometric means, intra-subject CV, t<sub>max</sub> median, t<sub>max</sub> range

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trt</th>
<th>n</th>
<th>Arithmetic Mean (CV%)</th>
<th>Geometric Mean</th>
<th>Contrast</th>
<th>Ratio (%)</th>
<th>90% Confidence Interval</th>
<th>Intra-Sbj CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>A</td>
<td>36</td>
<td>1566.6 (28)</td>
<td>1594.5</td>
<td>A vs B</td>
<td>101.10</td>
<td>94.53 - 108.14</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>1655.1 (31)</td>
<td>1577.1</td>
<td>A vs B</td>
<td>101.10</td>
<td>94.53 - 108.14</td>
<td>17</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt; (ng.h/mL)</td>
<td>A</td>
<td>36</td>
<td>1471.1 (29)</td>
<td>1412.8</td>
<td>A vs B</td>
<td>92.62</td>
<td>88.34 - 97.11</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>1571.9 (25)</td>
<td>1525.3</td>
<td>A vs B</td>
<td>92.62</td>
<td>88.34 - 97.11</td>
<td>12</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>A</td>
<td>36</td>
<td>0.54 (26)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>36</td>
<td>0.61 (28)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Median, Range)

(Treatment A: Clopidogrel and Acetylsalicylic acid 75/100 mg Tablets
Treatment B: Aspirin® 100 mg Tablets (Bayer Vital GmbH, Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

(Treatment A: Clopidogrel and Acetylsalicylic acid 75/100 mg Tablets
Treatment B: Aspirin® N 100 mg Tablets (Bayer Vital GmbH, Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)
Table 6. Pharmacokinetic parameters of salicylic acid: non-transformed values; arithmetic and geometric means, intra-subject CV, t\text{max} median, t\text{max} range

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tnt</th>
<th>Arithmetic Mean (CV%)</th>
<th>Geometric Mean</th>
<th>Contrast</th>
<th>Ratio (%)</th>
<th>99% Confidence Interval</th>
<th>Intra-Sbj CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max}</td>
<td>A</td>
<td>6198.6 (18)</td>
<td>6099.7</td>
<td>A vs B</td>
<td>100.48</td>
<td>96.32 - 104.82</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>6212.3 (22)</td>
<td>0070.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AUC\text{t}</td>
<td>A</td>
<td>24514.6 (30)</td>
<td>23658.9</td>
<td>A vs B</td>
<td>96.11</td>
<td>94.19 - 98.07</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>25597.0 (31)</td>
<td>24616.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T\text{max}</td>
<td>A</td>
<td>1.14 (27)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.41 (31)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median Range</td>
<td></td>
<td>1.91 (2-50)</td>
<td>0.83-2.50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.38 (2-7)</td>
<td>0.67-3.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Treatment A: Clopidogrel and Acetylsalicylic acid 75/100 mg Tablets
Treatment B: Aspirin® N 100 mg Tablets (Bayer Vital GmbH, Germany) with Plavix® 75 mg Tablets (Sanofi-Pharma Bristol Myer Squibb SNC, France)

Conclusion on the pharmacokinetic studies

The pharmacokinetic variables are comparable between both treatments in both studies for both strengths for all three analytes determined in plasma. The 90% confidence intervals for the extent and rate of absorption are within the conventional acceptance criteria of 80.00% – 125.00% for clopidogrel as well as for acetylsalicylic acid and salicylic acid. Bioequivalence is established for both fixed dose combinations. The formulations were well tolerated, with no major side effects.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics

Clopidogrel and ASA modify platelet aggregation through two independent pathways and mechanisms of action. ASA inhibits platelet aggregation by the irreversible inhibition of platelet COX and thus inhibits the generation of thromboxane A2 (TXA2), an inducer of platelet aggregation and vasoconstriction. Clopidogrel is an ADP-receptor antagonist of the thienopyridine derivative class that selectively inhibits the binding of ADP to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

As the fixed-dose combination tablet of clopidogrel and acetylsalicylic acid is intended as a substitute for the co-administration of the separate constituents in the approved acute coronary syndrome indications, the submission of clinical pharmacodynamic data is not considered necessary.

IV.4 Clinical efficacy

The MAH provided a clinical overview on the efficacy of clopidogrel/ASA.

