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Pre-authorisation Evaluation of Medicines for Human Use

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This product was later resubmitted to the EMEA.
See here for information on the outcome of the resubmission.

WITHDRAWAL ASSESSMENT REPORT FOR DUOPLAVIN

International Nonproprietary Name (INN):
clopidogrel/acetylsalicylic acid

Procedure No. EMEA/H/C/874

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Rapporteur considers that the application for DuoPlavin, for the prevention of atherothrombotic events in patients suffering from acute coronary syndrome:

- Non- ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction).
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy

could be approvable provided that satisfactory responses are given to the list of outstanding issues.

The clinical outstanding issue that led to the applicant's withdrawal was the following: "The application is based on studies that do not use state-of-the-art methodology (bioanalytical assay for parent compound clopidogrel) as required by guidance in force at the time of the submission. The applicant is asked to discuss."

II. EXECUTIVE SUMMARY

II.1 Problem statement

Various types of therapeutic intervention should be considered for prevention of ACS. 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/NSTEMI 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. Acetylsalicylic acid (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) 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) results, clopidogrel in combination with ASA has been recently approved in Europe and in US and in 9 other countries (as of February 2007) for the prevention of atherothrombotic events in STEMI patients eligible for thrombolytic therapy. This use for the combination 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. The use of a fixed combination tablet in place of the individual administration of the two compounds is expected to improve patient compliance and may be of convenience for those patients by limiting the number of tablets they need to take. By using the right dose of ASA (less than or equal to 100 mg), the combinations will also provide a safety advantage.

This dossier is aimed to apply for approval of fixed-dose combination tablets of clopidogrel (75 mg) and ASA (75 mg or 100 mg).
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 labelling 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. The submission of clinical efficacy data is not considered necessary. In addition the applicant provided a letter of access to all clopidogrel dossiers previously submitted, along with non-clinical and clinical summary data for clopidogrel (mainly based on the existing MA dossier) and ASA (literature data).

II.2 About the product

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 A_2 (TXA_2), 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

This application contains information to support regulatory approval of 2 film-coated immediate-release tablet formulations of clopidogrel/ASA each containing 75 mg clopidogrel and 2 doses of ASA, i.e., 75 and 100 mg. Bioequivalence studies were performed for film-coated immediate-release tablet formulations of clopidogrel/ASA each containing 75 mg clopidogrel and ascending doses of ASA.

II.3 The development programme

The development plan is an abbreviated one because the fixed-dose combination of ASA + clopidogrel is intended to substitute the individual components. In the clinical part only bioequivalence studies are new.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The new studies conducted for the quality part and the bioequivalence studies are GMP and GCP compliant. The company is requested to provide GLP Compliance statements of the test facilities by a GLP Monitoring Authority at the time of performing the study.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Introduction

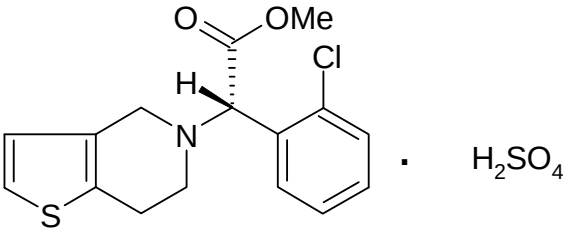
DuoPlavin is presented as film-coated tablets containing two active substances: clopidogrel and acetylsalicylic acid (ASA). Two strengths of the drug product, with the same amount of clopidogrel but with different amounts of ASA were proposed. Each tablet of the first strength contains 75 mg of clopidogrel and 75 mg of acetylsalicylic acid. Each tablet of the second strength contains 75 mg of clopidogrel and 100 mg of acetylsalicylic acid.
The excipients used in the formulation of DuoPlavin are well known excipients typically used in the tablet formulation.

Drug 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(4*H*)-acetic acid, alpha-(2 chlorophenyl)-6,7-dihydro-, methyl ester, (*S*) (CAS).

