



European Medicines Agency

London, 17 December 2009
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CHMP ASSESSMENT REPORT

FOR

DuoCover

International Nonproprietary Name: **clopidogrel / acetylsalicylic acid**

Procedure No. EMEA/H/C/001144

TABLE OF CONTENTS

1.	BACKGROUND INFORMATION ON THE PROCEDURE	3
1.1	Submission of the dossier	3
1.2	Steps taken for the assessment of the product.....	4
2.	SCIENTIFIC DISCUSSION	5
2.1	Introduction.....	5
2.2	Quality aspects	6
2.3	Non-clinical aspects	11
2.4	Clinical aspects	15
2.5	Pharmacovigilance.....	35
2.6	Overall conclusions, risk/benefit assessment and recommendation	35

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 04 March 2009 an application for Marketing Authorisation to the European Medicines Agency for DuoCover, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 29 September 2008.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.

The application submitted is a complete dossier:
a new fixed combination medicinal product.

The applicant applied for the following indication:

DuoCover is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoCover is a fixed-dose combination 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

Information on Paediatric requirement

Pursuant to Article 7, the application included an Agency Decision (Waiver Decision Number P/47/2008) for the following condition:

- Treatment of coronary atherosclerosis.

on the granting of a class waiver

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

This new fixed combination medicinal product has been given a Marketing Authorisation in Singapore on 08 August 2008 and in Australia on 14 September 2009.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Cristina Sampaio** Co-Rapporteur: **Pieter Neels**

1.2 Steps taken for the assessment of the product

- The application was received by the European Medicines Agency on 04 March 2009.
- The procedure started on 25 March 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 June 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2009. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 20-23 July 2009 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 November 2009.
- During the meeting on 14-17 December 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting Marketing Authorisation to DuoCover on 17 December 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 December 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Various types of therapeutic intervention should be considered for prevention of ACS (Acute coronary syndrome), a clinical syndrome of acute cardiac ischaemia related to coronary artery disease (CAD). These include therapeutic interventions aimed at preventing coronary plaque formation (mainly primary prevention and treatment of risk factors), interventions aimed at preventing plaque rupture (with potential for an anti-inflammatory approach), and interventions aimed at interfering with the final step of thrombosis, i.e., formation of the clot. In UA (unstable angina)/NSTEMI (non-ST segment elevation MI) patients, the aim of therapeutic intervention is to prevent thrombosis from extending to complete coronary occlusion and then MI. Due to the high risk of vascular events in these patients, and the key pathophysiologic role of platelets, antiplatelet therapy is a logical therapeutic approach. ASA has for a long time been recommended as a first approach to treating all types of ACS indications, and based on the EFC3307 (CURE) study results, the use of clopidogrel in combination with ASA was approved in Europe, US, and 89 countries worldwide, and this approach is now also recommended in international guidelines and becomes the standard of care. Based on the EFC7018 (COMMIT/CCS-2) and EFC5133 (CLARITY-TIMI 28) study results, clopidogrel in combination with ASA has been more recently approved (February 2007) in Europe, in the US and several other countries for the prevention of atherothrombotic events in STEMI patients eligible for thrombolytic therapy. Its use in combination with ASA has also been recommended by international guidelines, and has become the standard of care.

Therefore, the combination of clopidogrel with ASA is the standard of care in a broad ACS population, given the well-recognized demonstration of its efficacy and safety and the broad regulatory approval of the combined use of the two compounds, clopidogrel and ASA. (For further information please refer to the Iscover (clopidogrel) [EPAR](#)).

This dossier applies for marketing authorization for DuoCover, which contains a fixed-dose combination of clopidogrel (75 mg) and acetylsalicylic acid (ASA) (75 mg or 100 mg) as film-coated immediate-release tablet formulations.

The use of a fixed-dose combination tablet instead of the individual administration of the two compounds is expected to be more convenient to patients (and thus to improve compliance) by limiting the number of tablets they need to take.

This fixed-dose combination of antiplatelet agents is aimed to cover a substitution therapy of clopidogrel and ASA administered at the same dose level, dosing interval, and dose timing in the indications where the labeling of clopidogrel mentions it should be administered concomitantly with ASA [i.e., the prevention of atherothrombotic events in patients suffering from acute coronary syndrome (ACS): Non-ST-segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) and ST-segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy].

The clinical dossier is mainly based on bioequivalence studies testing the rate and extent of absorption of each component of the combination as compared to each substance administered in monotherapy. These are the only clinical studies performed with the fixed-dose combination. In addition the applicant provided a letter of access to all data previously submitted for clopidogrel, which is authorized in the EEA via a Centralised procedure (EMEA/H/C/0175 - EU/1/98/070- Iscover), along with non-clinical and clinical summary data for clopidogrel (mainly based on the existing clopidogrel MA dossier) and for ASA (literature data).

The claimed indication reads as follows:

“DuoCover is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoCover is a fixed-dose combination 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 “

2.2 Quality aspects

Introduction

DuoCover is presented as film-coated tablets containing two active substances. Tablets are bilayer: clopidogrel and acetylsalicylic acid (ASA). Two strengths of the medicinal product, with the same amount of clopidogrel but with different amounts of ASA have been proposed. Each tablet of the first strength contains 97.875 mg of clopidogrel hydrogen sulphate (equivalent to 75 mg clopidogrel) and 75 mg of acetylsalicylic acid. Each tablet of the second strength contains 97.875 mg of clopidogrel hydrogen sulphate (equivalent to 75 mg clopidogrel) and 100 mg of acetylsalicylic acid.

The excipients used in the formulation of DuoCover are well known excipients typically used in the tablet formulation such as mannitol, macrogol 6000, microcrystalline cellulose, low substituted hydroxypropylcellulose, maize starch, hydrogenated castor oil, stearic acid and anhydrous colloidal silica (present in the core of the tablet), lactose, hypromellose, titanium dioxide, triacetin, yellow iron oxide for 75 mg/75 mg strength or red iron oxide for 75 mg/100 mg strength (present in the coating), and carnauba wax as a polishing agent.

DuoCover 75 mg/75 mg tablets are yellow, oval, slightly biconvex, film-coated, engraved with «C75» on one side and «A75» on the other side.

DuoCover 75 mg/100 mg tablets are light pink, oval, slightly biconvex, film-coated, engraved with «C75» on one side and «A100» on the other side.

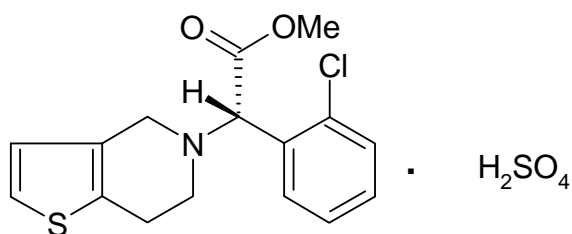
The tablets are packed in aluminium blister packs or in aluminium perforated unit-dose blister packs.

Active Substance

Clopidogrel

Clopidogrel is chemically designated as methyl (+)-(S)- α -(o-chlorophenyl)-6,7-dihydrothieno [3,2-c] pyridine-5-(4H) acetate (INN), methyl (S)-2-chlorophenyl (4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5yl) acetate (BAN) or as thieno [3,2-c] pyridine-5(4H)-acetic acid, α -(2 chlorophenyl)-6,7-dihydro-, methyl ester, (S) (CAS).

The active substance used for manufacture of the product is the hydrogen sulphate salt of clopidogrel. It is chemically designated as thieno [3,2-c] pyridine-5(4H)-acetic acid, α -(2 chlorophenyl)-6,7-dihydro-, methyl ester, (S) -, sulphate (1:1) and has the following structure:



Clopidogrel hydrogen sulphate is a white to off-white powder, non-hygroscopic, which melts at ± 177 °C. It is freely soluble in water and methanol, practically insoluble in ether. The octanol / water partition coefficient at pH 7.4 is about 3.9, its pKa is about 4.55. It is a chiral substance due to presence of one chiral centre. Three positional isomers and one optical isomer exist. The substance used in the manufacture of DuoCover is the (S) enantiomer.

Two polymorphic forms (form I and II) of clopidogrel hydrogen sulphate are known. The substance used in the manufacture of the medicinal product is clopidogrel hydrogen sulphate form II which is thermodynamically more stable than form I.

- **Manufacture**

Clopidogrel hydrogen sulfate is manufactured according to two alternative synthesis routes, so called Synthesis Route 1 and Synthesis Route 2. Both synthetic routes are adequately described and were approved for clopidogrel active substance used in Iscover.

A detailed description of the manufacturing process including process flow diagram and in-process controls were provided in the restricted part of the Active Substance Master File (ASMF). All critical steps with accompanying in-process controls have been identified. Appropriate specifications for the starting materials and reagents have been established.

The chemical structure of clopidogrel hydrogen sulfate has been confirmed by IR, UV, ^1H , ^{13}C and ^{15}N NMR spectroscopy, mass spectrometry (MS), absolute configuration study, specific optical rotation and elemental analysis. Configuration of the asymmetric carbon has been determined by crystallography and verified by chiral chromatography.

Assessment of polymorphism was performed using X-ray powder diffraction, differential scanning calorimetry and IR spectroscopy. Two polymorphic forms (form I and II) have been identified. Initial manufacturing process of the active substance produced polymorphic form I. After discovery of polymorphic form II which was thermodynamically more stable form, the manufacturing process was adapted to consistently produce form II.

- **Specification**

The active substance specifications include tests for appearance and solubility, identification (IR, HPLC and reaction of sulphates), appearance of solution, particle size, enantiospecific assay (HPLC), impurities (HPLC), volatile substances (GC), water content (Karl Fisher), heavy metals, sulphated ash. The same specifications are applicable to the active substance whether manufactured according to Synthesis Route 1 or Synthesis Route 2.

Analytical methods have been sufficiently described and validated. The HPLC method for determination of impurities has been validated with regards to specificity, repeatability, limit of detection and limit of quantitation, recovery, linearity and accuracy of precision. The GC method for volatile substances has been validated with regards to ruggedness, repeatability, linearity, accuracy and limit of detection - limit

of quantitation. The enantiospecific HPLC assay method has been validated with regards to specificity, repeatability, linearity, recovery and precision.

Batch analysis data on production scale batches of clopidogrel hydrogen sulfate form II originating from the two Synthesis Routes 1 and / or 2 was also provided. In addition batch analysis data was provided on three batches used in clinical studies and manufactured according to Synthesis Route 1. All results were consistent from batch to batch and complied with the requirements in the active substance specification.

- **Stability**

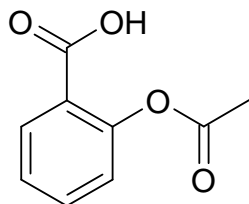
Stability studies have been performed on the active substance manufactured according to Synthesis Routes 1 and 2. The active substance manufactured according to the Synthesis Route 1 was stored up to 36 months at 25°C/60 % RH (long term conditions), up to 24 months at 30°C/60 % RH (intermediate conditions) and up to 6 months at 40°C/75 % RH (accelerated conditions). The active substance manufactured according to the Synthesis Route 2 was stored up to 36 months at 25°C/60 % RH (normal conditions) and up to 6 months at 40°C/75 % RH (accelerated conditions).