The rationale for the development of the clopidogrel/ASA fixed dose combination is based on:
- the fact that they belong to different classes of anti-coagulants recommended for the management of cardiac ischaemic events by current European guidelines, and that the interest of their combination is recognized.
- the efficacy as an anti-coagulant of each component is supported by the demonstration of their clinical benefit from large programs of clinical trials performed with each of them administered alone or in combination.
- the synergy of the mono-components effects,
- their favourable acceptability and safety profile,
- the long-term experience with these agents, marketed since 40 years for ASA and since more
than 10 years for clopidogrel and commonly used by practitioners in the treatment of acute coronary syndromes,
• and finally, their compatibility from a pharmacokinetic point of view (once daily administration).

The efficacy of clopidogrel in combination with ASA was evaluated in ACS patients with or without ST-segment elevation in a number of double-blind studies e.g. CURE, COMMIT and CLARITY. The clear benefit of clopidogrel in combination with ASA in a broad ACS indication (unstable angina/NSTEMI and STEMI patients) demonstrated by these 3 studies, supported the registration for these indications in Europe as well as in other countries.

In these indications the standard approved regimen of clopidogrel is a single 300 mg loading dose followed by a 75 mg clopidogrel dose once daily, in combination with ASA. The daily dose of ASA used in the studies described above ranged from 75 to 325 mg once daily. Since higher doses of ASA were associated with higher bleeding risk, the EU SmPC for clopidogrel recommends that the dose of ASA should not be higher than 100 mg daily.

IV.5 Clinical safety

Clopidogrel in association with ASA is a widely used combination in ACS patients, and the safety of each component separately as well as in combination is well known. Safety data on interactions of clopidogrel and ASA with other medicinal products is in line with the SmPC approved in the different EU member states of ASA and clopidogrel containing products.

The safety data supporting the fixed-dose combination of clopidogrel with ASA as a 75/75 mg or 75/100 mg strength in ACS patients without or with ST-elevation MI (NSTEMI and STEMI) are based on a number of studies that evaluated co-administration. The safety profile of the combination product is adequately reflected in the SmPC.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clopidogrel/Acetylsalicylzuur Billev.

<table>
<thead>
<tr>
<th>Summary table of safety concerns as approved in RMP</th>
</tr>
</thead>
</table>

Important identified risks
- Bleeding; including gastrointestinal bleeding and intracerebral haemorrhage
- Damage to gastrointestinal mucosa; including gastric erosions, gastrointestinal ulcers
- Chronic salicylate intoxication
- Drug interaction: NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, thrombolytics, anticoagulants, methotrexate
- Hypersensitivity
- Liver impairment
- Renal impairment
- Blood dyscrasias: thrombocytopenia, agranulocytosis, pancytopenia, aplastic anaemia, thrombotic thrombocytopenic purpura
- Reduced efficacy of clopidogrel in poor CYP2C19 metabolizers

Important potential risks
- Reduced efficacy of clopidogrel when inhibitors of CYP2C19 are used concomitantly

Missing information
- Product use in paediatric patients
- Product use in pregnancy and lactation
The member states considered this RMP acceptable. No additional risk minimization activities are considered necessary at the moment.

**IV.7 Discussion on the clinical aspects**

The combined use of clopidogrel and ASA is well established. The literature data submitted by the MAH support the use of the fixed dose combination. The bioequivalence studies show satisfactory results: a single tablet of Clopidogrel/Acetylsalicylzuur Billev can be used instead of co-administration of the separate products: Plavix 75 mg in combination with ASS 75 mg or Aspirin 100 mg. Risk management is adequately addressed.

**V. USER CONSULTATION**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The testing process involved: one pilot test with three participants followed by two main tests on ten participants each. Seventeen questions about the most critical parts of the package leaflet and three general questions about the package leaflet were used. There were sufficient questions about the critical sections. The patient information leaflet did not need to be adapted taking into account the results of the tests. Taking into account the results for each question, more than 90% of the participants were able to find the section and answer the question correctly. In conclusion, the results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

**VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg and 75 mg/100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are considered an acceptable fixed dose combination. Both clopidogrel and acetylsalicylic acid are well known, established substances which are used as a combination in clinical practice.

The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate reference products Plavix 75 mg + ASS 75 mg or Aspirin 100 mg. The efficacy and safety profile is considered the same as for the monocomponents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC closely resembles the approved SmPC for Plavix and ASA containing components. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The Member States, on the basis of the data submitted, considered that this fixed dose combination is approvable, since bioequivalence has been demonstrated with the innovator products of the individual components. The decentralised procedure was finalised with a positive outcome on 6 June 2014.