The drug substance used for manufacture of the product is the hydrogen sulphate salt of clopidogrel and has the following structure:



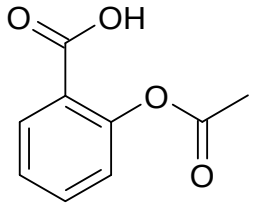
Clopidogrel hydrogen sulphate used for the proposed formula is the same as that already approved for manufacturing Plavix 75 mg tablets.

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 active substance has been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that clopidogrel can be reproducibly manufactured.

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:



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.

Acetylsalicylic acid is described in the European Pharmacopoeia and its manufacturer has confirmed the drug substance complies with these requirements.

Drug Product

Pharmaceutical Development

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

No modifications have been introduced to the formula, batch size and manufacturing process of the clopidogrel. The acetylsalicylic acid blend was developed to optimise the good compressibility properties of the tablet. The weight of the acetylsalicylic acid blend varies proportionally in order to achieve the various strengths of the combination.

Manufacture of the Product

The manufacturing process consists of the preparation of the granules for compression, film coating, and packaging and is adequately described.
Operations follow standard procedures.

The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

Specifications and Analytical Procedures

The drug product specifications include tests for appearance, identification of clopidogrel and acetylsalicylic acid (HPLC), uniformity of dosage units for clopidogrel and acetylsalicylic acid, assay of clopidogrel and acetylsalicylic acid, dissolution (HPLC), impurities (HPLC), water content and bioburden.

The analytical methods have been sufficiently described and validated, some of them are compendial methods described in the PhEur.

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

Stability

Stability studies have been performed according to the ICH guidelines. 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 SPC.

III.2 Non clinical aspects

Pharmacology

The mechanism of the antiplatelet action of clopidogrel is related to the specific inhibition of adenosine diphospate (ADP) receptors on platelets through a metabolite which structure has been identified still during the process of regulatory assessment of the marketing authorization application of the Plavix 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.

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.

For Clopidogrel/ASA combination, the synergistic overpotentiation obtained when aspirin and clopidogrel are given in combination has been demonstrated in some studies, 3 of which are referred in the DuoPlavin file. The observed additive effect strongly suggests that the combined inhibition of COX (and subsequently of thromboxane synthesis) by ASA and ADP receptors by clopidogrel can provide substantial protection against platelet aggregation and thrombosis at the site of endothelial injury, in humans.

Safety pharmacology or secondary pharmacodynamic studies with the fixed-dose combination were not performed and are not requested in view of the use of the combined individual drugs at the specified dosage now being filed in the DuoPlavin application.

Pharmacokinetics

Clopidogrel**:** The metabolism and disposition of clopidogrel were assessed from 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.

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 an hepatic first-pass effect. The second step, the metabolic conversion of salicylate and subsequent formation of conjugates and their renal excretion, is dose-dependent. Salicyluric acid is the main and rate-limiting metabolite in humans.

The PK of combined Clopidogrel/ASA has not been addressed in dedicated studies. Both compounds are highly protein bound and undergo hepatic metabolism. Although these aspects might raise the possibility for pharmacokinetic interaction, such will have been covered in the clinic, 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 in what concerns general toxicity and specific aspects like genotoxicity, carcinogenicity or reproductive toxicity are well know from previously performed studies with Plavix and from published, and clinical information and experience regarding the use of both drugs including their combined use in the dose ratio included in DuoPlavin. No studies were performed with DuoPlavin combination which is acceptable. None of the two drugs were found to be genotoxic or carcinogenic. The reproductive toxicity profile, particularly of aspirin raises concern in relation to early (embryofoetal development) or late (dystocia and foetal mortality) pregnancy, many of the effects being associated to the inhibitory effect on prostaglandin synthesis. The use in pregnancy of DuoPlavin is not to be contraindicated due to the severity of the condition but appropriate precautionary information is to be included in section 4.5 of the SPC, to restrict appropriately the use.
The submitted environmental risk assessment (ERA) evaluates both active substances: clopidogrel and ASA. Concluding, phase II analysis is incomplete for clopidogrel and studies are requested before any conclusion can be taken.
The PIL/SPC (section 6.6) must be corrected. Questions to the Applicant are posed accordingly.