In addition results from forced degradation studies were provided. The active substance, in solid state and in solution, was exposed to variety of stress conditions including elevated temperature, elevated humidity, photolytic, acidic, basic and oxidative conditions.

Results indicate that the active substance obtained from Synthesis Routes 1 and 2 is stable when stored according to proposed conditions and confirmed the re-test period.

Acetylsalicylic acid (ASA)

Acetylsalicylic acid is chemically designated as Benzoic acid, 2-(acetyloxy) (CAS) or 2-(acetyloxy)-benzoic acid (IUPAC). It is also commonly known as Aspirin and has the following structure:



It is white crystalline powder with melting point at 156 - 161 °C, freely soluble in alcohol, soluble in chloroform, ethyl acetate and ether, slightly soluble in water. Its octanol / water partition coefficient is 13.49 and pKa 3.5.

- **Manufacture**

The manufacturer of acetylsalicylic acid obtained a Certificate of suitability with requirements of European Pharmacopoeia (CEP). The detailed information on characterisation and control of the substance, reference materials and container closure system was provided to the EDQM and assessed before granting the CEP.

It has been confirmed that no changes in the manufacturing process, specifications and analytical methods, were introduced since the granting of the CEP.

- Specification

Acetylsalicylic acid is described in the European Pharmacopoeia and its manufacturer has confirmed the active substance complies with these requirements. A copy of the CEP has been provided. The CEP includes a test for residual solvent used during the synthesis.

- Stability

A retest period and storing conditions of the active substance are confirmed in the CEP.

Medicinal Product

- Pharmaceutical Development

The objective of the formulation development was to obtain fixed-dose combination tablets, which would be equivalent to therapy consisting of Iscover 75 mg tablets combined with commercially available acetylsalicylic acid tablets.

The product has been developed as film-coated bilayer tablets containing two active substances. The aim of a preliminary development was to define the technology to be used for manufacturing tablets containing two active substances. Film-coated tablets were finally selected.

The 75 mg clopidogrel granulate corresponds to the already marketed Iscover 75 mg core formula and is granulated according to the existing processing for this product. No modifications have been introduced to the formula, batch size and granulation process of the clopidogrel granulation.

Further formulation development was performed on the blend containing acetylsalicylic acid. Various grades of acetylsalicylic acid granulated with maize starch with varying particle size distribution were mixed with additional excipients in order to achieve a homogenized blend. The weight of the acetylsalicylic acid blend varies proportionally in order to achieve the various strengths of the combination.

The acetylsalicylic acid granulation blend was optimised for consistent release of acetylsalicylic acid and to produce granulation with good flow and compressibility properties.

- Adventitious Agents

Among excipients used in the medicinal product only lactose present in the coating is of the animal origin. Declarations from the lactose suppliers were provided, stating that lactose was sourced from healthy animals under the same conditions as milk collected for human consumption.

Stearic acid used in the formulation is of vegetable origin.

- Manufacture of the Product

The tablets are manufactured from two distinct granulations, one containing clopidogrel hydrogen sulfate and the second containing acetylsalicylic acid. The medicinal product manufacturing process consists of four steps (1) preparation of granulates for compression (for both active substances), (2) compression, (3) film coating, and (4) packaging. The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

The applicant committed to perform validation on the commercial scale batches of the medicinal product, according to the provided validation protocol. Validation will be performed on marketed strengths. It will be conducted in three phases according to the different process steps: granulation, compression and

coating. This was acceptable as the formula / granulation containing clopidogrel hydrogen sulphate has already been satisfactorily manufactured in the proposed manufacturing site for several years at the same scale. In addition for the blend containing acetylsalicylic acid parameters identified during development were then further studied during the manufacture of the process validation batches.

- **Product Specification**

The product specifications include tests for appearance, identification of clopidogrel and acetylsalicylic acid (HPLC), identification of titanium dioxide and ferric oxide, uniformity of dosage units for clopidogrel and acetylsalicylic acid, assay of clopidogrel and acetylsalicylic acid, dissolution (HPLC of both active substances), impurities (HPLC of both active substances), water content (Karl Fisher) and microbiological quality.

The analytical methods have been sufficiently described, some of them are compendial methods described in the Ph Eur.

The HPLC method for chromatographic purity and the HPLC method for assay are in-house methods which have been adequately validated with regards to specificity, limits of detection and quantitation, linearity, accuracy, repeatability, intermediate precision and robustness.

With regard to the dissolution parameters, the following factors have been tested: solubility of clopidogrel and acetylsalicylic acid in dissolution medium (demonstration of “SINK” conditions), influence of the deaeration of the dissolution medium, influence of the pH of the dissolution medium, influence of the composition of the dissolution medium on the dissolution profile and robustness. The HPLC method used in the dissolution test is comparable to the one used for the assay with adjustments in the concentrations of the test solutions and in the mobile phase. The method has been validated with respect to specificity, stability of solution, linearity, accuracy, repeatability and intermediate precision.

Batch analysis results on several commercial scale batches of each strength of the medicinal product indicated satisfactory uniformity and compliance with agreed specifications. The results are consistent from batch to batch.

- **Stability of the Product**

Stability studies according to the ICH guidelines have been performed on a total number of 26 batches of the medicinal product. Stability studies have been performed under stress conditions (photostability study), long term (25°C/60 % RH), and intermediate (30°C/65 % RH) up to 30 months and accelerated conditions (40°C/75 % RH) up to 6 months. No significant changes during the stability studies have been observed.

The results generated during the stability studies and statistical analyses support the proposed shelf life and storage conditions as defined in the SmPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substances and the medicinal product have been appropriately characterised and generally satisfactory documentation has been provided. The excipients used in the preparation of the product and manufacturing process selected are typical for tablets. The results indicate that the active substances and the medicinal product can be reproducibly manufactured.

2.3 Non-clinical aspects

Introduction

No preclinical studies with the FDC were performed. This is acceptable as the combination clopidogrel plus ASA has not introduced any additional impurities to the product that are not present in clopidogrel 75 mg tablets, or in a range of ASA products.

An extensive preclinical development program had been carried out for clopidogrel, and a letter of access to the Iscover dossier was provided in the FDC dossier.

For ASA preclinical literature data were included in the dossier and these are sufficient to assess potential safety issues with ASA at dose levels proposed for use in humans. A summary of the main findings for clopidogrel and ASA respectively was provided in the dossier.

Pharmacology

- Primary pharmacodynamics

Clopidogrel

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

The mechanism of the antiplatelet action of clopidogrel is mediated through a metabolite, the structure of which has been identified during the process of regulatory assessment of the marketing authorization application of the Iscover file. This metabolite has been isolated and its structure characterized as a thiol derivative of 2 oxo clopidogrel. *In vitro*, in the absence of hepatic biotransformation no effect on platelet aggregation by clopidogrel could be observed, demonstrating the metabolite associated effect. The pharmacological target of this active metabolite is a Gi2 coupled receptor designated as P2Y12. The molecular interaction between the clopidogrel active metabolite and the P2Y12 receptor consists in the formation of a disulfur bridge between the reactive thiol of the molecule and cysteine 97 of P2Y12, causing the disruption of receptor complexes and translocation from platelet membrane microdomains. The activity of clopidogrel on platelet aggregation was appropriately evaluated *in vitro* and *ex vivo*.

Acetylsalicylic acid (ASA)

ASA inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A₂, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

The pharmacological profile of ASA as a cyclooxygenase (COX) inhibitor (both COX-1 and COX-2) has been extensively established.

- It is active in most conventional models of inflammation, irrespective of their different mechanisms.
- ASA has also been shown to be a peripheral analgesic and antipyretic.
- The anti-thrombotic activity of ASA is based on a specific anti-platelet activity due to selective acetylation of thrombocyte COX-1 and on a fibrinolytic activity due to N-acetylation of fibrinogen.

Clopidogrel/ASA combination

The synergistic overpotentiation obtained when ASA and clopidogrel are given in combination has been demonstrated in some studies, 3 of which are referred in the DuoCover file¹²³. The observed additive

1 Bierbach B, Horstick G, Berg O, Heimann A, Münzel T, Vahl CF, et al. Potent low dose platelet inhibitory effects of clopidogrel and aspirin on coronary thrombus formation in an animal model of acute unstable angina. *Thromb Haemost* 2006;95(2):354-61.

effect strongly suggests that the combined inhibition of 1/ COX (and subsequently of thromboxane synthesis) by ASA and 2/ ADP receptors by clopidogrel can provide substantial protection against platelet aggregation and thrombosis at the site of endothelial injury, in humans.

- Secondary pharmacodynamics

Secondary pharmacodynamic studies with the combination were not performed and are not requested in view of the extensive data available on the use of combined individual medicinal products at the dosage now being applied for in the DuoCover application.

- Safety pharmacology programme

Safety pharmacology studies with the combination were not performed and are not requested given the extensive data available on the use of combined individual medicinal products at the dosage being applied for in the DuoCover application.

- Pharmacodynamic drug interactions

No pharmacodynamic studies were conducted with the combination. Based on the fact that there is sufficient clinical experience with combined use of the individual medicinal products in patients, nonclinical interaction studies have not been requested by the CHMP.

Pharmacokinetics

Clopidogrel

The metabolism and disposition of clopidogrel were evaluated in several *in vitro* and *in vivo* studies performed in the mouse, rat, rabbit and baboons. The pharmacokinetics of ASA has been investigated in the rat (with some further limited data in the dog and monkey) and is largely documented in humans.

Clopidogrel is well absorbed (at least 50%), and undergoes extensive metabolism. Twenty metabolites were identified. In all species, the primary biotransformation pathways consist of: hydrolysis of the ester function by carboxylesterases (leading to the formation of SR26334, the main circulating metabolite); sulfoxidation, oxidation of the tetrahydropyridine moiety, and glucuronidation of SR26334. The main metabolite found in plasma, the carboxylic acid derivative (SR26334), is inactive. The peak plasma concentration of SR26334 was observed 1 to 2 hours after oral administration of clopidogrel in all the studied animal species. The active thiol metabolite of clopidogrel isolated following incubation of clopidogrel with hepatic microsomal fractions has not been detected in plasma.

The binding of clopidogrel and SR26334 to plasma proteins was high (98% and 94% respectively) in all species and distributed widely in tissues. Radioactivity was slowly eliminated from the tissues, and in particular from arterial wall, thyroid gland, cartilage, skin and spleen. Transfer of the radioactivity to the developing foetus was observed in pregnant rats and rabbits. The majority of radioactivity was excreted within 48 hours in all species. In lactating rats, clopidogrel and/or its metabolites levels in milk were 0.5 to 2.6 times higher than the maternal plasma levels.

2 Herbert JM, Dol F, Bernat A, Falotico R, Lalé A, Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. *Thromb Haemost* 1998;80(3):512-8

3. Harker LA, Marzec UM, Kelly AB, Chronos NR, Sundell IB, Hanson SR, et al. Clopidogrel inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. *Circulation* 1998;98(22):2461-9.

ASA

After oral administration, ASA is rapidly absorbed to give appreciable concentrations in plasma even after 30 minutes before a gradual decline with conversion of ASA to salicylate. Both ASA and salicylate are rapidly and extensively distributed in body fluids (including breast milk). They are localized in excretory organs (liver and kidney) and glandular stomach and cross the placental barrier. ASA binds strongly to plasma proteins and may displace certain compounds including other acidic nonsteroidal anti-inflammatory drugs (NSAID) or coumarins. The biotransformation of ASA proceeds in two steps. The first step is independent of dose and involves conversion to salicylate by pre-absorptive hydrolysis in the gut mucosa and a hepatic first-pass effect. The second step, the metabolic conversion of salicylate and subsequent formation of conjugates and their renal excretion, is dose-dependent. Salicylic acid is the main and rate-limiting metabolite in humans.