There were no post-approval commitments made during the procedure.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>
Summary Public Assessment Report

non-generics

Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg
and 75 mg/100 mg film-coated tablets

(clopidogrel and acetylsalicylic acid)

NL/H/2953/001-002/DC

Date: 16 September 2014
Summary Public Assessment Report

non-generics

Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg and 75 mg/100 mg film-coated tablets

Active substances: clopidogrel and acetylsalicylic acid

This is a summary of the public assessment report (PAR) for Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg and 75 mg/100 mg film-coated tablets. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Clopidogrel/Acetylsalicylzuur Billev.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Clopidogrel/Acetylsalicylzuur Billev and what is it used for?

This medicine contains two active substances: clopidogrel and acetylsalicylic acid. These substances are also available as separate tablets marketed under several trade names such as Plavix (clopidogrel) and Aspirin® (acetylsalicylic acid).

Clopidogrel/Acetylsalicylzuur Billev is used to prevent atherosclerotic and thrombotic events (problems caused by blood clots and hardening of the arteries), such as a heart attack, in adults who are already taking both clopidogrel and acetylsalicylic acid as separate tablets.

It is prescribed to patients who are having ‘unstable angina’ (a severe type of chest pain) or who have had a myocardial infarction (heart attack). These patients may have had a stent (a short tube) inserted into an artery to prevent it from closing up.

How does this medicine work?

Both active substances, clopidogrel and acetylsalicylic acid, are ‘inhibitors of platelet aggregation’. This means that they help to prevent blood cells called platelets from aggregating (sticking together) and forming clots. Clopidogrel stops the platelets aggregating by blocking a substance called ADP from attaching to a special receptor on their surface. This stops the platelets becoming ‘sticky’, reducing the risk of a blood clot forming. Acetylsalicylic acid stops the platelets aggregating by blocking an enzyme called prostaglandin cyclo-oxygenase. This reduces the production of a substance called thromboxane, which normally helps clots to form by binding platelets together. When taken together, the two active substances can reduce the risk of blood clots forming, helping to prevent another heart attack. Earlier studies in more than 60,000 patients with an acute coronary syndrome demonstrated that the combination of clopidogrel and acetylsalicylic acid used as separate tablets shows benefit in the prevention of atherosclerotic complication such as myocardial infarction.

How is this medicine used?

The pharmaceutical form of Clopidogrel/Acetylsalicylzuur Billev is a film-coated tablet and the route of administration is oral. The medicine can only be obtained with a prescription.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

How has this medicine been studied?

Because Clopidogrel/Acetylsalicylzuur Billev is intended for substitution of separate tablets containing clopidogrel and acetylsalicylic acid, studies in patients have been limited to tests to determine that it is bioequivalent to the individual tablets taken at the same time. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

The studies have shown that the same amount of clopidogrel and acetylsalicylic acid is produced in the blood after administration of the combination tablet or the two separate tablets.

What are the possible side effects from this medicine?

The most common side effects with Clopidogrel/Acetylsalicylzuur Billev (which may affect up to 1 in 10 people) are haematoma (a collection of blood under the skin), epistaxis (nosebleeds), gastrointestinal
haemorrhage (bleeding in the stomach or gut), diarrhoea, abdominal pain (stomach ache), dyspepsia (heartburn), bruising and bleeding where the skin is punctured.

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet.

**Why is this medicine approved?**
The Medicines Evaluation Board of the Netherlands decided that Clopidogrel/Acetylsalicylzuur Billev’s benefits are greater than its risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of this medicine?**
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Clopidogrel/Acetylsalicylzuur Billev, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

**Other information about this medicine**
In the Netherlands, the marketing authorisation for Clopidogrel/Acetylsalicylzuur Billev 75 mg/75 mg and 75 mg/100 mg film-coated tablets was granted on 1 August 2014.

The full PAR for this medicine can be found on the website [http://mri.medagencies.org/Human](http://mri.medagencies.org/Human). For more information about treatment with Clopidogrel/Acetylsalicylzuur Billev, read the package leaflet ([http://mri.medagencies.org/download/NL_H_2953_001_FinalPL.pdf](http://mri.medagencies.org/download/NL_H_2953_001_FinalPL.pdf)) or contact your doctor or pharmacist.

This summary was last updated in September 2014.