Conclusion on Non-clinical aspects of DuoPlavin

The pharmacological and toxicological profile of clopidogrel and acetylsalicylic acid are well known (from Plavix supportive studies and from published studies in animals, men and in vitro models).
No dedicated studies with clopidogrel/ASA fixed dose combination have been performed. This is acceptable because there is extensive human experience on the combined use of individual drugs at the doses proposed for this application. 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 DuoPlavin efficacy and safety and therefore dedicated non-clinical studies are not needed.
Some aspects raised in relation to ERA are to be further discussed.

III.3 Clinical aspects

Pharmacokinetics

This is an application for a fixed-dose combination of clopidogrel (75 mg) and ASA (75 and 100 mg).

The pharmacokinetics of ASA is well known from its long use and extensively published literature. However the information presented in this dossier is scarce and the applicant is invited to provide a more complete and detailed review of ASA pharmacokinetics, especially regarding its absorption and bioavailability characteristics as well as data on extrinsic (namely food effect) and intrinsic factors to support SPC recommendations.

The current knowledge on the pharmacokinetics of clopidogrel is unfortunately very limited. Clopidogrel is a pro-drug. The active metabolite, a thiol derivative, is formed by oxidation to 2-oxo-clopidogrel and subsequent hydrolysis, but it is undetectable in plasma. This and animal data suggest that either the active metabolite is a very reactive molecular entity or is not circulating free in plasma. Also, it has been shown that the active metabolite binds irreversibly to platelet ADP receptors. All these findings led to the hypothesis that after oral administration of clopidogrel the active metabolite is formed mainly during the first-pass processes and then is bound irreversibly to platelet receptors, so that there is no "free" active metabolite circulating in plasma. In addition, after chemical synthesis, this active metabolite was unstable. Due to the lack of a stable standard, it was not possible to develop and validate a sensitive assay method in human plasma using the usual quality standards for validation of an assay method.

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. Hence, the pharmacokinetics of SR26334 was used to characterise the absorption and pharmacokinetics of clopidogrel as well as the bioavailability of the clopidogrel formulations used in clinical investigations and as marketed.

The in vivo bioequivalence of the clopidogrel/ASA 75/75 and 75/100 mg tablets versus the marketed 75 mg clopidogrel tablets and ASA immediate-release tablets were assessed in bioequivalence studies. These were the only original data provided in this application. The bioequivalence studies were performed in fasted conditions since no food interaction is reported for the clopidogrel tablet and ASA tablet and that they can be taken independently as regard to meal.

The studies provided establish bioequivalence for clopidogrel and ASA between the proposed formulations with different ratios of clopidogrel to ASA (including 75/75 and 75/100 mg) based on the respective measurable metabolites: SR26334 for clopidogrel and salicylic acid (SA) for ASA, respectively. All the 95% CI's for C_{max} and AUC were within the acceptance range for all formulations. This is acceptable in principle. However, the quantification of ASA was possible and the applicant provides the relevant parameters for this species. For the 75/75; 75/100 mg of clopidogrel to ASA, the C_{max} CI for the ratio of ASA in these formulations as compared to ASA in the reference formulation is clearly outside the acceptance interval. Since the parent compound (ASA) reflects absorption better than the metabolite (SA), this means that there is a significant difference in this bioavailability parameter (C_{max}) for the formulation and reference respectively. The applicant provides an explanation based on the variability of ASA C_{max} in formulations and dosage forms distinct from the ones applied for.

It has been shown previously that clopidogrel absorption is not influenced by food. Therefore no special recommendation for the administration of clopidogrel with regard to food has been included in the SPC. However the applicant is invited to provide evidence that this is the case with ASA.