Clopidogrel/ASA combination

The PK of combined Clopidogrel/ASA has not been addressed in dedicated studies. Based on the pharmacokinetic characteristics of clopidogrel and ASA and on the drug-drug interaction profiles of each of these drugs, no pharmacokinetic interactions between the 2 compounds are expected.

Both compounds are highly protein bound and undergo hepatic metabolism. Although these aspects might raise the possibility for pharmacokinetic interaction, this is expected to have been covered in the clinical use, since the combined use of both compounds has been taking place already. Therefore, it is considered that there is no need for dedicated pharmacokinetic and interaction studies with the fixed dose combination.

Toxicology

The general safety aspects associated to clopidogrel and ASA regarding general toxicity and specific aspects like genotoxicity, carcinogenicity or reproductive toxicity are well known from previously performed studies with Iscover and from published data and clinical information on and experience with the use of both drugs, including their combined use in the dose ratio included in DuoCover.

- Single dose toxicity

Single dose studies have shown that oral toxicity of both ASA and clopidogrel is low.

- Repeat dose toxicity (with toxicokinetics)

The toxicity after repeated use of both drugs is generally related to their pharmacodynamics and mainly involves gastrointestinal disturbances. However these effects occurred only at very high dosages of each drug representing more than 300 or 30 times the usual human dosage on a mg/kg basis for clopidogrel or ASA, respectively.

Repeat dose toxicity data for ASA show specific effects of ASA on other target organs comprising the central nervous, cardiovascular and respiratory systems, sensory organs, kidney and in Reye's syndrome.

The main toxicological finding at doses up to 400 mg/kg/day clopidogrel correspond to increased liver weight associated with hypertrophy of the smooth endoplasmic reticulum in centrilobular hepatocytes corresponding to an effect on hepatic enzymes. The no-effect level, based on increased liver weight, is 27 mg/kg/day in rats and 65 mg/kg/day in baboons and corresponds to an exposure of at least 7 times (rats) and more than 10 times (baboons) higher than that observed in humans at the recommended therapeutic dose.

Neither clopidogrel nor ASA, even when administered at very high dose levels, induce any spontaneous haemorrhages. Bleeding complications are the most often described adverse effects of any anticoagulation

therapy. As expected given the pharmacological activity of the compounds, increases in bleeding time were observed following occasional vascular lesions.

- Genotoxicity

No genotoxicity/ carcinogenicity studies were performed with the fixed-dose combination, which is acceptable. None of the two drugs were found to be genotoxic or carcinogenic. Although ASA has not been tested in contemporary carcinogenicity studies in rodents, the vast human experience suggests that ASA is not carcinogenic in humans at therapeutic doses.

- Carcinogenicity

Please see under Genotoxicity.

- Reproduction Toxicity

The reproductive toxicity profile, particularly of aspirin raises concern in relation to early (embryofetal development) or late (dystocia and foetal mortality) pregnancy, many of the effects being associated to the inhibitory effect on prostaglandin synthesis. Precautionary information has been included in sections 4.3 and 4.6 of the SPC, to appropriately restrict its use. The use in pregnancy of DuoCover is not to be completely contraindicated due to the severity of the condition. A contra-indication for third trimester of pregnancy was added to the product information, while use during the first 2 trimesters of pregnancy is not recommended unless the patient's clinical condition requires treatment with clopidogrel/ASA.

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk and breast-feeding should not be continued during treatment with DuoCover (see SPC section 4.6 and 5.3)

- Local tolerance / Other toxicity studies

No data have been submitted with the combination nor the individual compounds. No specific studies were considered necessary by CHMP in the light of the available nonclinical data as well as the clinical evidence available for the two components alone or in combination.

Ecotoxicity/environmental risk assessment

The submitted environmental risk assessment (ERA) includes a phase II tier A analysis. However, the ERA Phase II tier A analyses for clopidogrel have not been completed.

The adsorption/desorption study (OECD106) submitted with the Applicant's responses to the CHMP D120 LOQ (List of Questions) indicate that clopidogrel is not expected to pose a risk to the terrestrial compartment. The aerobic transformation study in aquatic sediment system (OECD308), also submitted with the Applicant's responses to the CHMP D120 LOQ, indicates the need to perform a sediment organism toxicity test.

The applicant commits to submit an updated ERA that includes the ongoing and agreed studies, namely: the log Kow determination and if required a bioconcentration test (OECD 305), the repetition of the activated sludge respiration inhibition test (OECD 209) and the consequent revision of the PEC/PNEC ratio, and the sediment organism toxicity test. The commitment includes identifying the metabolite (transformation product > 10% as well as in water as in sediment, detected in chromatography region 4) as requested in OECD guideline 308.

This was acceptable to CHMP.

Discussion on the non-clinical aspects

The pharmacological and toxicological profile of clopidogrel and acetylsalicylic acid are well known (from Iscover supportive studies and from published studies in animals, men and *in vitro* models).

As there is no evidence to suggest a possible negative interaction between clopidogrel and ASA, and both drugs have been extensively used in humans in monotherapy or in combination for a long period and the safety of this combination is well documented, nonclinical studies with the clopidogrel/ASA combination are not considered necessary. Non-clinical studies with clopidogrel/ASA fixed dose combination have not been performed. The rationale for the pharmacological association has some supportive primary pharmacology studies in animals. Three published studies, one of which dated 2006 have been submitted. It is considered that the existing clinical experience is the supportive information for DuoCover efficacy and safety and therefore specific nonclinical studies with the clopidogrel/ASA fixed dose combination are not needed. Concerns regarding the reproductive toxicity profile, particularly of aspirin in relation to early pregnancy (embryofoetal development) or late pregnancy (dystocia and foetal mortality) have been addressed by adding precautionary information in section 4.3 and 4.6 of the SPC, to appropriately restrict its use.

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk and breast-feeding should not be continued during treatment with DuoCover.

An updated ERA is requested, but this does not impact on the approval of Clopidogrel/ASA fixed dose combination. Therefore, from a nonclinical perspective, the file is satisfactory and no non-clinical follow-up measures other than those related to ERA are raised.

2.4 Clinical aspects

Introduction

The active substances in the fixed-dose combination DuoCover, i.e. clopidogrel (75 mg) and acetylsalicylic acid (ASA) (75 mg or 100 mg as film-coated immediate-release tablet formulations) are already approved for combination therapy of ACS (see details in section 3.1 “Introduction” to the Scientific Discussion)

The use of a fixed-dose combination tablet instead of the individual administration of the two compounds is expected to be more convenient to patients. This fixed-dose combination of antiplatelet agents is aimed to cover a substitution therapy of clopidogrel and ASA administered at the same dose level, dosing interval, and dose timing in the indications where the labeling of clopidogrel mentions it should be administered concomitantly with ASA.

Bioequivalence studies testing the rate and extent of absorption of each component of the fixed-dose combination as compared to each substance administered in monotherapy are the only clinical studies performed with the fixed-dose combination.

The applicant provided a letter of access to all data previously submitted for clopidogrel, which is authorised in the EEA via a Centralised procedure (EMEA/H/C/0175 - EU/1/98/070- Iscover), along with clinical summary data for clopidogrel (mainly based on the existing clopidogrel MA dossier) and for ASA (literature data).

The applicant did not seek Scientific Advice from the CHMP for this development.

A paediatric development is not planned for this fixed dose combination.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetic development strategy for DuoCover focused on demonstration of bioequivalence between this FDC product and the concurrently administered individual dosage forms.

This section provides a summary of the available pharmacokinetic data on the individual active substances (previously submitted clinical data for clopidogrel and literature data for acetylsalicylic acid) as well as details of the additional clinical studies specific for the fixed-dose combination.

- Absorption

Clopidogrel

After oral administration in humans, clopidogrel is well and rapidly absorbed. Its absorption is estimated to be at least 50% and maximum plasma concentration is reached 45 minutes post-dose. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. Clopidogrel is a pro-drug. The active metabolite, a thiol derivative, is formed by oxidation to 2-oxo-clopidogrel and subsequent hydrolysis most likely during the first-pass processes. The active metabolite is a very reactive molecular entity which binds irreversibly to platelet ADP receptors.

After oral administration, the major circulating metabolite of clopidogrel is a pharmacologically inactive de-esterified carboxylic acid metabolite (SR26334). SR26334 represents 85% of the total radioactivity in plasma following a single administration of [¹⁴C] clopidogrel 75 mg. SR26334 has an elimination half-life of 7 to 8 hours after both single and multiple dose administration of clopidogrel 75 mg once daily.

This metabolite is detected quickly in the plasma of healthy subjects after single oral administration of 75 mg of clopidogrel, with peak plasma levels of approximately 3000 ng/ml, 0.5 to 0.8 hours post-dose and is quantifiable over 36 to 48 hours post-dose.

ASA

Following absorption ASA is hydrolysed to salicylic acid (SA) with peak plasma levels of SA occurring within 1-1.5 hours of dosing, such that plasma levels of ASA are essentially undetectable 1.5-4 hours after dosing.

-Bioequivalence

An application was initially submitted in May 2007 for 2 film-coated immediate-release tablet formulations of clopidogrel and ASA, each containing 75 mg clopidogrel and 2 doses of ASA, i.e., 75 and 100 mg. In this initial application, bioequivalence was documented based on carboxylic acid inactive metabolite of clopidogrel (SR26334), ASA, and salicylic acid (SA). The application was withdrawn in May 2008 further to the CHMP's request regarding the need to document bioequivalence based on clopidogrel plasma levels in accordance to note for guidance on the Investigation on Bioavailability and Bioequivalence in force (CPMP/EWP/QWP/1401/98) and a Question & Answers on the Bioavailability and Bioequivalence Guideline (EMA/CHMP/EWP/40326/2006). To address the CHMP's request the applicant performed a new bioequivalence study measuring plasma levels of clopidogrel in addition to SR26334, ASA, and SA.

Three bioequivalence studies were performed to support this application. A new study evaluated bioequivalence of the clopidogrel 75 mg/ASA 100 mg strength based on the parent compounds (i.e., clopidogrel and ASA), the main inactive metabolites of clopidogrel (SR26334) and ASA (SA) being provided as supportive data ([BEQ10600]). The 2 other studies, submitted previously, evaluated the bioequivalence of the clopidogrel 75 mg /ASA 75 mg ([BDR4659]) and clopidogrel 75 mg/ASA 100 mg ([BDR5000]) strengths based on ASA, SA, and SR26334. The studies were performed in fasting conditions.

Bioequivalence testing based on parent clopidogrel was not performed in the latter 2 studies. The new bioequivalence study (BEQ10600) is the basis to demonstrate the bioequivalence of the clopidogrel 75 mg/ASA 100 mg strength, study BDR5000 being provided as supportive study. Study BDR4659 assesses the demonstration of the bioequivalence for the ASA part of the clopidogrel 75 mg/ASA 75 mg strength based on ASA (parent compound). For this strength, a waiver was sought for not having tested the bioequivalence based on parent clopidogrel, considering the similarity of the clopidogrel granules (75 mg in the two fixed-combination tablets) and dissolution profile of clopidogrel with the highest combination strength (clopidogrel 75mg/ASA 100 mg), and the demonstration of the bioequivalence based on clopidogrel in this combination strength.

Marketed clopidogrel 75 mg film-coated tablets as well as ASA immediate-release tablets (European: 75 mg and 100 mg and US: 325 mg), were used as reference tablets. Since the ASA blend of the clopidogrel/ASA tablets is an immediate-release formulation, reference ASA tablets were marketed immediate-release formulations with *in vitro* dissolution profiles similar to that of the immediate-release clopidogrel/ASA tablets. Given the wide range of ASA formulations available on the market (immediate-release tablet, effervescent tablet, buffered tablet, enteric-coated tablet, powder for solution), and that these can result in different absorption rates of ASA, a formulation similar to the one used in the fixed combination (i.e., immediate release) has been used for the bioequivalence study.

Dissolution studies for the formulations used in the bioequivalence studies

The dissolution profiles for clopidogrel were equivalent between the clopidogrel/ASA tablets and 75 mg clopidogrel tablet. In addition, the statistical calculation (similarity factor, f_2) performed for the clopidogrel dissolution results further confirm the equivalence of the *in vitro* profiles. The dissolution profiles for ASA were equivalent between the clopidogrel/ASA tablets and the ASA tablets of corresponding strengths. Given that ASA dissolves quickly at all pH ranges ($\geq 85\%$ within 15 minutes), the similarity factor was not calculated.

Dissolution studies for the commercial batches

In vitro dissolution profiles for clopidogrel/ASA 75/75, 75/100, 75/150, and 75/325 tablets were performed in order to demonstrate comparability of commercial tablets batches to those used in the bioequivalence studies. The f_2 factors calculated for clopidogrel profiles were greater than 50.

The comparison of the dissolution profiles clopidogrel 75 mg/ ASA 100 mg tablets versus the Iscover® 75 mg reference tablets and versus Aspirin® N Bayer 100 mg reference tablets are performed as complementary information to bioequivalence study BEQ10600.

The statistical calculation (similarity factor: f_2) performed for clopidogrel dissolution results demonstrated the similarity of the dissolution between the 2 tablets at pH 4.5 and 6.8 (f_2 value >50) while f_2 value was slightly below 50 (48) at pH 2.0. Nevertheless, the bioequivalence was demonstrated for clopidogrel between the 2 formulations in clinical bioequivalence study BEQ10600

The comparative *in vitro* dissolution profiles at pH 2.0, 4.5, and 6.8 for clopidogrel 75 mg/ ASA 75 mg tablets versus clopidogrel 75 mg/ ASA 100 mg reference tablets were performed. The batch of clopidogrel 75 mg/ ASA 100 mg reference tablets used for this comparative *in vitro* dissolution study is the one used in clinical bioequivalence study BEQ10600.

For clopidogrel, the f2 factors calculated for clopidogrel dissolution results are >50 regardless the pH demonstrating the similarity of the dissolution between the 2 tablets.

Primary objective, study design, test formulations, and reference formulations for the newly submitted bioequivalence study and the 2 previously submitted bioequivalence studies are listed in the table 1 below.

Table 1

Study No.	Primary Objective	Study Design	Test Formulation	Reference Formulation	PK Evaluation Criteria
BEQ10600 [5.3.1.2]	Bioequivalence	Open, randomized, 2-sequence, 2-period, 2-treatment crossover	Clopidogrel 75 mg/ ASA 100 mg	Plavix®/Iscover® 75 mg tablet Aspirin® N 100 mg tablet (Bayer, Germany)	Clopidogrel, SR26334, ASA and SA
BDR5000 [5.3.1.2]	Bioequivalence	Open, randomized, 2-sequence, 2-period, 2-treatment crossover	Clopidogrel 75 mg/ ASA 100 mg	Plavix®/Iscover® 75 mg tablet Aspirin® N 100 mg tablet (Bayer, Germany)	SR26334, ASA and SA
BDR4659 [5.3.1.2]	Bioequivalence	Open, randomized, 2-sequence, 2-period, 2-treatment crossover	Clopidogrel 75 mg/ ASA 75 mg	Plavix®/Iscover® 75 mg tablet ASA 75 mg tablet: Angettes®, (BMS, UK)	SR26334, ASA and SA

Study BDR4659: Bioequivalence between a tablet containing 75 mg of SR25990C and 75 mg of acetylsalicylic acid and the simultaneous administration of the separate formulations of the two drugs, to young healthy subjects. Open, crossover, randomized and single centre.

Table 2

Objectives:	<p>Primary: To verify the bioequivalence of the pharmacokinetic profile of clopidogrel and salicylic acid (SA) after single oral administration of a tablet containing the 2 drugs or after simultaneous administration of the 2 drugs in their respective commercial formulations.</p> <p>Secondary: To assess the clinical and biological tolerability of the acetylsalicylic acid (ASA) + clopidogrel association.</p>		
Methodology:	Single center, open-label, crossover, randomized, 2 treatments and single oral dose study		
Number of subjects:	Planned: 40	Randomized: 40	Treated: 40
Evaluated:	Pharmacokinetics: 40	Safety: 40	
Duration of treatment:	Two periods of 1-day treatment, separated by a 14-day washout period (inclusive of the treatment period)	<p>Duration of observation:</p> <ul style="list-style-type: none"> • Screening: 2 weeks • Treatment period: 3 days • End of study: 3 to 7 days after last blood sampling 	

Results are shown below in table 3 and figure 1:

Table 3

Mean (CV%) pharmacokinetic parameters of SR26334, salicylic acid, and ASA, treatment ratio estimates and 90% CI's for clopidogrel/ASA 75/75 mg tablets versus 75 mg clopidogrel tablets and 75 mg ASA tablets (N=40)

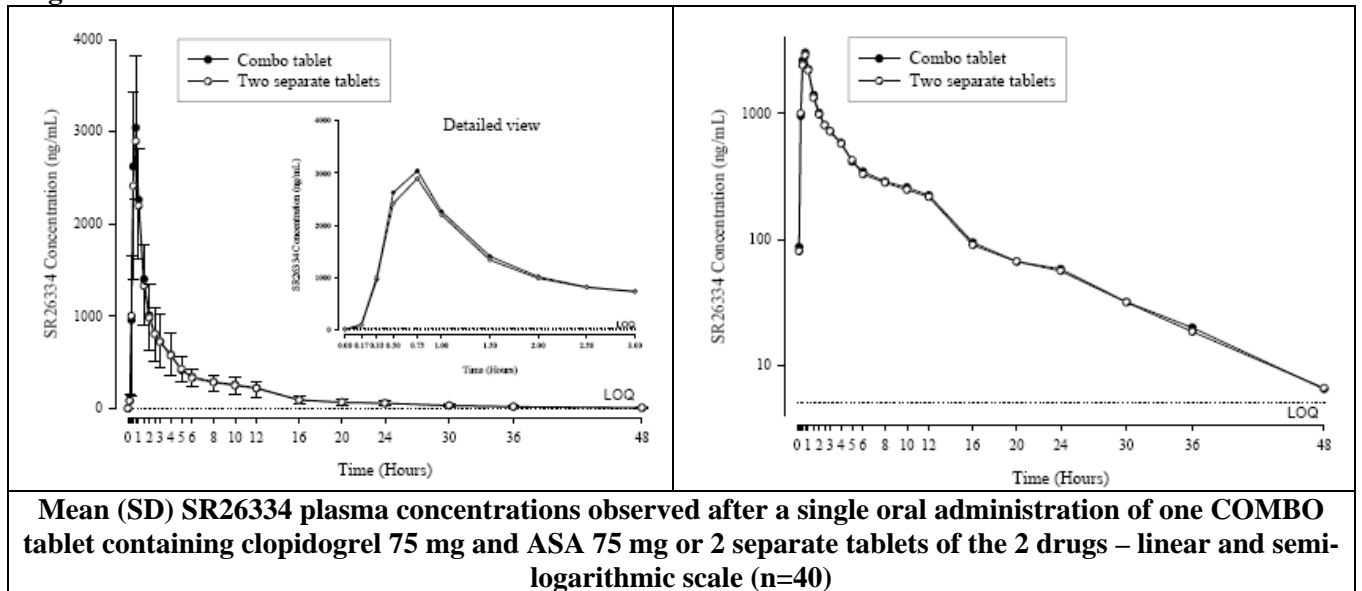
	Clopidogrel/ASA 75/75 mg Tablets	Clopidogrel 75 mg + ASA 75 mg Tablet	Ratio Estimate ^b [90% CIs]
SR26334			
C _{max} (ng/mL)	3319 (26)	3105 (27)	1.08 [0.99;1.17]
t _{max} (h) ^a	0.75	0.75	0 [-0.10;0.01] ^c
AUC (ng.h/mL)	9215 (29)	8947 (27)	1.03 [0.98;1.07]
t _{1/2} (h)	8.48 (18)	8.55 (27)	-
Salicylic acid			
C _{max} (ng/mL)	3533 (16)	3094 (17)	1.15 [1.10;1.20]
t _{max} (h) ^a	1.0	1.5	-0.5 [-0.63;-0.27] ^c
AUC (ng.h/mL)	12217 (21)	11778 (19)	1.03 [1.00;1.06]
t _{1/2} (h)	1.94 (17)	1.94 (17)	-
ASA			
C _{max} (ng/mL)	1207 (25)	738 (26)	1.64 [1.51;1.78]
t _{max} (h) ^a	0.50	0.52	-0.13 [-0.20;-0.06] ^c
AUC (ng.h/mL)	936 (17)	826 (22)	1.15 [1.10;1.20]
t _{1/2} (h)	0.33 (21)	0.43 (35)	-

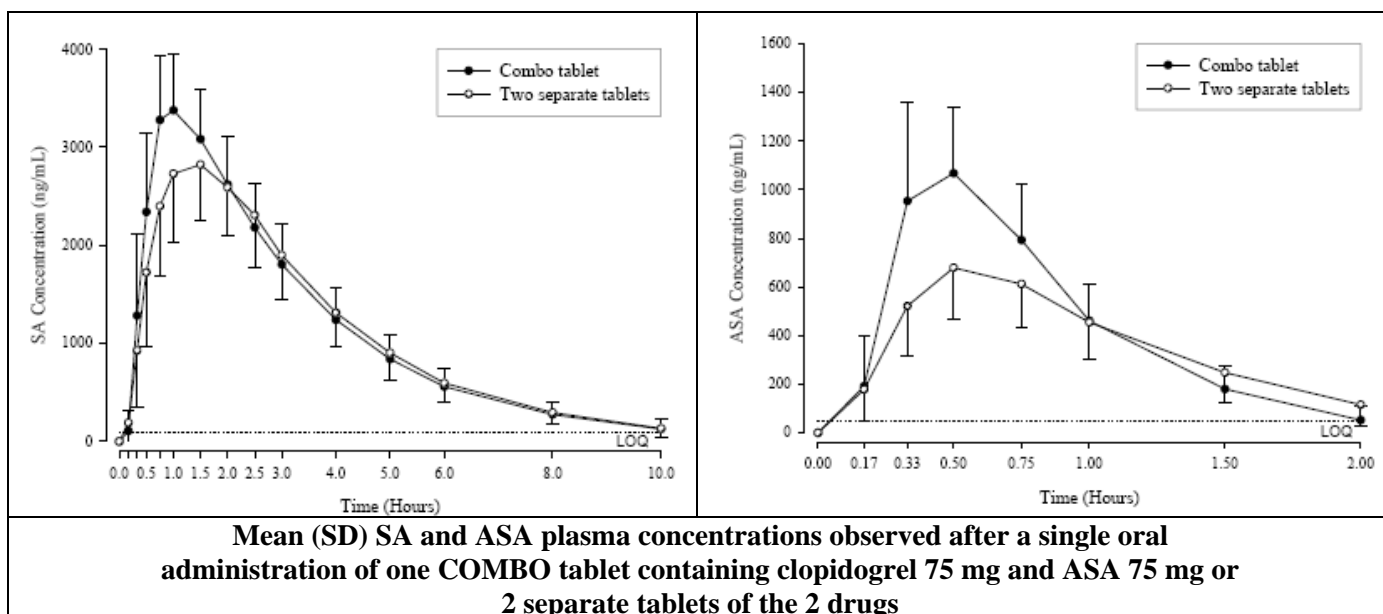
^a median

^b ratio clopidogrel/ASA 75/75 mg tablets versus 75 mg clopidogrel and 75 mg ASA tablets

^c median difference and 90% CIs

Figure 1





Study BDR5000: Bioequivalence between a tablet containing 75 mg of SR25990C and 100 mg of acetylsalicylic acid and the simultaneous administration of the separate formulations of the two drugs, to young healthy subjects. Open, crossover, randomized and single centre.