The applicant discusses 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.
A few issues should be adequately addressed by the applicant before a CHMP opinion can be granted:
The application is based on studies that do not use state-of-the-art methodology (bioanalytical assay for parent compound clopidogrel).

Pharmacodynamics

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.

This dossier is for an application for approval of 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 applicant considered that the submission of clinical pharmacodynamic data is not necessary.

Efficacy

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.

Safety

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:
Safety data on ASA in the ACS indication is reflected by the Summaries of Product Characteristics approved in the different EU member states. Bleeding, including upper gastro-intestinal bleeding is the most common reaction reported with the different formulations of ASA. The similar safety profile and the better bioavailability of regular aspirin support the choice of the Marketing Holder (MAH) to use the fixed-dose combination with regular aspirin.

Safety of clopidogrel is based on extensive clinical data in more than 42 000 patients, including over 30 000 patients treated with clopidogrel in combination with ASA and over 9000 patients treated for 1 year or more. From the launch of clopidogrel up to November 2006, nearly 60 million of patients were treated with clopidogrel worldwide. Since the approval of the non-ST-segment elevation acute coronary syndrome indication in 2002 of clopidogrel in association with ASA, no safety signal related to this association has been detected in the post-marketing surveillance.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. PHARMACOVIGILANCE AND RISK MANAGEMENT PLAN

The Pharmacovigilance system is considered adequate.

There is no need for a specific Risk Management Plan for DuoPlavin since the Pharmacovigilance procedures in place for Plavix are considered sufficient. The safety profile is well established and the fixed-dose combination is not likely to be associated with new potential risks.

VI. BENEFIT RISK ASSESSMENT

VI.1 Clinical context

The current application intends to support a fixed-dose combination that fits the concept of substitution. In substitution concept a patient is treated with 2 medicinal products and the fixed-dose combination allows for the replacement of those 2 medicinal products. In the current dossier the target are 2 of the approved indications where the state of the art recommends that ASA and clopidogrel are used together. According with the state of the art and the international guidelines for treatment it is not legitimate to recommend the use of clopidogrel without the background ASA therapy. This means that for these 2 indications clopidogrel is always initiated on top of ASA. Since the option of using clopidogrel alone is not recommended there is a valid rationale for the existence of a fixed-dose combination. At the time of the first granting of the indications the pivotal trials quoted in this report were conducted on top of ASA because it would be unethical to do otherwise. Therefore the use of clopidogrel in the 2 target indications is by definition done in addition to ASA.

Given the evaluation done in this report there are some quality and PK aspects that need clarification however these do not seem to impact negatively on the benefit/risk assessment. We have no clinical objections regarding this fixed combination.

VI.2 Benefits

The benefits are those established for clopidogrel. The fixed-dose combination might introduce an element of commodity for the patients and a theoretical increase in compliance.

At the time of the first granting of the indications the pivotal trials quoted in this report were conducted on top of ASA because it would be unethical to do otherwise. Therefore the use of clopidogrel in the 2 target indications is by definition done in addition to ASA. The only critical decision in the process of developing the fixed combination was the choice of the formulation and dose of ASA which has a relative wide range of possibilities. However given that the current SPC for clopidogrel recommends a dose of ASA up to 100mg the choice of 2 strengths 75 and 100 mg is appropriately reflecting the current practice and it is therefore endorsed.

VI.3 Risks

The risks are those described for clopidogrel. In addition there is a theoretical risk that the discontinuation of the fixed combination might increase the risk of thromboembolic events more than the interruption of just one of its components.

The uncertainties found in the bioequivalence studies might be considered a potential risk of the fixed combination.

VI.4 Balance

Overall the benefits translated in more comfort and eventual better compliance are considered to outweigh the risks associated with the fixed combination

VI.5 Conclusions

The Benefit Risk evaluation is considered favourable provided the outstanding issues are solved.