Table 4

Objectives:	<p>Primary: To verify the bioequivalence of the pharmacokinetic profile of clopidogrel and salicylic acid (SA) after single oral administration of a tablet containing the 2 drugs or after simultaneous administration of the 2 drugs in their respective commercial formulations.</p> <p>Secondary: To assess the clinical and biological tolerability of the acetylsalicylic acid (ASA) + clopidogrel association.</p>		
Methodology:	Single center, open-label, crossover, randomized, 2 treatments and single oral dose study		
Number of subjects:	Planned: 40	Randomized: 40	Treated: 40
Evaluated:	Pharmacokinetics: 40	Safety: 40	
Duration of treatment:	Two periods of 1-day treatment, separated by a 14-day washout period (inclusive of the treatment period)		Duration of observation:
			<ul style="list-style-type: none"> • Screening: 2 weeks • Treatment period: 3 days • End of study: 3 to 7 days after last blood sampling

Results are shown in table 5 and figure 2 below:

Table 5: Mean (CV%) pharmacokinetic parameters of SR26334, salicylic acid, and ASA, treatment ratio estimates and 90% CI's for clopidogrel/ASA 75/100 mg tablets versus 75 mg clopidogrel tablets and 100 mg ASA tablets (N=40)

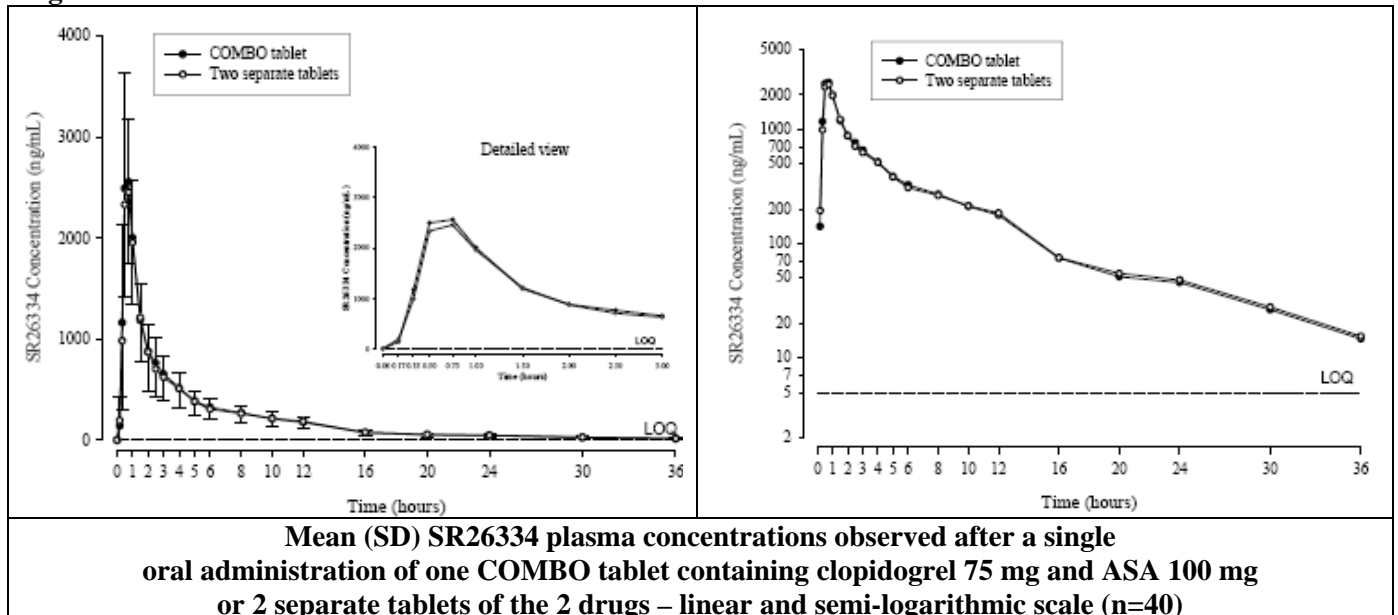
	Clopidogrel/ASA 75/100 mg Tablet	Clopidogrel 75 mg + ASA 100 mg Tablet	Ratio Estimate ^b [90% CIs]
SR26334			
C_{max} (ng/mL)	3042 (25)	2810 (26)	1.08 [0.98;1.20]
t_{max} (h) ^a	0.67	0.56	0.00 [0.04;0.13] ^c
AUC (ng.h/mL)	8059 (19)	8004 (26)	1.03 [0.98;1.07]
$t_{1/2}$ (h)	8.70 (23)	8.90 (21)	-
Salicylic acid			
C_{max} (ng/mL)	4878 (14)	4189 (16)	1.17 [1.12;1.22]
t_{max} (h) ^a	1.00	1.50	-0.50 [-0.63;-0.37] ^c
AUC (ng.h/mL)	17791 (32)	17225 (30)	1.03 [1.01;1.05]
$t_{1/2}$ (h)	2.08 (30)	2.06 (28)	-
ASA			
C_{max} (ng/mL)	1492 (26)	964 (23)	1.54 [1.41;1.69]
t_{max} (h) ^a	0.50	0.50	-0.11 [-0.17; -0.04] ^c
AUC (ng.h/mL)	1131 (16)	1007 (21)	1.13 [1.08;1.19]
$t_{1/2}$ (h)	0.34 (33)	0.41 (35)	-

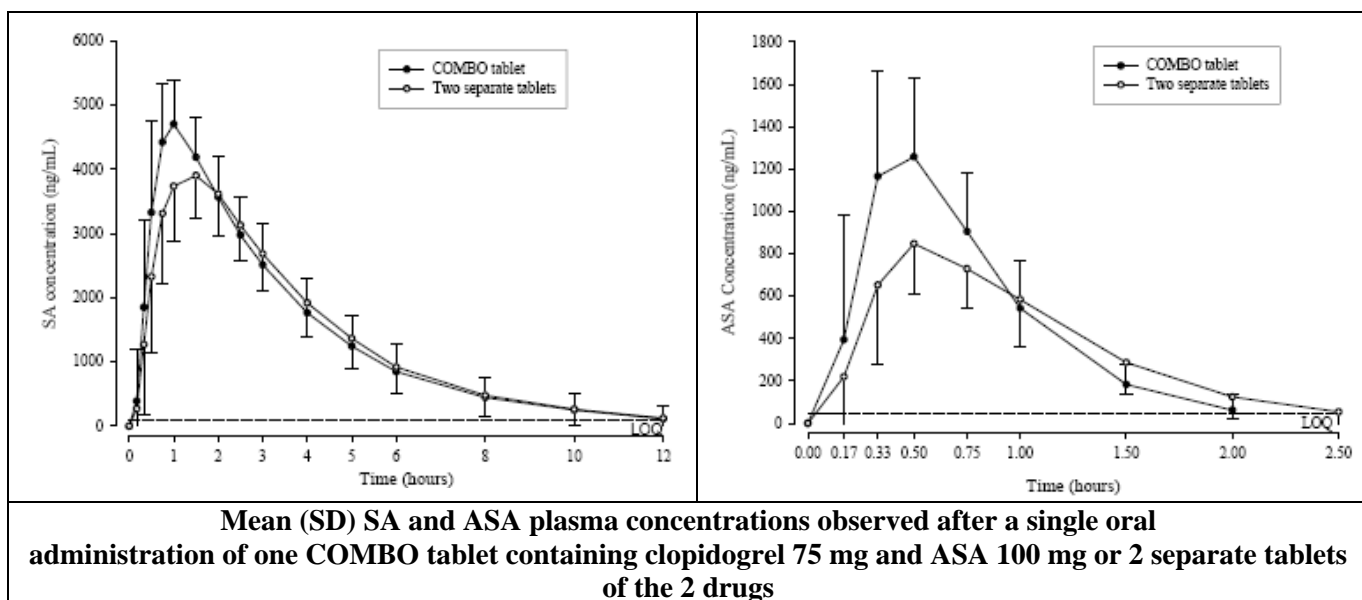
^a median

^b ratio clopidogrel/ASA 75/100 mg versus 75 mg clopidogrel tablets and 100 mg ASA tablets

^c median difference and 90% CIs

Figure 2





STUDY BEQ10600: An open-label, randomized, single-dose, two-sequence crossover bioequivalence study comparing a tablet containing 75 mg of SR25990C and 100 mg of acetylsalicylic acid versus the simultaneous administration of the separate formulations of the two drugs in healthy young male and female subjects

Study design: An open-label, randomized, single-dose, two-sequence, two-period, two-treatment crossover study with at least 10-day washout period between the two administrations by oral route in fasted conditions.

Number of subjects

Planned: 120 randomized subjects for at least 114 assessable subjects (a minimum of 30% of either gender)

Completed: 113

Evaluated Pharmacokinetics: 121 (117 assessable for each formulation); Safety: 121

Test and reference products

Fixed dose combination 75 mg clopidogrel + 100 mg ASA, single dose versus 75 mg Clopidogrel (Plavix®) as a tablet co-administered with Aspirin® 100 mg as a tablet

Pharmacokinetics

Primary analysis: Assessment of bioequivalence on clopidogrel and ASA:

For log transformed C_{max} (except for ASA), AUC and AUC_{last}, the relative bioavailability between the two formulations was assessed using a linear mixed effects model with fixed terms for formulation, period, sequence, and sex, and with an unstructured R variance covariance matrix for subject within sequence-by-sex blocks using SAS PROC MIXED.

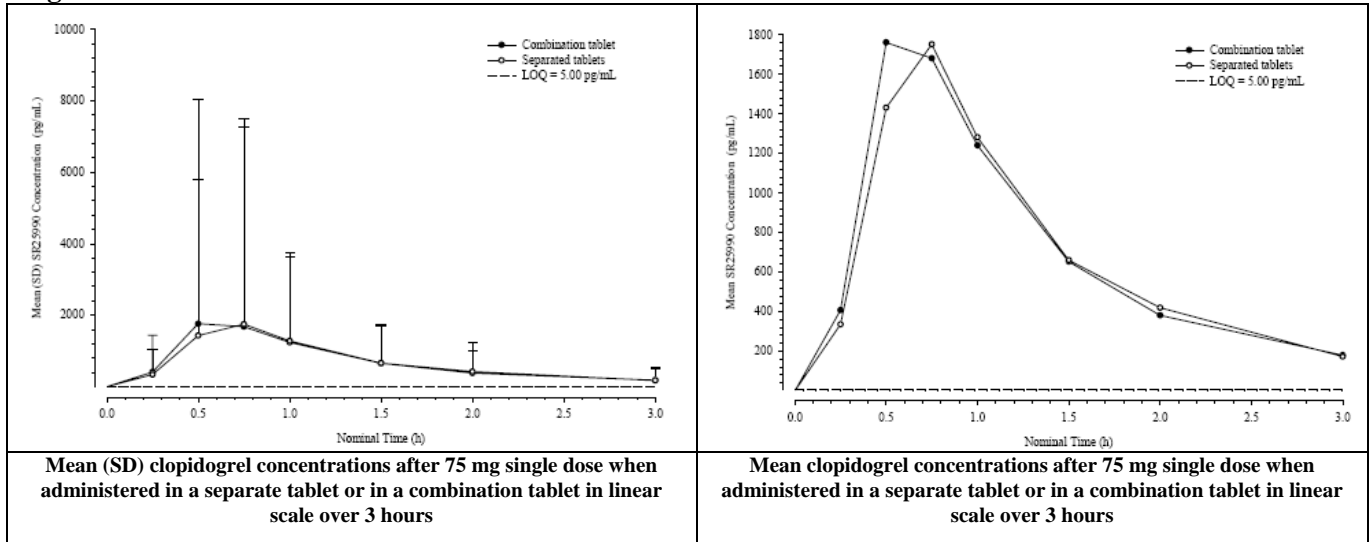
Estimates and 90% confidence intervals (CIs) for the ratios of geometric means between the two formulations were obtained by computing estimates and 90% CIs for the differences between formulation means within the mixed model, and converting to ratios by the antilog transformation. Equivalence was concluded if the 90% CIs for the ratios of primary criteria parameters are entirely within the 0.80 to 1.25 equivalence specifications.

Secondary analysis: Assessment of bioequivalence on SR26334 and SA

For SR26334 and SA, the ratios for C_{max} , AUC, and AUClast were estimated with their 90% CIs, based on SR26334 and SA PK data using the same model structure as in the primary analysis. ASA C_{max} was analyzed in the same way.

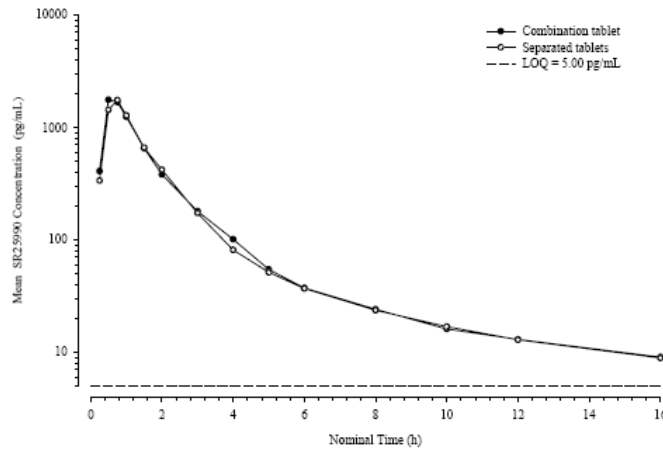
Results are shown in the tables 6 and figure 3 below.

Figure 3:



Mean (SD) clopidogrel concentrations after 75 mg single dose when administered in a separate tablet or in a combination tablet in linear scale over 3 hours

Mean clopidogrel concentrations after 75 mg single dose when administered in a separate tablet or in a combination tablet in linear scale over 3 hours



Mean clopidogrel concentrations after 75 mg single dose when administered in a separate tablet or in a combination tablet

Table 6:

Mean ± SD (CV%) [Geometric Mean] of clopidogrel pharmacokinetic parameters

PK Parameter	Combination tablet (n=117)	Separated tablets (n=117)
C_{max} (pg/mL)	2490 ± 7630 (306) [1050]	2230 ± 5680 (255) [972]
t_{max} (h)	0.75 (0.25, 3.00)	0.75 (0.25, 2.00)
t_{last} (h)	16.00 (5.00, 23.00)	16.00 (5.00, 23.00)
$t_{1/2z^*}$ (h)	6.08 ± 2.10 (34) [5.63]	6.14 ± 2.47 (40) [5.56]
AUC_{last} (h.pg/mL)	2600 ± 5550 (213) [1420]	2530 ± 4970 (196) [1330]
AUC^* (h.pg/mL)	2740 ± 5750 (210) [1540]	2720 ± 5130 (189) [1490]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} and t_{last} where values are Median (Min, Max)

*n=110 for combination tablet and n=111 for separated tablet

Point estimates and 90% CIs for clopidogrel for combination tablet / separate tablets (n=121)

Parameter	Comparison	Estimate	90% CI
C_{max}	Combination tablet vs. Separated tablets	1.08	(0.94; 1.23)
AUC	Combination tablet vs. Separated tablets	1.03	(0.92; 1.15)
AUC_{last}	Combination tablet vs. Separated tablets	1.05	(0.95; 1.18)

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Figure 4:

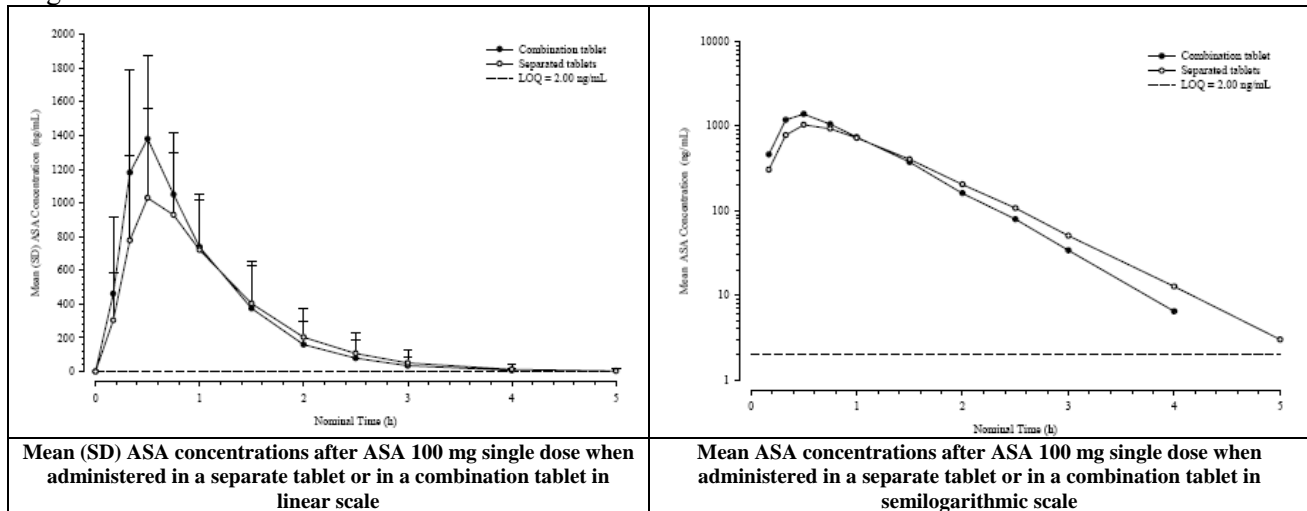


Table 7:

Mean \pm SD (CV%) [Geometric Mean] of ASA pharmacokinetic parameters

PK Parameter	Combination tablet (n=117)	Separated tablets (n=117)
C_{max} (ng/mL)	1580 \pm 497 (31) [1500]	1230 \pm 425 (35) [1160]
t_{max} (h)	0.50 (0.17 , 1.50)	0.50 (0.17 , 2.50)
t_{last} (h)	4.00 (3.00 , 23.00)	4.00 (3.00 , 23.00)
$t_{1/2\alpha}$ (h)	0.419 \pm 0.0895 (21) [0.411]	0.428 \pm 0.139 (32) [0.415]
AUC _{last} (h.ng/mL)	1440 \pm 341 (24) [1400]	1310 \pm 288 (22) [1280]
AUC* (h.ng/mL)	1440 \pm 343 (24) [1400]	1300 \pm 290 (22) [1270]

Tabulated values are Mean \pm SD (CV%) [Geometric Mean] except for t_{max} and t_{last} where values are Median (Min, Max)

* n=116 for combination tablet and n=111 for separated tablets

Point estimates and 90% CIs for ASA combination tablet / separate tablets (n=121)

Parameter	Comparison	Estimate	90% CI
C_{max}	Combination tablet vs. separated tablets	1.30	(1.22; 1.39)
AUC	Combination tablet vs. separated tablets	1.10	(1.07; 1.13)
AUC _{last}	Combination tablet vs. separated tablets	1.10	(1.07; 1.13)

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Table 8:

Mean \pm SD (CV%) [Geometric Mean] of SR26334 pharmacokinetic parameters

PK Parameter	Combination tablet (n=117)	Separated tablets (n=117)
C_{max} (ng/mL)	3640 \pm 1080 (30) [3460]	3590 \pm 1080 (30) [3430]
t_{max} (h)	0.75 (0.25 , 3.00)	0.75 (0.50 , 2.00)
t_{last} (h)	48.00 (30.00 , 48.12)	48.00 (23.00 , 48.12)
$t_{1/2\alpha}$ (h)	12.0 \pm 4.86 (41) [11.1]	12.8 \pm 5.75 (45) [11.8]
AUC _{last} (h.ng/mL)	9570 \pm 2300 (24) [9300]	9570 \pm 2540 (27) [9260]
AUC (h.ng/mL)	9830 \pm 2420 (25) [9550]	9860 \pm 2650 (27) [9530]

Tabulated values are Mean \pm SD (CV%) [Geometric Mean] except for t_{max} and t_{last} where values are Median (Min, Max)

Point estimates and 90% CIs for SR26334 combination tablet / separate tablets (n=121)

Parameter	Comparison	Estimate	90% CI
C_{max}	Combination tablet vs. Separated tablets	1.01	(0.96; 1.06)
AUC	Combination tablet vs. Separated tablets	1.00	(0.98; 1.02)
AUC _{last}	Combination tablet vs. Separated tablets	1.00	(0.98; 1.03)

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Table 9:

Mean \pm SD (CV%) [Geometric Mean] of SA pharmacokinetic parameters

PK Parameter	Combination tablet (n=117)	Separated tablets (n=117)
C_{max} (ng/mL)	5390 \pm 1200 (22) [5270]	5030 \pm 1050 (21) [4920]
t_{max} (h)	1.00 (0.50 , 3.00)	1.50 (0.75 , 4.00)
t_{last} (h)	12.00 (10.00 , 23.00)	12.00 (10.00 , 23.00)
$t_{1/2\alpha}$ (h)	2.32 \pm 0.602 (26) [2.25]	2.23 \pm 0.644 (29) [2.16]
AUC _{last} (h.ng/mL)	21400 \pm 6140 (29) [20700]	20600 \pm 5780 (28) [19900]
AUC* (h.ng/mL)	21700 \pm 6210 (29) [20900]	20900 \pm 5870 (28) [20200]

Tabulated values are Mean \pm SD (CV%) [Geometric Mean] except for t_{max} and t_{last} where values are Median (Min, Max)

*n=116 for combination tablet and n=117 for separated tablets

Point estimates and 90% CIs for SA combination tablet / separate tablets (n=121)			
Parameter	Comparison	Estimate	90% CI
C_{max}	Combination tablet vs. separated tablets	1.07	(1.04; 1.10)
AUC	Combination tablet vs. separated tablets	1.03	(1.02; 1.04)
AUC_{last}	Combination tablet vs. separated tablets	1.03	(1.02; 1.04)

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Discussion on bio-equivalence

The formulation chosen by the applicant for the fixed combination consists of a film-coated tablet containing two active substances: clopidogrel and ASA. The clopidogrel granules were prepared with the same granules used to produce clopidogrel (75 mg tablets). The blend containing ASA is qualitatively similar and proportionally similar between the different strengths.

Compared to the previous application, which was withdrawn by the applicant, the current dossier contains one new study seeking to establish bioequivalence between the fixed dose combination of clopidogrel (75 mg) and ASA (100 mg) and separate tablets of the same strengths of clopidogrel and ASA. The study demonstrates bioequivalence for both AUC and C_{max} based on parent compound data. The study also demonstrates bioequivalence for ASA clopidogrel based on parent compound plasma concentrations for AUC but not for C_{max} . The applicant argues that this is not clinically relevant “Given the various types of ASA formulations available on the market (immediate-release tablet, effervescent tablet, buffered tablet, enteric-coated tablet, powder for solution), and recognizing that these can result in differences in the rate of absorption of ASA, a formulation similar to the one used in the fixed combination (i.e., immediate release) has been used as reference for the bioequivalence studies”. Furthermore “Considering the large number of ASA formulations on the market with an approved indication in the cardiovascular field, the clinical practice and the clinical studies evaluating the benefit/risk of clopidogrel in combination with ASA, the slight difference in ASA C_{max} is considered as clinically non-relevant”. This justification is accepted by the CHMP.

Moreover, the applicant submits supportive data from the same study and from two other previously submitted studies for the inactive metabolite of clopidogrel SR26334 and for the ASA metabolite salicylic acid (SA). AUC and C_{max} for both compounds comply with bioequivalence requirements.

In conclusion, based on data from the new bioequivalence study and supportive data, as well as the argumentation that there is a large range of ASA products in the market that have been used with an approved indication in the cardiovascular field, the slight difference in ASA C_{max} can be considered as clinically non-relevant. Therefore the fixed dose combination of clopidogrel (75 mg) and ASA (100 mg) is considered bio-equivalent to separate tablets of the same strengths of clopidogrel and ASA.

The applicant provided evidence of fulfilment of the conditions as stated in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Therefore it is acceptable to grant a biowaiver for the strength of the FDC with clopidogrel (75 mg) and ASA (75 mg)

- Distribution

Clopidogrel and SR26334 are highly bound to plasma proteins with no saturation within a range of concentrations encompassing those reached at therapeutic doses.

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10L). Its metabolite, salicylic acid (SA), is highly bound to plasma proteins and it shows a concentration dependent binding (nonlinear). At low concentrations (< 100mg/L) approximately 90% of SA is bound to albumin. SA is widely distributed to all tissues and fluids, including the central nervous system, breast milk and foetal tissues.

- Elimination

Clopidogrel

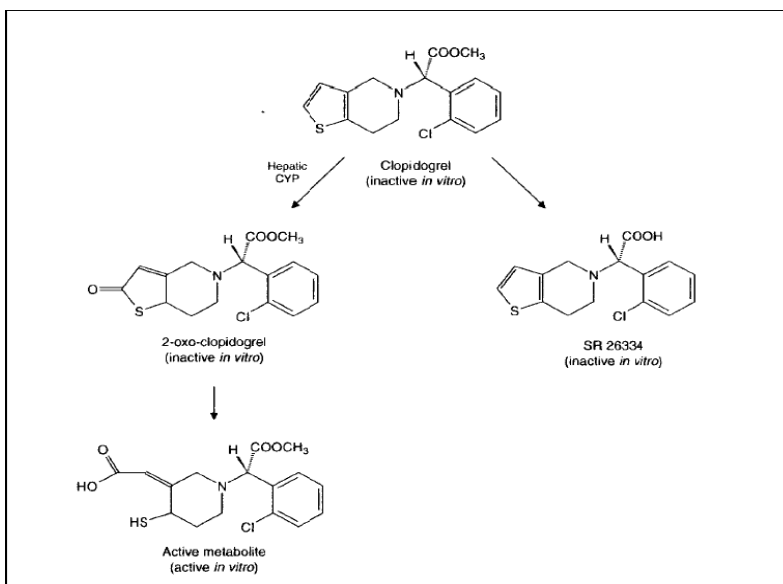
In humans, clopidogrel is highly metabolized primarily by 2 main pathways:

- One leading to the formation of the active metabolite and mediated by several CYPs including the CYP2C19, CYP3A4, CYP2B6 and CYP1A2.
- The other mediated by esterases and leading to the formation of the carboxylic acid metabolite SR26334 which is inactive.

A reliable assay for the active metabolite has only recently become available but there is enough evidence that clopidogrel is a prodrug exerting its anti platelet activity through its active unstable metabolite, which binds irreversibly to the ADP platelet P2Y₁₂ receptor. The active metabolite is formed in a 2 step reaction (1) formation of 2-oxo-clopidogrel; and (2) followed by hydrolysis forming a structure with an opened thiophene ring, a highly reactive thiol function and a free carboxylic group. Both steps are mediated through a CYP-450 dependent pathway of metabolism. The precise extent of involvement of each of these has not been determined.

The metabolic pathways for clopidogrel are provided in figure 5 below

Figure 5



In plasma, the main circulating compound was the acid metabolite SR26334, representing 85% of the total radioactivity circulating in plasma and which is not active. Two other minor metabolites were detected: the glucuronide conjugate of SR26334 and 2-oxo thiomethyl clopidogrel. In urine, SR26334 and its glucuronoconjugated forms were the main metabolites identified. No unchanged clopidogrel was recovered in urine.

SR26334 has an elimination half-life of 7 to 8 hours after both single and multiple dose administration of clopidogrel 75 mg once daily.

Interaction of CYP3A4 inhibitors and inducers with clopidogrel is sufficiently illustrated.

The excretion of clopidogrel, following a single dose of 75 mg of [14C] clopidogrel given alone or at the end of a ten-day dosing period of unlabelled drug, accounted for 92-98% of the radioactive dose administered, equivalent percentages being excreted through the faecal and urinary routes (46 and 50%

respectively). From the newly submitted bioequivalence study, the half-life of clopidogrel is ca. 6 h with an overall variability of 34 – 40%.

ASA

The ASA in DuoCover is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in DuoCover has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (1020 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged active substance depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid.

- Dose proportionality and time dependencies

The dose proportionality of clopidogrel was assessed using data on its main metabolite SR26334. Clopidogrel SR26334 exhibits dose independent kinetics. In a range from 50 to 150 mg of clopidogrel, SR26334 exposures (as measured by C_{max} and AUC) increased in a dose proportional manner. After repeated administration of clopidogrel 75 mg, the steady state of SR26334 was reached by Day 3, with an accumulation ratio of about 1.1. The pharmacokinetics of SR26334 remained linear over time and single dose pharmacokinetics of SR26334 predicts its steady state pharmacokinetics.

Following toxic doses (10 to 20g) of ASA, the plasma half-life of SA may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher.

- Special populations

No studies were conducted in children.

The pharmacokinetics of the active metabolite of clopidogrel is not known in special populations.

Renal impairment

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

- Pharmacokinetic interaction studies

The applicant discussed the possible mechanisms of interaction for either clopidogrel on ASA or ASA on clopidogrel: protein binding displacement (both clopidogrel and salicylic acid are strongly bound to albumin) and esterase metabolism (both clopidogrel and ASA are de-esterified in one of the respective metabolic pathways). None of these mechanisms is likely to be responsible for interactions.

No food interaction is reported for the ASA tablet. The applicant's data for clopidogrel from studies on pharmacodynamics and indirect measures of the inactive metabolite, showed that clopidogrel absorption is not influenced by food. At 400 mg, where clopidogrel C_{max} and pharmacodynamic parameters were investigated, no effect is observed. In addition, no recommendations for clopidogrel intake were specified in studies EFC3307 (CURE), EFC5133 (CLARITY) and EFC7018 (COMMIT) as well as in the Summary of Product Characteristics for clopidogrel.

However new evidence suggested that there is a significant food effect, when measuring unchanged clopidogrel plasma concentrations. Using an analytical technique for unchanged clopidogrel, the investigation of food intake influence on the bioavailability of clopidogrel has been recently investigated⁴. The data available so far, show that food intake clearly increases the BA of clopidogrel (500 up to 600 %) and enhances moderately the systemic exposure to the major but inactive carboxy-acid metabolite (approximately 10-20 %). In response to the CHMP D120 LOQ the applicant commented on these contradictory results. The applicant addressed these concerns adequately: one PK and PD study demonstrated that even though there is a marked effect of food on the absorption of clopidogrel (several fold increase in both AUC and C_{max}) this effect does not translate into significant effects on the active metabolite AUC and on the PD effect (platelet aggregation assay).

Based on the data available to date, CHMP concludes that food slightly decreases the rate of absorption of ASA, but does not significantly modify the extent of absorption. Therefore no special recommendation for the administration of clopidogrel with regard to food has been included in the SPC. DuoCover may be given with or without food.

Discussion on clinical pharmacokinetics

No major issues have been identified in the pharmacokinetics section of this dossier. However at the request of CHMP the applicant addressed a few concerns, mainly related to the food effect and the extent to which genetic polymorphism affects clopidogrel pharmacokinetics of metabolites.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by CYP2B6 and CYP3A4, which do not exhibit genetic polymorphism, and to a lesser extent by CYP1A1, CYP1A2 and CYP2C19, of which the two latter ones exhibit genetic polymorphism.

The extent to which genetic polymorphism affects clopidogrel pharmacokinetics as related to the active metabolite and the clinical consequences thereof was discussed by the applicant in the response to CHMP D120 LOQ based on preliminary data from an ongoing study.

Based on the data submitted to date, the CHMP consider that polymorphism due to CYP1A2 is of no concern due to the low prevalence and the minor role that this isozyme plays in clopidogrel metabolism.

⁴ **2006:** Nirogi Ramakrishna V S; Kandikere Vishwottam N; Mudigonda Koteswara Effect of food on bioavailability of a single oral dose of clopidogrel in healthy male subjects. *Arzneimittel-Forschung* 2006; 56(11):735-9.

Polymorphism due to CYP2C19 has been adequately addressed in the SPC (Sections 4.2, 4.4, 4.5 and 5.2); furthermore the applicant commits to amend the SPC should this be required pending the outcome of the CHMP analysis on interaction between clopidogrel and Proton Pump inhibitors.

Regarding the food effect, CHMP concluded based on the data available to date that food does not significantly modify the extent of absorption. The applicant committed to submit study reports on ongoing studies, and to subsequent updates of the product information should this be required

Pharmacodynamics

- Mechanism of action

Clopidogrel and ASA modify platelet aggregation through 2 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.

- Primary and Secondary pharmacology

This dossier is for an application for fixed-dose combination tablets of clopidogrel and acetylsalicylic acid (ASA) (75 mg/75 mg and 75 mg/100 mg) as a substitution for the coadministration of the separate constituents in the approved acute coronary syndrome (STEMI and NSTEMI) indications (see CHMP/EWP/191583/2005). Therefore, since the concomitant administration of the 2 drugs for these indications at these dosages has already been approved, and the use of clopidogrel alone in those indications is not recommended, the submission of clinical pharmacodynamic data is not considered necessary.

Clinical efficacy

- Dose response study(ies)
- Main study(ies)

The efficacy of clopidogrel in combination with ASA was evaluated in ACS patients with or without ST-segment elevation in 3 double-blind studies [EFC3307 (CURE), EFC7018 (COMMIT/CCS-2), and EFC5133 (CLARITY-TIMI 28)]. EFC3307 (CURE), EFC7018 (COMMIT/CCS-2), and EFC5133 (CLARITY-TIMI 28) were randomized, double-blind, placebo-controlled studies comparing clopidogrel 75 mg/day in combination with ASA to ASA alone. In EFC7018 (COMMIT/CCS-2), the patients did not receive a loading dose of clopidogrel the first day, whereas in the 2 other studies a loading dose of 300 mg was given. Patients included in the EFC3307 (CURE) study were followed up to 12 months (minimum of 3 months) or to a common study end date (pre-specified as 3 months after the last patient was randomized), whichever came first, and patients included in the 2 STEMI studies were followed up to 4 weeks.

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 in these indications in Europe, as well as in the US and 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 SPC for clopidogrel recommends that the dose of ASA should not be higher than 100 mg daily; hence the doses of ASA in the current application.

Clinical safety

- Patient exposure

Clopidogrel in association with ASA is a widely used association in ACS patients, and the safety of each component separately as well as in association is well known. The safety data supporting the benefits of a fixed-dose combination of clopidogrel with ASA (75/75 mg; 75/100 mg) in ACS patients without or with ST-elevation MI (NSTEMI and STEMI) are provided by the results of 3 studies: 1) in NSTEMI patients EFC3307/CURE that included 12 562 patients; and 2) in STEMI patients, EFC7018/COMMIT/CCS-2 that included 45 852 patients and 3) EFC5133/CLARITY-TIMI 28 that included 3491 patients.

No safety concern was raised in the bioequivalence studies and pharmacovigilance data on clopidogrel. Even if this population (using clopidogrel in combination with ASA) cannot be formally identified, it is included in the general post-marketing surveillance data of clopidogrel collected by the company.

- Adverse events/serious adverse event/deaths/other significant events

Safety data on ASA in the ACS indication is reflected by the Summaries of Product Characteristics approved in the different EU member states. 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. Since the approval of the non-ST-segment elevation ACS indication in 2002 for clopidogrel in association with ASA, no safety signal related to this association has been detected in the post-marketing surveillance.

To reflect the safety data of each compound of the fixed-dose combination, the proposed Summary of Product Characteristics for this clopidogrel/ASA fixed-dose combination product has been prepared based on the current European Union Summary of Product Characteristics for clopidogrel hydrogen sulphate (30 October 2008) and on various European Union Summaries of Product Characteristics for low-dose acetylsalicylic acid products that included an indication for secondary prevention of risk of mortality, or for secondary prevention of thrombotic cerebrovascular, or cardiovascular disease.

- Laboratory findings

Commonly occurring laboratory findings are prolonged bleeding time, decreased neutrophil count, and decreased platelet count. Very rare laboratory findings are: abnormal liver function test, blood creatinine increased.

- Safety in special populations

The safety and efficacy of DuoCover in children and adolescents have not been established.

Therapeutic experience with clopidogrel plus ASA is limited in patients with mild to moderate renal impairment. Therefore DuoCover should be used with caution in these patients. DuoCover must not be used in patients with severe renal impairment (SPC Sections 4.2, 4.3 and 4.4)

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. DuoCover should therefore be used with caution in this population. DuoCover must not be used in patients with severe hepatic impairment. (SPC Sections 4.2, 4.3 and 4.4)

- Safety related to drug-drug interactions and other interactions

Based on the available experience with combined use of clopidogrel plus ASA, the following information has been proposed for the DuoCover SPC Section 4.5:

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

Glycoprotein IIb/IIIa inhibitors: DuoCover should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

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 DuoCover 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). The safety of the concomitant administration of DuoCover with other thrombolytic agents has not been formally established and should be undertaken with caution (see section 4.4).

NSAIDs: in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs including Cox-2 inhibitors is not recommended (see section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other concomitant therapy with clopidogrel: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of medicinal products that inhibit CYP2C19 should be discouraged (see sections 4.4 and 5.2).

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Proton Pump Inhibitors: Although the evidence of CYP2C19 inhibition varies within the class of Proton Pump Inhibitors, clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of Proton Pump Inhibitors should be avoided unless absolutely necessary. There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic (PK) 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 co-administration 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.

Other concomitant therapy with ASA: Interactions with the following medicinal products have been reported with ASA:

Uricosurics (benzbromarone, probenecid, sulfapyrazone): Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Methotrexate: Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with DuoCover as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Other interactions with ASA: Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycemic agents.

Other interactions with clopidogrel and ASA: More than 30,000 patients entered into clinical trials with clopidogrel plus ASA at maintenance doses lower than or equal to 325 mg, and received a variety of concomitant medicinal products including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicinal product interaction information described above, interaction studies with DuoCover and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed.

- Discontinuation due to adverse events

If the use of DuoCover is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

- Post marketing experience

Post marketing experience with the fixed-dose combination is very limited. The experience available for the combined use of clopidogrel and ASA has been discussed in the sections above.

- Discussion on clinical safety

Possible issues related to the risks of a fixed combination (both active substances increase bleeding risk; fixed combination is less flexible with respect to dose adjustments) were resolved through the Product Information (SPC Sections 4.2, 4.4 and 4.5).

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The applicant provided a justification for not submitting a Risk management plan. In view of the established positive benefit / risk ratio of the approved indications of clopidogrel associated with ASA, its safe use in extensive clinical and post-marketing experience, and the fact that the fixed-dose combination tablet is merely replacing co-administration of clopidogrel and ASA, the CHMP agreed that routine pharmacovigilance (including PSURS) is sufficient to monitor the safety profile of the FDC and did not require the MAA to submit a risk management

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

PSURs

The PSUR cycle of DuoCover is aligned with the one of the product Iscover, until otherwise specified.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The active substances and the medicinal product have been appropriately characterised and generally satisfactory documentation has been provided. The excipients used in the preparation of the product and manufacturing process selected are typical for tablets. The results indicate that the active substances and the medicinal product can be reproducibly manufactured.

Non-clinical pharmacology and toxicology

The pharmacological and toxicological profile of clopidogrel and acetylsalicylic acid are well known (from Iscover supportive studies and from published studies in animals, men and *in vitro* models).

As there is no evidence to suggest a possible negative interaction between clopidogrel and ASA, and both drugs have been extensively used in humans in monotherapy or in combination for a long period and the safety of this combination is well documented, nonclinical studies with the clopidogrel/ASA combination are not considered necessary.

It is considered that the existing clinical experience suffices as the supportive information for DuoCover efficacy and safety and therefore specific nonclinical studies with the clopidogrel/ASA fixed dose combination are not needed. Concerns regarding the reproductive toxicity profile, particularly of aspirin in relation to early pregnancy (embryofoetal development) or late pregnancy (dystocia and foetal mortality) have been addressed by adding precautionary information in sections 4.3 and 4.6 of the SPC, to appropriately restrict its use.

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk and breast-feeding should not be continued during treatment with DuoCover (see SPC section 4.6 and 5.3).

An ERA was submitted, but not all studies were completed yet. The applicant has committed to update the ERA with ongoing studies.

Efficacy

The efficacy of the combination clopidogrel/ASA was evaluated in 3 double-blind studies including over 60 000 patients (CURE, COMMIT and CLARITY). Based on these studies clopidogrel (in combination with ASA) received the indications that are now applied for with this new fixed combination. As the indication claimed for the fixed combination tablets is a mere “substitution” indication, no new clinical efficacy studies were performed to support this fixed combination of clopidogrel and ASA. The Applicant refers to the “Q&A document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention.” CHMP/EWP/191583/2005, and provided a letter of access to all data in the Iscover dossier.

Therefore the fixed combination dossier is mainly based on pharmacokinetic data. The assessment of data from the new bioequivalence study and supportive data concluded that the fixed dose combination of clopidogrel (75 mg) and ASA (100 mg) is considered bio-equivalent to separate tablets of the same strengths of clopidogrel and ASA. A biowaiver has been granted for the strength of the FDC with clopidogrel (75 mg) and ASA (75 mg). No major issues have been identified in the pharmacokinetic section; however a few concerns, mainly related to the food effect and the extent to which genetic polymorphism affects clopidogrel pharmacokinetics of metabolites were discussed.

Polymorphism due to CYP2C19 has been adequately addressed in the SPC. Polymorphism due to CYP1A2 is of no concern due to the low prevalence and the minor role that this isozyme plays in clopidogrel metabolism.

CHMP concluded based on the data available to date that food does not significantly modify the extent of absorption of clopidogrel; DuoCover can be taken with or without food. The applicant has committed to submit study reports on ongoing studies.

The benefit of this new fixed combination is a simplification of treatment, i.e. patients need to take one instead of two tablets.

Safety

The safety of the combination clopidogrel and ASA was evaluated in 3 double-blind studies including over 60 000 patients (CURE, COMMIT and CLARITY). Based on these studies clopidogrel (in combination with ASA) received the indications that are now applied for with this new fixed combination. Therefore, this dossier is mainly based on bioequivalence studies.

Possible issues related to the risks of a fixed combination (both active substances increase bleeding risk; fixed combination is less flexible with respect to dose adjustments) were resolved through the Product Information (SPC 4.2, 4.4, and 4.5).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

- User consultation

The applicant has provided the results of the User Testing concerning the PIL for DuoCover, aiming at ensuring that the information is legible, clear and easy to use so that patients can locate important information within the package leaflet, understand it and act appropriately.

A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PIL and 90% can show that they understand and can act upon it.

Results of the 2 rounds of user testing, following a preliminary test showed:

- The main objectives of the readability testing were met by this user test (locating, understanding and adequate use by the participants).
- The key messages for safe use of DuoCover have been identified and the questions reflect the key messages.
- According to the minimum 90% of positive results in both finding and understanding the information, the results of the tests (at least 95% and 90%) are acceptable.

Risk-benefit assessment

The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of DuoCover in the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA) was favourable and therefore recommended the granting of the marketing authorisation.

The full description of the agreed indication is as follows:

DuoCover is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoCover is a fixed-dose combination 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